Filed on behalf of Patent Owners Genentech, Inc. and City of Hope by:

David L. Cavanaugh
Reg. No. 36,476
Heather M. Petruzzi
Reg. No. 71,270
Robert J. Gunther, Jr.
Pro Hac Vice
Wilmer Cutler Pickering
Hale and Dorr LLP
1875 Pennsylvania Ave., NW
Washington, DC 20006

Adam R. Brausa
Reg. No. 60,287
Daralyn J. Durie
Pro Hac Vice
Durie Tangri LLP
217 Leidesdorff Street
San Francisco, CA 94111

Jeffrey P. Kushan
Reg. No. 43,401
Peter S. Choi
Reg. No. 54,033
Sidley Austin LLP
1501 K Street, N.W.
Washington, D.C.
20005

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

GENENTECH, INC. AND CITY OF HOPE,
Patent Owners

Case IPR2015-01624
Patent 6,331,415

PATENT OWNERS' RESPONSE

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

I. INTRODUCTION

The invention at issue in this proceeding is based on one of the foundational discoveries of modern biotechnology: proof that functional antibodies can be produced recombinantly by co-expressing their heavy and light chains in just one host cell. That revolutionary invention gave rise to the therapeutic use of recombinant monoclonal antibodies, and is protected by U.S. Patent No. 6,331,415 ("the Cabilly '415 patent") (Ex. 1001). Recognizing the importance of the Cabilly '415 invention, dozens of the world's most sophisticated biotechnology companies have paid well over a billion dollars in licensing royalties for the right to utilize it in producing therapeutic antibodies for a wide range of diseases.

The antibody production methods claimed in the Cabilly '415 patent were remarkable considering the state of the art when it was filed in April 1983. By that time, an established path for producing monoclonal antibodies (using "hybridoma" techniques) had already been developed, and the use of hybridomas was continuing to expand. But the Cabilly inventors chose not to take that proven route and instead pursued antibody production using recombinant DNA techniques.

By the early 1980s, only a few relatively simple proteins had been produced recombinantly. And while some scientists had speculated that it might be possible in the future to produce antibodies recombinantly, even persons of extraordinary skill (including Nobel Laureates) were uncertain whether such a technique could

be used to make antibodies. Indeed, Petitioners' expert, Dr. Jefferson Foote, now agrees that, as of April 1983, producing an antibody recombinantly would have been a major task without any certainty of success, and that the Cabilly inventors were the first to successfully perform that undertaking.

The Cabilly inventors' success in producing an antibody recombinantly was itself a revolutionary advance in April 1983. But even more remarkable was that the Cabilly inventors achieved that result by defying conventional wisdom and co-expressing the heavy and light chains in a single host cell. Dr. Foote agrees that, before April 1983, no one had produced ***any*** type of multimeric eukaryotic protein by recombinantly producing its constituent polypeptides in a single host cell. Indeed, the only multimeric eukaryotic protein that had been produced recombinantly by that time was insulin, and it was made using ***two separate host cells***—one for each polypeptide chain. And even the references Petitioners cite show that highly-skilled scientists were perplexed by their inconsistent and frequently unsuccessful efforts to produce even a single antibody heavy chain or light chain on its own. The fact that the Cabilly inventors succeeded by pursuing a path contrary to the conventional standards at the time by co-expressing both heavy and light chains in a single host cell was a major breakthrough.

Now, decades later, Petitioners seek to rewrite this history leading up to the Cabilly '415 patent by attributing its groundbreaking invention to others. But the

only way to reach that result is through a hindsight-driven analysis that is contrary to the disclosure of the asserted references, the state of the art, and the real-world objective evidence demonstrating non-obviousness. Petitioners rely on precisely such an analysis, grounded almost exclusively in assertions by Dr. Foote. But at his deposition, Dr. Foote was repeatedly forced to concede facts that directly conflict with his declaration assertions and that are fatal to Petitioners' obviousness arguments.

Petitioners cannot sustain their burden to prove obviousness based on such a flawed, hindsight-driven analysis. Accordingly, Patent Owners respectfully request that the Panel affirm the patentability of the challenged claims.

II. SUMMARY OF ARGUMENT

In its Institution Decision, the Panel found a reasonable likelihood that certain challenged claims of the Cabilly '415 patent would have been obvious over U.S. Patent No. 4,495,280 ("Bujard") (Ex. 1002) combined with either of two articles (Riggs & Itakura (Ex. 1003) or Southern (Ex. 1004)). The full record now refutes those initial conclusions.

Bujard: Bujard is the primary reference underlying both instituted grounds, but discloses nothing about how to make an antibody. Indeed, Bujard's ***only*** mention of antibodies is in a large, generic list of "proteins of interest"—which Dr. Foote originally cited as evidence that the Bujard inventors supposedly intended to

suggest making antibodies in a single host cell. But the record now shows that same list of proteins (including antibodies) appears in dozens of unrelated applications that Bujard's prosecuting attorney had filed for others starting in 1975. When confronted with that evidence, Dr. Foote admitted that Bujard's list was likely just recycled from those earlier applications. Petitioners can hardly infer any key insight concerning antibody production from a list that has nothing to do with Bujard's invention.

The Panel pointed to isolated statements in Bujard referring to "a plurality of genes, including multimers" and "one or more structural genes" as suggesting the co-expression of antibody heavy and light chains in a single host cell. But that is not how Bujard uses those terms, and certainly not how a skilled artisan would have interpreted them in April 1983. Indeed, the only evidence supporting the Panel's initial interpretation of "multimers" was Dr. Foote's opinion that the term ***always*** refers to "a protein with more than one subunit." But Dr. Foote now concedes that his only citation for that assertion was a source from ***2016***, and that other references now in the record—including from the Bujard inventors—use the same term to refer to repeating copies of the same gene, just as it was used in Bujard.

Nor did Bujard use the phrase "one or more structural genes" to refer to co-expression of genes that encode different proteins of interest. Dr. Foote now

agrees that Bujard expressly defines a "structural gene" as including markers, and that Bujard does not include ***any*** embodiment involving two genes encoding for different proteins of interest.

Simply put, Bujard does not disclose or suggest co-expressing the heavy and light chains in a single host cell. Had Bujard made that groundbreaking discovery, the patent would have no doubt touted and claimed it—but it did not. And the scientific literature would have cited Bujard for that remarkable advance—but Bujard has never been cited for that purpose. The record also now includes testimony from Dr. Reiner Gentz, who worked in Dr. Bujard's lab in the early 1980s and co-authored the scientific paper corresponding to the Bujard patent. Dr. Gentz is not aware of anyone in Dr. Bujard's lab who contemplated using their DNA constructs to co-express different eukaryotic proteins of interest in a single host cell.

That testimony is confirmed by what became of the Bujard patent: it was allowed to expire only four years after it issued for failure to pay maintenance fees. That is hardly a result one would expect for a patent that supposedly renders obvious one of the foundational inventions of modern biotechnology, and it underscores how divorced Petitioners' arguments are from the reality of what Bujard actually discloses and how a skilled artisan in April 1983 would have understood it.

Ground 1: Petitioners' arguments based on an obviousness combination with Riggs & Itakura does not cure the elements missing from Bujard, and only highlights the non-obviousness of the challenged claims. Riggs & Itakura is a review article describing the production of insulin from recombinant DNA, and does not disclose any details that would have led to the Cabilly '415 invention. The technique that Riggs & Itakura describes for insulin undisputedly could ***not*** be used to produce antibody polypeptides; different techniques would have to be developed and used, as Dr. Foote admits. And even if its teachings had been considered together with Bujard, Riggs & Itakura would have led a skilled artisan away from co-expression; it describes producing insulin using ***two separate*** host cells, one for each polypeptide subunit. Petitioners' implausible theory that a skilled artisan would have ignored the central teaching of Riggs & Itakura and pursued the opposite approach to arrive at the Cabilly '415 invention rests on hindsight.

The Panel also concluded that the claimed invention would have been obvious to try based upon the combination of Bujard with Riggs & Itakura. But all of the prerequisites for that conclusion are absent here: (1) Bujard does not present a finite number of options to pursue—it presents "millions," as Dr. Foote admits; (2) it was not predictable at the time that a recombinant DNA technique to make an antibody would have led to success—as Dr. Foote also admits; and (3) the single

host cell approach claimed in the Cabilly '415 patent was not an identified solution that anyone had used before—which Dr. Foote now concedes as well.

Ground 2: The combination of Bujard with Southern fares no better. Southern does not mention antibodies at all; it simply describes a new selectable marker for use in eukaryotic cells. As Dr. Foote admits, Bujard's bacterial expression constructs would not be compatible in the host expression systems addressed in Southern, and vice versa. Petitioners rely on Southern for its supposed mention of two vectors used to express different genes of interest. But Southern's only discussion of a two-vector approach relates to unspecified experiments supposedly "in progress" (but never reported) for testing markers (not genes of interest). In fact, Southern does not disclose ***any*** embodiment involving even one gene of interest. Thus, a skilled artisan in April 1983 would have viewed the challenged claims as a significant and non-obvious advance over Southern.

Objective Indicia: Although not addressed in the Panel's Institution Decision, the record now includes substantial evidence of objective indicia of non-obviousness: (1) the biotechnology industry has widely embraced the validity of the Cabilly '415 patent by taking numerous licenses at rates above industry averages, amounting to licensing revenues well over a billion dollars; (2) using the Cabilly '415 patent invention, Genentech and others have made many commercially successful products; and (3) at a time when leading scientists were

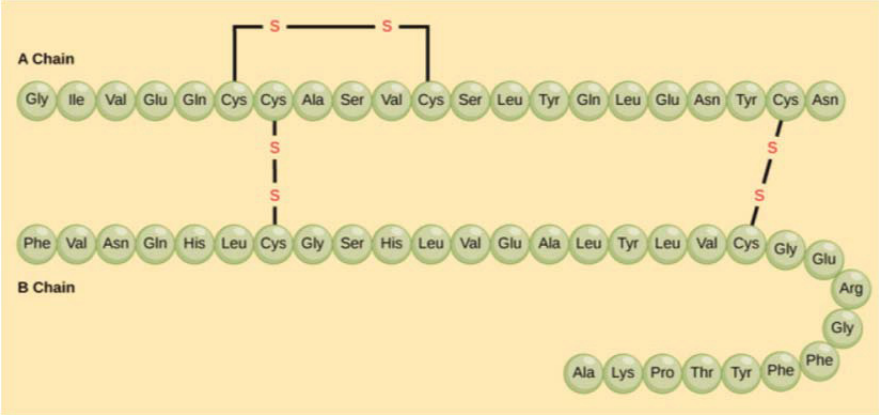
skeptical that the many challenges to producing an antibody from recombinant DNA could be overcome, the Cabilly inventors not only succeeded, but did so in an unexpected way—by co-expressing the heavy and light chains in a single host cell. This objective evidence weighs heavily against a hindsight-based finding of obviousness.

III. TECHNOLOGY BACKGROUND

A. Proteins Vary In Size And Complexity.

There are a vast number of proteins, which vary in size and complexity. Monomeric proteins consist of a single polypeptide chain, while multimeric proteins are more complex structures that consist of multiple polypeptide chains held together by covalent and/or non-covalent interactions. To perform their intended biological function, a protein's polypeptide chains must fold and assemble into a particular three-dimensional shape. (Ex. 2019, Fiddes Decl. ¶¶ 24-34.)

There are a wide variety of multimeric eukaryotic proteins. A simple example 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.)

This proceeding involves antibodies (also called immunoglobulins), which are larger and far more complex than insulin. Antibodies play a critical role in the body's immune system by binding to "antigens"—foreign substances that provoke an immune response. Each antibody consists of at least four chains—typically, two identical heavy chains, and two identical light chains that assemble into a "Y"-shape, as shown in Figure 1 from the Cabilly '415 patent:

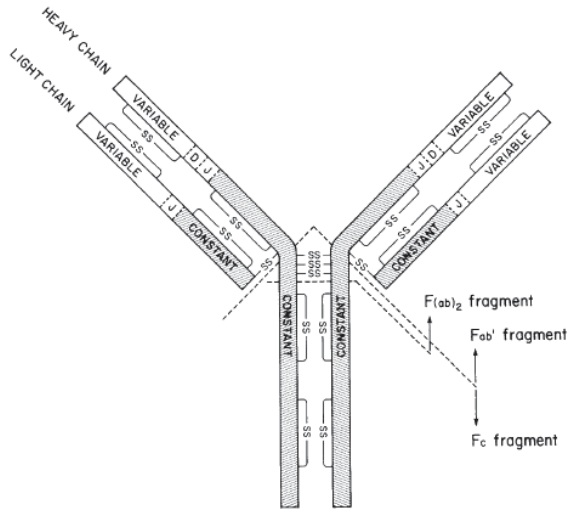
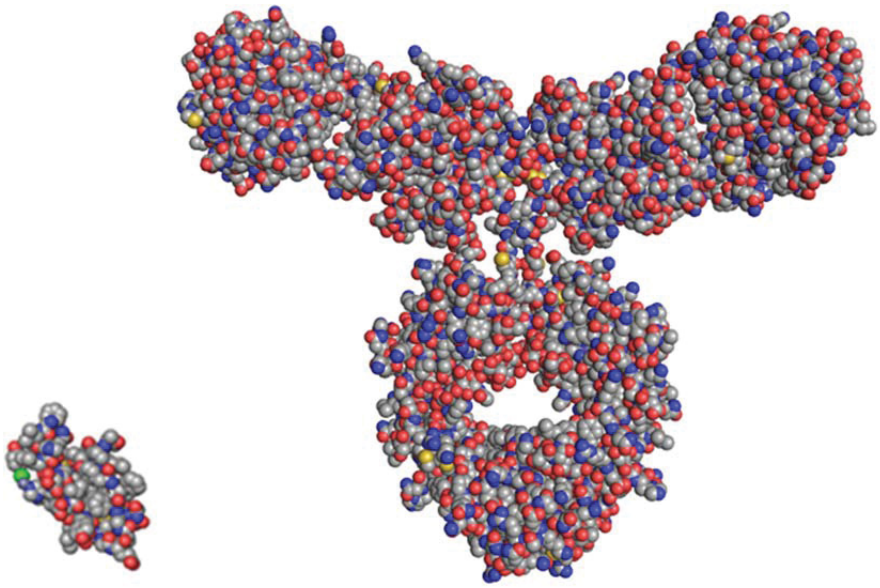


Fig. 1.

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



(Ex. 2019, Fiddes Decl. ¶¶ 43-45.) An antibody of the immunoglobulin G ("IgG") isotype[1] contains more than 1300 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; Ex. 2020, Foote Dep. 105-06.)

[1] There are five classes of antibodies (IgG, IgD, IgE, IgA, and IgM), and each is further divided into multiple different isotypes. (Ex. 2019, Fiddes Decl. ¶ 38.)

B. Prior Art Antibody Production Techniques

1. As of April 1983, polyclonal techniques were well known.

For decades before the Cabilly '415 patent, antibodies could be produced by immunizing an animal (*e.g.*, mouse, rabbit) with an antigen, which generates 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.)

2. As of April 1983, hybridoma techniques were being widely used to make monoclonal antibodies.

Many diagnostic and therapeutic applications require compositions that contain only one type of antibody with uniform binding characteristics, called "monoclonal" antibodies. Such monoclonal antibodies may be produced using "hybridoma" techniques, which involve fusing an antibody-producing B cell with a cancer cell. (Ex. 2019, Fiddes Decl. ¶¶ 48-50.)

Dr. César Milstein developed the first hybridoma technique in 1975 (for which he won the Nobel Prize). By April 1983, hybridomas were being used extensively to produce monoclonal antibodies, and these uses were "expanding very rapidly," with "many commercial companies beginning to market them." (Ex. 1039, Milstein at 407; Ex. 2019, Fiddes Decl. ¶ 50; Ex. 2020, Foote Dep. 37, 48-49 (hybridomas were a "very big" deal in the early 1980s due to "significant achievements"); Ex. 1001, 1:64-2:11.)

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

Recombinant DNA techniques allow for the production and isolation of a protein of interest in a foreign, *i.e.*, "heterologous," host organism, usually a cell or "host cell." Among other things, recombinant techniques allow scientists to introduce a new gene into a host cell that does not naturally contain that gene, and then to use the inserted (or "cloned") gene and cellular machinery of the host to produce a desired protein. (Ex. 2019, Fiddes Decl. ¶¶ 51-56.)

By April 1983, many of the biological mechanisms controlling the expression of foreign DNA and assembly of the resulting proteins were poorly understood. Indeed, Dr. Foote agrees that, as of April 1983, it was "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. 2020, Foote Dep. 135; Ex. 1027, Harris at 129.) Dr. Foote also admits that efforts at that time to use recombinant DNA to produce proteins remained fraught with problems. (Ex. 2020, Foote Dep. 136-46 (discussing problems, including from unknown behavior of "intervening sequences," "post-translational modifications," and "inclusion bodies"); Ex. 1027, Harris at 131, 156, 173 ("Further work is clearly needed towards gaining an understanding of the conformation of eukaryotic proteins during their synthesis by *E. coli*.").)

Because of these obstacles and the nascent state of the field, only a small number of relatively simple proteins had been recombinantly-produced by April 1983—as reflected in an article published that very month, 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.) As the author of that article, Dr. Timothy Harris, has explained, the proteins produced recombinantly at that time were limited to "relatively small polypeptides with simple tertiary structures." (Ex. 2004, Harris Decl. ¶ 16; Ex. 2020, Foote Dep. 76-79; Ex. 2019, Fiddes Decl. ¶ 57.)

The Harris article itself identifies a number of the perceived problems with producing eukaryotic proteins recombinantly in prokaryotic hosts as of April 1983, 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 131-133, 156, 173.) Dr. Foote agrees with Harris's summary of the many challenges that existed with recombinant DNA techniques as of April 1983 (Ex. 2020, Foote Dep. 136-46), which explains why the only reported recombinantly-produced eukaryotic proteins at that time were relatively simple (Ex. 2019, Fiddes Decl. ¶¶ 58-74).

Using recombinant DNA to produce a multimeric protein was especially challenging. By April 1983, only one multimeric eukaryotic protein (insulin) was reported to have been produced recombinantly. That recombinant 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 polypeptide subunits afterward. (Ex. 2019, Fiddes Decl. ¶¶ 81-91; Ex. 2020, Foote Dep. 103, 109-11; Ex. 2005, Harris Decl. II ¶ 14.)

This insulin work reflected a basic reality of recombinant eukaryotic protein techniques back in 1983: all used ***one host cell per polypeptide***. Indeed, Dr. Foote admits that the record is devoid of evidence that ***anyone*** had co-expressed the subunits of ***any multimeric eukaryotic protein*** in the same host cell before the Cabilly inventors. (Ex. 2020, Foote Dep. 114-15; *id.* at 111-12 ("all of the examples described in [Harris] involved production of one polypeptide in one transformed host cell").) That critical admission is reinforced by other evidence that multiple persons of ***extraordinary skill***—all of whom also are unaware of anyone who had independently expressed the multiple subunits of a eukaryotic protein in a single host cell before April 1983. (Ex. 2019, Fiddes Decl. ¶¶ 127-28; Ex. 2005, Harris Decl. II ¶¶ 15-16; Ex. 2003, McKnight Decl. II ¶ 5; Ex. 2006, Rice Decl. ¶ 15.)

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 polypeptides in a single host cell is a far more complicated task in almost every way compared to the prior art multiple host cell approach. 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. (Ex. 2019, Fiddes Decl. ¶¶ 129-37; Ex. 2021, Gentz Decl. ¶¶ 27-30.)

D. As Of April 1983, Highly Acclaimed Scientists Were Uncertain Whether It Was Even Possible To Make Antibodies Using Recombinant DNA Techniques.

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, because antibodies were believed to require certain chaperone proteins to coordinate the timing, 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 one of the most prominent scientists in the antibody field at the time. 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 those lines." He did not offer any specific 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." (Ex. 1039, Milstein at 409-10 (emphases added); Ex. 2020, Foote Dep. 47-60 (agreeing Milstein's comments are "directed towards possible things that might be done in the future, nothing that [Dr. Milstein] or his colleagues, or anyone that he knows, has currently done").)

In fact, Dr. Milstein conceded that his wishful idea might not work: "we have to face the possibility that bacteria might not be able to handle properly the separated heavy and light chains so that correct assembly becomes possible." He said that because the basic science presented "very serious problems," was "not so well established," and was "clouded by uncertainties and multiple possibilities." (Ex. 1039, Milstein at 410.) Dr. Foote admits that he has no basis to dispute this description of the uncertain state of the art. (Ex. 2020, Foote Dep. 55-61; *see also* Ex. 2019, Fiddes Decl. ¶¶ 102-07.)

The years leading up to the Cabilly '415 patent confirmed that those doubts were justified. Leading scientists studying antibody gene regulation and control encountered significant problems and uncertainties with the expression of even a single antibody chain:

- In 1982, Falkner & Zachau could not explain why they had failed to get antibody light chain to express in certain host cells, 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 September 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.)
- In March 1983, Ochi et al. introduced the gene encoding for an 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 "variability in gene expression" observed. (Ex. 1021 at 341-42.)

(*See* Ex. 2019, Fiddes Decl. ¶¶ 108-20.)

This uncertainty and unpredictability continued up to April 1983. Indeed, even Dr. Foote's mentor, Sir Gregory Winter—who Dr. Foote describes as "a person of extraordinary skill in April of 1983" (Ex. 2020, Foote Dep. 164-67)—was "uncertain in the spring of 1983 about how to express recombinant antibodies," and believed that any solution "would be a major undertaking without any certainty of success" (Ex. 2023, Winter Rep. ¶ 61). Dr. Foote admits 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);
- "[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. 178-79);

- "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.)

In fact, Dr. Foote—who was a researcher in Dr. Winter's lab in the 1980s—admits that he had not considered whether it was possible to produce an antibody from recombinant DNA before April 1983. (Ex. 2020, Foote Dep. 184; *see also* Ex. 2019, Fiddes Decl. ¶¶ 121-26.)

Given all of these remaining uncertainties, unknowns, and skepticism as of April 1983, it is not surprising that the record lacks evidence of a single instance in the prior art in which anyone had independently expressed the subunits of ***any*** multimeric eukaryotic protein in a single host cell, or had recombinantly produced an antibody—using any number of host cells.

IV. THE CABILLY '415 PATENT

A. The Invention Of The Cabilly '415 Patent

The state of the art changed dramatically in April 1983 with the claimed invention of the Cabilly '415 patent—which Dr. Foote admits was the first reported instance in which anyone had achieved the successful transcription and

translation of recombinant DNA sequences encoding both the heavy and light chains of an antibody in a single host cell. (Ex. 2020, Foote Dep. 191-92 ("yes, that was the first transcription and translation of light and heavy chain . . . [i]n a single host cell"); Ex. 2024, Winter Dep. 68 (same).)

The team of co-inventors included some of the leading scientists in the field. Dr. Arthur Riggs was a molecular biologist at the City of Hope, who had collaborated with scientists at Genentech to achieve some of the earliest advances in recombinant DNA technology, such as the production of the somatostatin in 1977 (Ex. 2025) and human insulin in 1978 (Ex. 2011). In 1980, Dr. Riggs came to Genentech on sabbatical "to explore the possibility of producing antibodies in bacteria." (Ex. 2026, Riggs Decl. ¶ 3.)

After completing his sabbatical, Dr. Riggs proposed a further collaboration between Genentech and his lab to pursue making antibodies recombinantly. (*Id.*) At the time, Genentech was a small startup company, but it had assembled a talented group of 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 the next several years to develop recombinant techniques for producing antibodies. (Ex. 2026, Riggs Decl. ¶¶ 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.) They hoped that uncertain research would lead to advantages over existing hybridoma techniques by allowing for "manipulation of the genome so as to produce antibodies with more effective design components than those normally elicited in response to antigens from the mature B cell in situ." (Ex. 1001, 2:63-66.)

By early 1983, the Cabilly inventors had successfully co-expressed the heavy and light chains of a monoclonal antibody directed against human carcinoembryonic antigen in a single host cell, which the inventors had folded and assembled into a functional antibody. (Ex. 2032, Cabilly Decl. ¶¶ 4-8.) That groundbreaking achievement was the first proof of concept for their visionary idea that antibodies could be produced recombinantly in a single host cell, and opened the possibility of developing new antibody therapies tailored to specific disease targets. (*See* Ex. 2019, Fiddes Decl. ¶¶ 138-42.)

The challenged claims reflect the Cabilly inventors' novel single host cell approach. Claims 1, 3-4, 11-12, 14, 19, and 33 (Ground 1) recite a process for producing an antibody "in a single host cell" by "independently expressing" its heavy and light chains "as separate molecules." Claims 1, 2, 18, 20, and 33 (Ground 2) cover a process wherein the DNA sequences encoding for the heavy and lights 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. Widespread Industry Recognition Of The Cabilly '415 Invention

The industry has recognized the Cabilly '415 patent as one of the foundational inventions of modern molecular biology; indeed, it has resulted in an entire new industry involving therapeutic antibodies. The world's leading biotechnology companies have recognized this significance by licensing the Cabilly '415 patent over 70 times, at above average rates, generating royalties well over a billion dollars to date. (Ex. 2033, Davis Decl. ¶¶ 37-48.) And the patent has been cited as prior art over 600 times by more than 200 companies during the prosecution of their own patents, further confirming its foundational importance. (Ex. 2136.)

The Cabilly '415 patent also has contributed to the success of multiple Genentech products, as well as products sold by other companies. (Ex. 2033, Davis Decl. ¶¶ 54-68; Ex. 2135, 1/9/2015 Foote Dep. 48-49.)

Although the Cabilly '415 patent has enjoyed broad industry recognition and commercial success, its success was unexpected, even to those of extraordinary skill—who, as discussed above, were skeptical that recombinant antibody production was possible as of April 1983, even without the added challenge of doing so in a single host cell.

V. PROCEDURAL HISTORY

A. The Panel's Institution Decision

The Panel has instituted on two grounds: (1) under Ground 1, claims 1, 3-4, 11-12, 14, 19, and 33 are challenged as obvious over Bujard in combination with Riggs & Itakura, and (2) under Ground 2, Claims 1, 2, 18, 20, and 33 are challenged as obvious over Bujard in combination with Southern. (Paper 15 at 17-22.) The Panel rejected Petitioners' anticipation challenge based upon Bujard, recognizing that "Bujard does not teach—either expressly or inherently—that genes encoding for both the heavy and light chains must be incorporated into the same vector or otherwise expressed within a single host cell." (*Id.* at 15.)

B. Prior Proceedings Involving The Cabilly '415 Patent

The Office has already considered the patentability of the Cabilly '415 patent at length—both through its original examination and reexamination. The Cabilly '415 patent also has been tested multiple times in litigation. Despite these extensive proceedings, Petitioners have not identified a single instance in which anyone before April 1983 successfully produced a functional antibody from recombinant DNA in any manner—much less in a single host cell by co-expressing the heavy and light chains as separate molecules. As noted above, even Dr. Foote agrees the Cabilly inventors were the first to accomplish that significant achievement. (Ex. 2020, Foote Dep. 191-92.)

C. Person Of Ordinary Skill In The Art

For purposes of these proceedings, Patent Owners do not dispute the level of ordinary skill in the art identified by Petitioners. Dr. Foote admits that he has no basis to dispute that Patent Owners' expert Dr. John Fiddes was at least a person of ordinary skill as of April 1983. (Ex. 2020, Foote Dep. 27-28.)

D. Claim Construction

Patent Owners have not identified any claim terms requiring construction.

VI. ARGUMENT

A. The Panel Should Reject Both Grounds Because Bujard Does Not Suggest Co-Expression In A Single Host Cell.

1. Summary of Bujard

The primary reference cited for both instituted grounds is Bujard, a patent filed in May 1981. On its face, Bujard addresses a very different problem than the Cabilly '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 Decl. ¶¶ 157-59.) Promoters are short DNA sequences that provide instructions to the cell's transcription equipment, indicating when to start transcription; they do not encode actual proteins and therefore are not themselves expressed as a final protein product. (Ex. 1002, 1:25-35, 3:11-38; Ex. 2019, Fiddes Decl. ¶ 54.)

Bujard does not purport to disclose any novel methods for expressing proteins. Instead, 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, 3/11/83 Amend. at 6; 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.)

2. Bujard does not disclose any process for producing antibodies.

Bujard does not solve (or even attempt to address) the problem that the Cabilly '415 patent addresses: how to produce antibodies recombinantly. Indeed, Bujard was filed only two months after the publication of Dr. Milstein's comments warning of the "very serious problems" and "uncertainties" surrounding any effort to produce antibodies recombinantly, and noting his belief that those problems and uncertainties might never be overcome. (Ex. 1039 (published 3/27/81); *see supra* p. 16.) Dr. Foote concedes that Bujard did not show how to solve those problems (which Bujard does not even mention). (Ex. 2020, Foote Dep. 73-74.)[2]

[2] 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 that testimony is irrelevant given Dr. Foote's admission that the art

Despite this lack of disclosure, Petitioners urged the Panel to accept 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." (Paper 15 at 19; *see* Paper 1 at 2, 26, 28, 37.) That conclusion is incorrect for several reasons.

First, Bujard does not teach anything specific to antibody production. Bujard mentions antibodies only in a laundry list of "proteins of interest"—a list that Dr. Foote admits 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 not a disclosure for each of those targets. *Amgen, Inc. v. AbbVie Biotechnology Ltd.*, IPR2015-01514, Paper 9, at 18 (Jan. 14, 2016); *Apotex Inc. v. Merck Sharpe & Dohme Corp.*, IPR2015-00419, Paper 14, at 11 (June 25, 2015) (skilled artisan would not have selected specific compound for development disclosed in "laundry list of 600 other specific compounds").

---

still remained "unpredictable" and "uncertain" in April 1983, despite those "developments." (*Id.* at 172-90.)

Second, relying on Dr. Foote, the Panel 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," but not "free heavy chains." (Ex. 1006, Foote Decl. ¶¶ 69-71; Ex. 2020, Foote Dep. 228-31.) But as Dr. Foote now admits, those assumptions were unjustified because 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. 2036-2059; Ex. 2020, Foote Dep. 233-56, 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.) And consistent with that conclusion, the scientific paper corresponding to Bujard contains no list of proteins and no mention of antibodies. (Ex. 2060.) Petitioners can hardly attribute a novel method of producing antibodies to Bujard based upon a lengthy generic list of proteins lifted from other, unrelated patents.

Third, the Panel's conclusion is contrary to how the scientific community has interpreted Bujard. Nobody (outside of litigation) has cited Bujard or its related publication for any teachings about the production of antibodies. Indeed, Dr. Foote had not even heard of Bujard before Petitioners' lawyers provided it to him (Ex. 2020, Foote Dep. 209-10), was not aware that Bujard had expired in 1989 (*id.* at 222), and admits he cannot identify anyone who has used Bujard's vectors to

produce an antibody (in a single host cell or otherwise) (*id.* at 298-99). This too confirms that Petitioners' interpretation of Bujard rests on pure hindsight.

Petitioners' reading of Bujard is also refuted by testimony from Dr. Gentz—who worked in Dr. Bujard's lab at the time and co-authored the paper corresponding to the Bujard patent (Ex. 2060). Dr. Gentz did not contemplate using the vectors described in Bujard 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.) The fact that Petitioners now years later seek to attribute discoveries to Bujard that even those from Dr. Bujard's own lab do not claim to have made only highlights their reliance on hindsight.

In sum, Bujard does not disclose any teaching concerning the recombinant production of antibodies, let alone suggest the Cabilly '415 patent's novel single host cell approach. That alone compels a finding that Petitioners have not carried their burden to demonstrate that the challenged claims are unpatentable under either instituted ground.

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

Even if wrongly read to teach ***something*** about making recombinant antibodies, Bujard still cannot be read to teach the Cabilly '415 patent's central innovation: making both chains of an antibody in a "single host cell." Petitioners' effort to find that central teaching 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 how to use recombinant DNA to express both chains of an antibody in a single host cell, that would have been the headline of their patent.

In its Institution Decision, the Panel faulted Patent Owners for failing to take account of these stray phrases, and ultimately relied upon Dr. Foote's then-untested declaration as to what they meant. (Paper 15 at 18-19.) But the full record before the Panel confirms that Petitioners' reading of Bujard cannot be reconciled with either Bujard or the other record evidence.

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

The Panel interpreted Bujard's use of the term "multimers" "as referring to genes encoding for proteins with more than one subunit." (Paper 15 at 19.) However, the only expert evidence that the Panel considered 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." (Paper 1 at 26-27 & n.12; Ex. 1006, Foote Decl. ¶ 67.) The record refutes that assertion in several respects.

First, Bujard's sole use of the word "multimers" appears in a paragraph describing "***the DNA sequence***" of Bujard's vector (not a protein), and in a sentence explicitly describing "multimers" as types of "genes" ("a plurality of ***genes***, ***including multimers***") (Ex. 1002, 3:39-48 (emphases added).) In this context, "multimers" plainly refers to a ***gene***, and not a multimeric protein. (Ex. 2019, Fiddes Decl. ¶¶ 170-74.) Indeed, the Panel itself found that Bujard refers to "'multimer' ***genes*** in the vector." (Paper 15 at 23.)

Second, Bujard uses the term "multimer" to refer to repeating DNA sequences—in other words, multiple copies of the same gene—which is consistent with its usage in the art. The record now includes multiple references in which persons of skill used the term "multimer" to refer to repeating DNA sequences, and not a multimeric protein—including a 1978 paper from Bujard co-inventors Stanley Cohen and Annie Chang, and a later patent from Bujard. (Exs. 2016-2017; Exs. 2061-2068; Ex. 2020, Foote Dep. 361-65 (admitting later Bujard patent (Ex. 2068) uses "multimerized" to refer to a repeating DNA sequence that does not express any protein); Ex. 2019, Fiddes Decl. ¶¶ 175-80; Ex. 2021, Gentz Decl. ¶¶ 42-47.) These references refute Dr. Foote's assertion that persons of skill only used "multimer" to refer to proteins.

Third, 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, and is a type of publication used to help look up references (not define terms). (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 in forming his opinion (Ex. 2020, Foote Dep. 357), which does not use the term "multimer" at all. (Ex. 2069.)

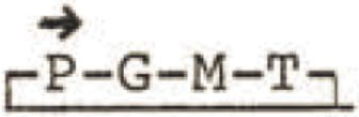
In sum, Petitioners cannot transform Bujard's single use of the word "multimers" into a supposed disclosure of the novel co-expression approach of the Cabilly '415 patent. Consistent with Bujard's stated reliance on "conventional" methods (Ex. 1002, 7:40-41) and focus on stably cloning strong promoters 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).

b) "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 assertions from Petitioners and Dr. Foote, the Panel pointed to generic statements in Bujard 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 "suggesting" co-expressing the polypeptide subunits of a multimeric protein in a single host cell. But the record now shows that a person of ordinary skill would not have understood these general statements as teaching recombinant constructs containing genes encoding for ***different*** eukaryotic proteins of interest.

First, even Petitioners do not contend that Bujard discloses an embodiment in which genes encoding two different eukaryotic polypeptides of interest are located between the promoter and terminator. (Ex. 2020, Foote Dep. 302.) In fact, aside from multimers of DNA for the same gene and bacterial operons,[3] the only time the Bujard inventors disclosed multiple "structural genes" between a promoter (P) and terminator (T) was the following example depicted in the file history involving a single gene of interest (G) and a marker (M):



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

(Ex. 2035, 3/11/83 Amend. at 4; Ex. 2020, Foote Dep. 334-43; Ex. 2019, Fiddes Decl. ¶¶ 185-89.)

That is not an example of co-expressing two genes encoding for different proteins of interest in a single host cell—such as genes encoding the heavy and light chains of an antibody. Rather, as Dr. Foote has explained, a marker simply "permit[s] scientists 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 of co-expressing different proteins of interest is confirmed by Dr. Gentz, who was not thinking then about using Bujard's vectors to co-express multiple different eukaryotic proteins in a single host cell and is not aware of anyone in Dr. Bujard's lab who was. (Ex. 2021, Gentz Decl. ¶¶ 23-26, 31-34, 37-38, 49.)

Second, the Panel misinterpreted Bujard's use of the term "structural genes" by concluding that it refers to multiple different genes "encoding for the subunits of a multimeric protein." (Paper 15 at 18-19.) Bujard expressly defines "structural genes" as including markers: "a structural gene which may be a marker." (Ex.

1002, 2:42; Ex. 2020, Foote Dep. 342.)[4] Accordingly, "structural genes" would have been understood to include a gene for the protein of interest and a marker. (Ex. 2019, Fiddes Decl. ¶ 188.) This definition makes sense given that Bujard's disclosed examples involve: a marker alone (Ex. 1002, 11:31-36); or a "gene of interest" and a marker (Ex. 2035, 3/11/83 Amend. at 4). None of Bujard's examples involves multiple genes encoding different eukaryotic proteins of interest. (Ex. 2020, Foote Dep. 302; Ex. 2019, Fiddes Decl. ¶¶ 185-89.)

Third, even if "one or more structural genes" could be read as including "multiple genes of interest," a skilled artisan in April 1983 would have understood that phrase to refer to multiple copies of the ***same*** gene of interest 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 of interest within a construct was a known technique to increase yield of a desired protein—for example, as described in the Axel patent. (Ex. 1018, 3:62-68 ("By inserting multiple copies of genes coding for desired materials into eucaryotic cells it is possible to produce eucaryotic cells which yield desired materials in high concentrations ….").) Other publications

[4] Bujard uses the word "gene" when discussing a marker, and refers to multiple "genes" when discussing a gene of interest and marker. (Ex. 1002, 3:4-3:38.)

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.)

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

The Panel 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." (Paper 15 at 19.) But 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. ¶¶ 191-96.)

Bujard's reference to multiple stop codons makes sense to offset the effects of its "strong" promoter. A person of ordinary skill 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 the discussion of multiple stop codons in Bujard 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.)

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

Petitioners' misinterpretation of Bujard also rests on the notion that there was a "prevailing mindset" in April 1983 that "more than one mammalian gene could be introduced and expressed in a single host cell." (Paper 1 at 21-25; Ex. 1006, Foote Decl. ¶¶ 52-59.) But the only source for that supposed "mindset" is Dr. Foote—who did not meet his own definition of a person of ordinary skill in the art as of April 1983 (Ex. 2020, Foote Dep. 28-29), and admits that he was unaware of the patents that he cited as establishing the supposed "prevailing mindset" until Petitioners' attorneys gave them to him (and that he did not even read them in their entirety before submitting his declaration) (*id.* at 199-204).

Critically, Dr. Foote now concedes that none of the references cited on this issue describes any actual work co-expressing multiple eukaryotic genes of interest in a single host cell, and that no one had reported doing that in any other reference as of April 1983. (Ex. 2020, Foote Dep. 114-16, 205-08; *see* Ex. 2019, Fiddes

Decl. ¶¶ 96-100.) Petitioners can hardly establish that a "mindset" existed about something that admittedly had never previously happened.

The references that Dr. Foote cites include generic references to "one or more genes." (Ex. 1006, Foote Decl. ¶¶ 53-57.) But the Office previously considered similar generic references to "genes" in Axel (during the Cabilly '415 reexamination), and rightly concluded that they did not teach the Cabilly '415 invention. (Ex. 1025, NIRC at 4.) There is no reason to reach a different result here. (Ex. 2019, Fiddes Decl. ¶¶ 233-38.)[5]

4. Petitioners' remaining arguments about Bujard lack merit.

Petitioners point to two other portions of Bujard, which the Panel did not rely upon in its Decision. Neither supports Petitioners' obviousness theories.

a) "One or more hosts for gene expression"

Petitioners cite Bujard's statement that its strategy "can be used with one or more hosts for gene expression." (Paper 1 at 27 (quoting Ex. 1002, 8:1-3).) The

[5] The Panel stated that Bujard's teachings are "more specific and robust than the Axel reference." (Paper 15 at 16.) But as discussed above (p. 34), Bujard, like Axel, contains no suggestion to co-express multiple eukaryotic proteins of interest in a single host cell, and 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. ¶¶ 233-238.)

Panel cited that passage in finding no anticipation because (1) Bujard contains ***no*** "teaching that all 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 (2) "it is possible that a skilled artisan could have chosen to express the genes for the heavy and light chains in separate host cells, as also suggested by Bujard." (Paper 15 at 16, 20.) That same passage undermines Petitioners' obviousness arguments.

Bujard's generic statement that its strategy "can be used with one or more hosts for gene expression" would have made sense in April 1983 to skilled artisans reading Bujard's diverse list of "proteins of interest." (Ex. 1002, 4:30-6:6.) They would have understood the reference to "one" host as applicable to small, monomeric "proteins of interest" (most of the list), and the reference to "or more hosts" as applicable to larger and more complex multimeric proteins (like insulin, the only such eukaryotic protein produced recombinantly before April 1983). (Ex. 2019, Fiddes Decl. ¶¶ 230-32.) In addition, the full quotation for Bujard refers to "a ***vehicle*** which can be used with one or more hosts for gene expression" (Ex. 1002, 8:1-3 (emphasis added)), which a skilled artisan would have understood is a suggestion to use the disclosed plasmids as a shuttle between 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.)

Nothing in Bujard suggests a new "one-size-fits-all" approach that would permit producing any protein from a single host cell. If Bujard had made such a groundbreaking discovery, it would have required far more explanation at the time than a passing reference to "one or more hosts." Bujard had no such explanation because it did not make any such suggestion. In fact, Dr. Foote testified that he interpreted that "one or more hosts" language as simply referring to using ***different 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. ¶ 64.)

b) "Prepared as a single unit or as individual subunits"

Petitioners argue 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 immunoglobulin," from a single host cell. (Paper 1 at 28; Ex. 1006, Foote Decl. ¶ 73.) That interpretation fails for multiple reasons.

First, the quoted passage says nothing about the number of host cells used to produce the proteins. But if it specified the number of host cells, the most natural reading supports the conventional approach of expressing only one polypeptide of interest per host cell, consistent with its description of producing proteins as a "single unit" (for a monomeric protein) or as "individual subunits" that are "then

joined together" (for a multimeric protein, as in the separate host cell approach for insulin).

Second, the ***only*** approach used at the time to produce a eukaryotic multimeric protein involved expressing the "individual subunits" in separate host cells and then joining them in vitro, as done with insulin. (Ex. 2019, Fiddes Decl. ¶¶ 227-30.) If Bujard had actually disclosed preparing an antibody "as a single unit" in a single host cell, it would have been a critically important discovery; one warranting more explanation than mere reference to "a single unit," and one that would have caused others to cite Bujard for that disclosure (which they did not). (*See* Ex. 2020, Foote Dep. 220, 298-99.)

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

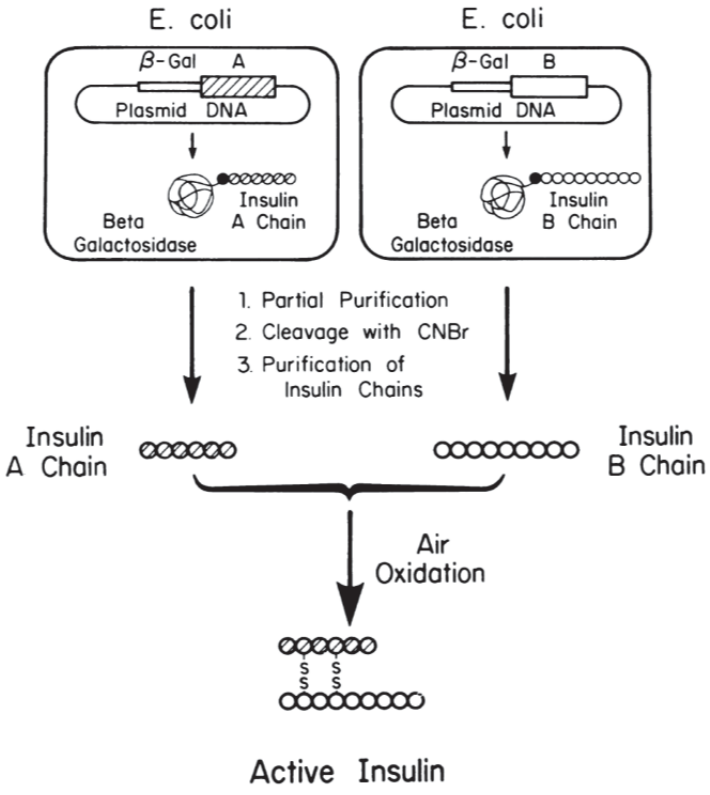
Despite correctly finding that Bujard does not anticipate any challenged claim, the Panel found that Bujard "suggests" the single-host cell invention of the Cabilly '415 patent when combined with "inferences gleaned from" Riggs & Itakura. (Paper 15 at 16.) But a skilled artisan wishing to produce antibodies 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 how to make antibodies). And even if combined, Riggs & Itakura teaches away from the Cabilly invention because it specifies the use of a

separate host cell for each polypeptide subunit of insulin (the only multimeric eukaryotic protein successfully produced recombinantly at that time).

The Panel alternatively found that using a single host cell approach for antibody production would have been obvious to try. (Paper 15 at 20.) But Petitioners do not explain ***why*** a skilled artisan would have chosen an antibody from Bujard's massive list, steered away from established hybridoma techniques, or abandoned the one-polypeptide-per-host-cell approach used for insulin. That obvious to try theory also ignores undisputed evidence showing even those of exceptional skill were uncertain in April 1983 whether antibodies could ever be produced recombinantly—using any method. Plainly, the invention claimed in the Cabilly '415 patent was not "obvious to try." It was an untested approach that had never been attempted, not one of "a ***finite*** number of ***identified***, ***predictable*** solutions." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) (emphasis added).

1. Summary of Riggs & Itakura

Riggs & Itakura does not disclose any new discoveries. Rather, it is a 1979 review article that summarizes prior work using a ***two-host*** 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 "speculation on additional potential applications," including antibody production (Ex. 1003, at 531, 537-38), without providing any details how that might be done (*id.* at 537). Dr. Foote agrees this statement is mere speculation about the future. (Ex. 2020, Foote Dep. 377.)

2. A person of ordinary skill in the art would have had no reason to combine Bujard with Riggs & Itakura.

The combination of references underlying the first instituted ground rests on hindsight. A skilled artisan seeking to produce an antibody in April 1983 would have had no reason to consider Bujard combined with Riggs & Itakura.

As discussed above (pp. 25-29), Bujard does not describe any process specific to antibody production. Neither does Riggs & Itakura, which describes a fusion protein technique that cleaves polypeptide chains containing methionine. (Ex. 1003 at 531.) Even Dr. Foote agrees that particular technique would not work with antibodies. (Ex. 2020, Foote Dep. 373-77 ("[T]here are too many methionines in an antibody.").) As such, a skilled artisan seeking to apply Bujard's techniques to antibodies would have had no reason to look to Riggs & Itakura for guidance. (Ex. 2019, Fiddes Decl. ¶¶ 243-49.)

Real world evidence confirms that conclusion. If the teachings of Bujard and Riggs & Itakura were natural to combine, surely someone over the past three decades would have cited the two references together. Yet, Dr. Foote cannot identify any publication citing both references (nor are Patent Owners aware of any). (Ex. 2020, Foote Dep. 380-81.) This too demonstrates that Petitioners' combination of Bujard with Riggs & Itakura rests purely on hindsight, and not on how a skilled artisan would have viewed those references in April 1983.

3. 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. There is no dispute that Riggs & Itakura discloses only a two host cell

approach for producing insulin—the opposite of what the Cabilly '415 patent claims. (Ex. 2020, Foote Dep. 372-73.) That forecloses Petitioners' obviousness theory underlying Ground 1 because the only path disclosed would have been to follow the same one-chain-per-host-cell approach that Riggs & Itakura reported as successful with insulin. Science typically progresses by building on past successes, and this record establishes that the Cabilly inventors took a dramatic (and thus non-obvious departure) from the approach Riggs & Itakura had taken with insulin. (Ex. 2019, Fiddes Decl. ¶ 250.)

The Panel correctly recognized that "Riggs & Itakura takes a different approach than the 'single host cell' approach required by the claims" (Paper 15 at 19), but dismissed that difference 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, it improperly relies on a selective reading of Riggs & Itakura that ignores portions leading away from the challenged claims. *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."). The only way to know which portions of Riggs & Itakura to rely upon (and which portions to ignore) is with hindsight knowledge of the Cabilly '415 invention.

Second, Riggs & Itakura does teach away from the invention of the Cabilly '415 patent. As Dr. Fiddes confirms, an ordinarily skilled artisan reading Riggs & Itakura in April 1983 would have viewed the two separate host cell "alternative option" as the ***only option*** available for expressing multimeric proteins. (Ex. 2019, Fiddes Decl. ¶¶ 251-56.) Even Dr. Foote admits that he is not aware of any instance in which anyone had co-expressed the polypeptide subunits of any type of multimeric eukaryotic protein before the Cabilly inventors. (Ex. 2020, Foote Dep. 114-15.)

A single host cell approach for antibodies cannot be portrayed as having been "obvious" when nobody had previously utilized that approach for ***any*** type of multimeric eukaryotic protein, and when Riggs & Itakura expressly describes using a one-chain-per-host cell approach. (Ex. 2019, Fiddes Decl. ¶¶ 257-73.) Thus, consistent with the state of the art at the time, Riggs & Itakura teaches away from the one-host approach first disclosed by the Cabilly '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).

4. The Cabilly '415 invention was not obvious to try.

The Panel alternatively suggested that the "single host cell" solution of the Cabilly '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. (Paper 15 at 20 (quoting *KSR*, 550 U.S. at 421).) But to be obvious to try, a solution must be among "a ***finite*** number of ***identified***, ***predictable*** solutions." *KSR*, 550 U.S. at 421 (emphases added). None of the requirements for that limited doctrine is present here.

First, a skilled artisan reading Bujard would not have considered it to present a finite number of options to pursue. Indeed, Dr. Foote admits that Bujard's list of "proteins of interest" is so large that he cannot determine its size, even with a calculator—including "thousands" of histocompatibility proteins and "a million" variations of each listed protein due to differences across species. (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 select antibodies from Bujard's large and undifferentiated list of proteins of interest.

Second, recombinant DNA techniques would not have been a predictable path to success—as Dr. Foote admits. (*See supra* pp. 15-19.) Even Dr. Winter—a person of extraordinary skill in the art—opted to postpone his research given that unpredictable path, and his uncertainty as of April 1983 whether it could work at all. (Ex. 2023, Winter Rep. ¶ 61; Ex. 2020, Foote Dep. 178-79.) By contrast, hybridoma techniques were "expanding very rapidly" at the time (Ex. 1039, Milstein at 407; Ex. 2020, Foote Dep. 48-49), 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 Report ¶ 95; *see id.* ¶¶ 82-95). It would not have been obvious to try recombinant DNA techniques given their unknown and uncertain success, especially when hybridomas provided an established, successful alternative. *See Rolls-Royce, PLC v. United Techs. Corp.*, 603 F.3d 1325, 1339 (Fed. Cir. 2010) (obviousness 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 Cabilly '415

patent was not an "identified" option. It is undisputed that no one prior to the Cabilly 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.) Indeed, Dr. Foote admits that even the references he cites supposedly showing a "prevailing mindset" to co-express different eukaryotic proteins of interest in a single host cell do not disclose any work where a single host cell approach was actually used. (Ex. 2020, Foote Dep. 205-08.) A skilled artisan could not have considered the single host cell approach of the Cabilly '415 patent to have been 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 producing a multimeric eukaryotic protein from recombinant DNA was the ***separate*** host cell approach used for insulin.

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

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

Given the many admitted uncertainties and overall unpredictability of the art—which Petitioners ignore, and the Panel did not address—a person of ordinary skill in April 1983 would have had no reasonable expectation of success in producing an antibody recombinantly in a single host cell. (*See supra* pp. 15-19.) And there are several reasons why a skilled artisan would not have any reasonable expectation of success based upon the combination of Bujard with Riggs & Itakura in particular.

First, Riggs & Itakura discloses a recombinant technique for producing insulin. But there are significant physical differences between insulin and antibodies that would have caused a skilled artisan to have no reasonable expectation of success that those techniques could have been extended to antibodies. 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.) By contrast, antibodies consist of four large subunits—two heavy chains and two light chains, each of which contains hundreds of amino acids—that are joined together in a representative IgG1 class antibody by 12 interchain and 4 intrachain disulfide bonds. (Ex. 2019, Fiddes Decl. ¶¶ 39-45; Ex. 2020, Foote Dep. 86.) 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 chains of insulin were joined by "air oxidation." (Ex. 1003 at 531.) Neither Riggs & Itakura nor Bujard describes how to use that disclosed technique (or any other) to properly fold and achieve assembly of a large, complex protein, such as an antibody.

Third, as of April 1983, it was believed that certain chaperone proteins found in B cells were necessary to facilitate the translation and assembly of functional antibodies. (Ex. 2073, Wabl at 6975-77; Ex. 2019, Fiddes Decl. ¶¶ 95, 136.) Riggs & Itakura and Bujard contain no suggestion that functional antibodies could be assembled without those chaperone proteins. (Ex. 2019, Fiddes Decl. ¶ 263.) Indeed, as discussed above (p. 17), the leading scientists at the time were puzzled by their results trying to produce even a single antibody chain recombinantly.

Fourth, Riggs & Itakura and Bujard also do not discuss the uncertainty of "inclusion bodies"—*i.e.*, "a tangled mass of polypeptide chain" that results when

expressing eukaryotic proteins in a prokaryotic host—that Dr. Foote agreed was "an issue in terms of producing eukaryotic proteins 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").) Given these numerous uncertainties, a person of ordinary skill in the art 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.)

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

As detailed above, Bujard does not disclose the broad teachings that Petitioners attribute it—which is alone sufficient to reject Ground 2. Nor can Petitioners cure that lack of disclosure based on Southern, which does not even mention antibodies, let alone suggest they can be produced by co-expressing the light and heavy antibody chains in a single host cell.

Petitioners point to Southern as supposedly disclosing the use of two vectors encoding for different proteins, but Dr. Foote now admits 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. Nor would it have been obvious

to use two of Southern's vectors with a single host cell method of antibody production. Southern merely refers to unspecified experiments "in progress" and does not provide any guidance on how that might be done.[6]

1. 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 characterizing the *neo* gene as a selectable marker, including one in which a vector included the *neo* and *gpt* gene markers where "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 "genes

[6] Neither Petitioners nor the Panel advanced an obvious to try theory with respect to Ground 2. Nevertheless, any such theory would fail for the same reasons stated for Ground 1. (*See supra* pp. 46-48.)

of interest" are not ***different*** genes that express ***different polypeptides***. In fact, Southern did not include ***any*** non-selectable "genes of interest" in the vectors tested, let alone multiple "genes of interest"—as Dr. Foote admits. (Ex. 1006, Foote Decl. ¶ 90.) Southern's reference to "genes of interest" instead merely refers to the vector's ability to express various ***types*** of genes—not multiple different genes of interest at the same time. (Ex. 2019, Fiddes Decl. ¶¶ 302-04.)

The final sentence in Southern 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.) Southern never identified any results from the tests supposedly "in progress," and Dr. Foote is not aware of any subsequent reporting of any such results. (Ex. 2020, Foote Dep. 386; Ex. 2019, Fiddes Decl. ¶ 305.)

2. A person of ordinary skill in the art 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 person of ordinary skill to 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),[7] while Southern discloses vectors containing selectable

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

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 promoter), a person of ordinary skill starting with Bujard in April 1983 would have had no reason to look to Southern. Indeed, the expression constructs disclosed in Bujard would not be compatible in the host expression systems that Southern addressed, and vice versa. (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 those described in Southern. (Ex. 1002, 7:21-34.)

The real world evidence concerning Bujard and Southern further confirms that a person of ordinary skill would not have considered those references together in April 1983. Although Dr. Foote notes that Southern has been cited more than 3,500 times since its publication, he cannot identify any of those publications that also cites to Bujard. (Ex. 2020, Foote Dep. 388-90.) Moreover, no reference in the record using one of Southern's vectors prior to April 1983 did so in connection with using one Southern vector to produce the light chain of an antibody and another Southern vector to produce the heavy chain of an antibody—in a single host cell or otherwise. (Ex. 2019, Fiddes Decl. ¶¶ 307-14.) Indeed, Dr. Foote

admits that he had never thought about any such possibility as of April 1983, and that he failed in his own effort many years later to use Southern's vectors for antibody production. (Ex. 2020, Foote Dep. 150-61.)

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

Southern does not describe the expression of any particular gene of interest, let alone the heavy and light antibody chains in a single host cell. In fact, Southern does not describe any experiment where even a single gene of interest was expressed in a single host cell, let alone multiple genes of interest. (Ex. 1004 at 336-37; Ex. 2019, Fiddes Decl. ¶ 301.) Southern therefore cannot cure the deficiencies of Bujard because it too fails to describe the independent expression of the heavy and light chains of an antibody in a single host cell.

Petitioners do not appear to disagree. Instead, they only rely on Southern for the limited purpose of arguing that claim limitations requiring separate vectors for expression of heavy and light chains would have been obvious. (Paper 1 at 48-49.) But Southern shows "a significant reduction (10-fold or greater) in the number of stable transformants" when using two vectors versus one in its experiments using marker genes. (Ex. 1004 at 337.) It would have been a non-obvious choice to pursue a two-vector approach that Southern indicates was less efficient than a single vector.

In its Institution Decision, the Panel pointed to three statements in Southern, which it suggested may refer to expressing multiple genes of interest in a single host cell. But the full record confirms that Southern cannot fairly be read that way.

First, the Panel pointed to Southern's statement that "vectors containing these markers provide a way to cotransduce other genes whose presence and/or expression can not be selected." (Paper 15 at 12.) But that is a generic statement regarding the purpose of selectable markers, which are necessary to select host cells that are expressing a recombinant gene of interest.[8] That does not suggest expressing multiple genes of interest in a single host cell; a reading even Petitioners have not advocated. (Paper 1 at 47-50.)

Second, the Panel 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." (Paper 15 at 12, 22.) But as discussed above (pp. 52-53), Southern does not disclose any co-transformation technique; it describes experiments comparing the co-

[8] The quoted passage does not relate to work described in Southern, and instead 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 ….").)

transformation frequencies of the new *neo* vector relative to the *gpt* vector. (Ex. 1004 at 336; Ex. 2019, Fiddes Decl. ¶¶ 284-85.) Dr. Foote agrees that Southern does not disclose co-transformation with two different genes of interest, but dismisses that experimental design as mere "experimental convenience." (Ex. 1006, Foote Decl. ¶ 90.) But that mischaracterizes Southern—which describes a new selectable marker, not any techniques for co-expressing genes of interest. (Ex. 2019, Fiddes Decl. ¶¶ 292-301.)

Third, the Panel 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." (Paper 15 at 12.) But that passage does not suggest co-expressing the polypeptide subunits of a multimeric protein using separate vectors in the same host cell. At most, it states the need for future experimentation. And 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.").) Moreover, Southern does 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. 386; Ex. 2019, Fiddes Decl. ¶¶ 302-06.)

4. 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 Panel 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." (Paper 15 at 22.) But those references confirm that persons of ordinary skill have interpreted Southern just as Patent Owners do here. As the Panel recognized, each of those references (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 Petitioners suggest, there is no reason to believe that a person of ***ordinary*** skill would have.

5. A skilled artisan would have had no reasonable expectation of success in 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. As discussed above, Dr. Foote agrees that no one had reported producing

any type of multimeric eukaryotic protein by recombinantly producing its constituent polypeptides in a single host cell, or had reported recombinantly-producing an antibody as of April 1983—something that even leading scientists in the field still doubted could be done. (*See supra* pp. 15-19.) That alone forecloses any argument that a person of ordinary skill would have reasonably expected success.

Petitioners assert 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 1 at 48-49.) As discussed above (pp. 55-58), however, that argument mischaracterizes Southern—which does not teach that multiple proteins of interest could be expressed from separate vectors in a single host cell.

It also conflicts with Petitioners' cited references. Rice & Baltimore (Ex. 1020), Ochi (Ex. 1021), and Oi (Ex. 1031) all confirm 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* p. 17; Ex. 2019, Fiddes Decl. ¶¶ 307-14.) And leading scientists in the field have confirmed the uncertainty that existed in April 1983

regarding whether an antibody could be produced recombinantly—which Dr. Foote has admitted he has no basis to dispute. (*See supra* pp. 15-19.) Petitioners do not cite any teaching showing that a skilled artisan would have been "confident" that heavy and light chains could be made recombinantly with the same expression machinery, and ignore the contrary teachings undermining that assertion. (Paper 1 at 48-49; Ex. 1006, Foote Decl. ¶ 104; Ex. 2019, Fiddes Decl. ¶¶ 315-17.)

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

Even under Petitioners' flawed theory, the combination of Bujard with Southern would not have rendered obvious claims 1, 2, or 33—which are process claims that require the production of an assembled antibody, as Petitioners admit. (Paper 1 at 7.) Bujard does not teach antibody assembly; indeed, that is why Petitioners cite Riggs & Itakura in Ground 1 (which does not disclose that limitation either). Petitioners do not even argue that Southern discloses antibody assembly. Accordingly, Ground 2 cannot invalidate claims 1, 2, and 33.

D. Objective Indicia Of Non-Obviousness Confirm The Patentability Of The Challenged Claims.

The Federal Circuit has emphasized that evidence concerning the real world impact of a patented invention is a critical safeguard against hindsight reasoning. *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)). And the risk of hindsight reasoning is especially acute here given that the obviousness analysis depends upon the perspective of a skilled artisan from April 1983. Several objective indicia confirm the non-obviousness of the Cabilly '415 patent.

First, the Cabilly '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. (Ex. 2033, Davis Decl. ¶ 37.) The Cabilly '415 patent has been able to command an above average rate, and has generated total royalties well over a billion dollars. (*Id.* ¶¶ 37-48, 50-53.) There is a direct nexus between those licensing revenues and the challenged claims: Genentech received over a billion dollars in royalty payments during the period from March 2006 until April 2011, when the Cabilly '415 patent was the ***only*** issued patent covered by those licenses. (*Id.* ¶¶ 46, 53.) 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 Cabilly '415 patent and Bujard in this regard is striking. Petitioners can hardly contend that one of the most licensed foundational patents in the biotechnology industry is obvious in light of Bujard, which was allowed to expire after only four years for failure to pay the maintenance fees.[9]

Second, some of Genentech's most successful products embody the Cabilly '415 patent, including several "blockbuster" drugs. (Ex. 2033, Davis Decl. ¶¶ 54-63.) Products developed by other companies using the Cabilly '415 invention have also been highly successful. (*Id.* ¶¶ 64-68.) 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.* ¶¶ 55-57.) That process enables the efficient and stable manufacture of those products, which contributes 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 Cabilly '415 patent. (*See supra* pp. 15-19.) The Cabilly inventors' success in the face of

[9] The Cabilly '415 patent has been cited as prior art more than 600 times by over 200 different entities. (Ex. 2136.) These numerous citations are further objective evidence of the patent's place as a core invention in the field.

such skepticism underscores the non-obviousness of their invention. *See Kinetic Concepts*, 688 F.3d at 1367 (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 "the general skepticism" toward the claimed invention).

These objective indicia of non-obviousness reaffirm the conclusions detailed above—that the challenged claims of the Cabilly '415 patent are not obvious in view of either asserted prior art combination (or any others).

VII. CONCLUSION

The Panel should affirm the validity of the challenged claims.

Respectfully submitted,

Date: May 13, 2016

/David L. Cavanaugh/
David L. Cavanaugh
Registration No. 36,476

Robert J. Gunther, Jr.
Admitted *Pro Hac Vice*

Jeffrey P. Kushan
Registration No. 43,401

Counsel for Patent Owners

WILMER CUTLER PICKERING HALE AND DORR LLP
1875 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20006
TEL: 202-663-6000

FAX: 202-663-6363
EMAIL: david.cavanaugh@wilmerhale.com
robert.gunther@wilmerhale.com

SIDLEY AUSTIN LLP
1501 K Street, N.W.
Washington, D.C. 20005
TEL: 202-736-8914
FAX: 202-736-8711
EMAIL: jkushan@sidley.com

CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing, Patent Owners' Response, contains 13,948 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: May 13, 2016

/David L. Cavanaugh/
David L. Cavanaugh
Registration No. 36,476

CERTIFICATE OF SERVICE

I hereby certify that, on May 13, 2016, I caused a true and correct copy of the foregoing materials:

- Patent Owners' Response
- Exhibits 2019-2139
- Updated List of Exhibits
- Patent Owners' Motion to Seal

to be served electronically via FTP, as authorized by Richard McCormick on May 12, 2016, on the following attorneys of record:

Richard McCormick
Lisa M. Ferri
Brian W. Nolan
Mayer Brown LLP
1221 Avenue of the Americas
New York, NY 10020-1001
Rmccormick@mayerbrown.com
LFerri@mayerbrown.com
BNolan@mayerbrown.com
MB-Cabilly-IPR@mayerbrown.com

/Rebecca A. Whitfield/
Rebecca A. Whitfield
Reg. No. 73,756
Wilmer Cutler Pickering Hale and Dorr LLP
60 State Street
Boston, MA 02109

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

Patent Owners' Exhibit Number	Exhibit Name
2013	Kohler, G. and Milstein, C., *Continuous Cultures of Fused Cells Secreting Antibody of Predefined Specificity*, Nature 256:495-497 (Aug. 7, 1975) ("Kohler and Milstein")
2014	90/007,542 Office Action Response filed 2/13/2009
2015	Christie, N.T., *et al.*, *Selective amplification of variants of complex repeating unit in DNA of a crustacean*, Proc. Nat'l Acad. Sci., 77(5):2786-2790 (1980) ("Christie 1980")
2016	Frommer, *et al.*, *Simple repeated sequences in human satellite DNA*, Nuc. Acids Res. 10(2):547-563 (1982) ("Fromer 1982")
2017	Israelewski, N., *Structure and function of an AT-rich, interspersed repetitive sequence from Chironomus thummi: solenoidal DNA, 142 bp palindrome-frame and homologes with the sequence for site-specific recombination of bacterial transposons*, Nuc. Acids Res. 11(20):6985-6996 (1983) ("Israelewski 1983")
2018	Declaration of Robert J. Gunther Jr. in Support of Motion for Admission Pro Hac Vice
2019	Expert Declaration of John Fiddes, Ph.D., *Sanofi-Aventis U.S. LLC v. Genentech, Inc.*, IPR2015-01624 ("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., *Sanofi-Aventis U.S. LLC v. Genentech, Inc.*, IPR2015-01624 ("Gentz Decl.")
2022	Falko G. Falkner & Hans G. Zachau, *Expression of Mouse Immunoglobulin Genes in Monkey Cells*, Nature, 298:286-288 (1982)
2023	Expert Report of Sir Gregory Winter, CBE, FRS, Regarding Invalidity of U.S. Patent Nos. 6,331,415 and 7,923,221, *Eli Lilly and Co. v. Genentech, Inc.*, No. 2:13-cv-07248-MRP-JEMx (C.D. Cal.) (Oct. 13, 2014)
2024	Transcript of Deposition of Sir Gregory Winter, *Eli Lilly and Co. v. Genentech, Inc.*, No. 2:13-cv-07248-MRP-JEMx (C.D. Cal.) (Jan. 19, 2015) ("Winter Dep.")
2025	Keiichi Itakura et al., *Expression of Escherichia coli of a Chemically Synthesized Gene for the Hormone Somatostatin*, Science, New Series, 198:1056-1063 (1977)

Patent Owners' Exhibit Number	**Exhibit Name**
2026	Declaration of Arthur Riggs, *Cabilly v. Boss*, Interference No. 102,572 (Oct. 28, 1991)
2027	Declaration of Ronald Wetzel, *Cabilly v. Boss*, Interference No. 102,572 (Oct. 28, 1991)
2028	Declaration of Jeanne Perry, *Cabilly v. Boss*, Interference No. 102,572 (Oct. 27, 1991)
2029	Declaration of William Holmes, *Cabilly v. Boss*, Interference No. 102,572 (Oct. 28, 1991)
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)
2033	Declaration of Julie L. Davis, *Sanofi-Aventis U.S. LLC v. Genentech, Inc.*, IPR2015-01624 ("Davis Decl.") PROTECTIVE ORDER MATERIAL
2034	United States Patent and Trademark Office, Patent Bibliographic Data (Patent Number: 4,495,280)
2035	File History of U.S. Patent No. 4,495,280
2036	U.S. Patent No. 4,351,760
2037	U.S. Patent No. 4,439,356
2038	U.S. Patent No. 4,287,300
2039	U.S. Patent No. 4,174,384
2040	U.S. Patent No. 4,299,916
2041	U.S. Patent No. 3,996,345
2042	U.S. Patent No. 4,199,559
2043	U.S. Patent No. 4,277,437
2044	U.S. Patent No. 4,391,904
2045	U.S. Patent No. 4,374,925
2046	U.S. Patent No. 4,328,311
2047	U.S. Patent No. 4,281,061
2048	U.S. Patent No. 4,366,241
2049	U.S. Patent No. 4,318,846
2050	U.S. Patent No. 4,233,402
2051	U.S. Patent No. 4,261,968

Patent Owners' Exhibit Number	**Exhibit Name**
2052	U.S. Patent No. 4,275,149
2053	U.S. Patent No. 4,272,506
2054	U.S. Patent No. 4,256,834
2055	U.S. Patent No. 4,220,722
2056	U.S. Patent No. 4,235,869
2057	U.S. Patent No. 4,208,479
2058	U.S. Patent No. 4,220,450
2059	U.S. Patent No. 4,193,983
2060	Reiner Gentz et al., *Cloning and Analysis of Strong Promoters Is Made Possible By the Downstream Placement of a RNA Termination Signal*, Proc. Nat'l Acad. Sci. (USA) 78:4936-4940 (1981)
2061	Christie et al., *Selective Amplification of Variants of a Complex Repeating Unit in DNA of a Crustacean*, Proc. Nat'l Acad. Sci. (USA) 77(5):2786-2790 (1980)
2062	Orr-Weaver et al., *Multiple, Tandem Plasmid Integration in Saccharomyces cerevisiae*, Molecular and Cellular Biology 3:747-49 (1983)
2063	Takahashi et al., *Mechanism of pBR322 Transduction Mediated by Cytosine-Substituting T4 Bacteriophage*, Mol. Gen. Genet. 186:497-500 (1982)
2064	Marrero et al., *SP02 Particles Mediating Transduction of a Plasmid Containing SP02 Cohesive Ends*, J. Bacteriology 147:1-8 (1981)
2065	Bastin, *Molecular Cloning in Plasmid pBR322 Giving Altered Expression of the Tetracycline Resistance Gene*, J. General Microbiology 123:187-191 (1981)
2066	Potter et al., *On the Mechanism of Genetic Recombination: The Maturation of Recombination Intermediates*, Proc. Nat'l Acad. Sci. (USA) 74:4168-4172 (1977)
2067	Annie C. Y. Chang and Stanley N. Cohen, *Construction and Characterization of Amplifiable Multicopy DNA Cloning Vehicles Derived from the P15A Cryptic Miniplasmid*, J. Bacteriology, 134(3): 1141-1156 (1978)
2068	EP 1 532 260 B1

Patent Owners' Exhibit Number	Exhibit Name
2069	National Library of Medicine, Medical Subject Headings – Annotated Alphabetic List (1983)
2070	Shi-Hsiang Shen, *Multiple Joined Genes Prevent Product Degradation in Escherichia coli*, Proc. Nat'l Acad. Sci. (USA) 81:4627-4631 (1984)
2071	Brigitte von Wilcken-Bergmann et al., *A Synthetic Operon Containing 14 Bovine Pancreatic Trypsin Inhibitor Genes Is Expressed in E. coli*, EMBO J. 5(12):3219-3225 (1986)
2072	Expert Report of Carlo M. Croce, M.D., *Bristol-Myers Squibb Co. v. Genentech, Inc.*, No. 2:13-cv-05400 (C.D. Cal Nov. 9, 2014)
2073	Matthias Wabl and Charles Steinberg, *A Theory of Allelic and Isotypic Exclusion for Immunoglobulin Genes*, Proc. Nat'l Acad. Sci. (USA) 79:6976-6978 (1982)
2074	Wolfgang Kammerer et al., *Functional Dissection of Escherichia coli Promoters: Information in the Transcribed Region Is Involved in Late Steps of the Overall Process*, EMBO J. 5(11):2995-3000 (1986)
2075	Ulrich Deuschle et al., *Promoters of Escherichia coli: A Hierarchy of In Vivo Strength Indicates Alternate Structures*, EMBO J. 5(11):2987-94 (1986)
2076	Ulrich Deuschle et al., *lac Repressor Blocks Transcribing RNA Polymerase and Terminates Transcription*, Proc. Natl. Acad. Sci. (USA) 83(12):4134-37 (1986)
2077	Ursula Peschke et al., *Efficient Utilization of Escherichia coli Transcriptional Signals in Bacillus subtilis*, J. Mol. Biol. 186(3):547-55 (1985)
2078	Reiner Gentz and Hermann Bujard, *Promoters Recognized By Escherichia coli RNA Polymerase Selected By Function: Highly Efficient Promoters From Bacteriophage T5*, J. Bacteriol. 164(1):70-77 (1985)
2079	Hermann Bujard et al., *Insertion of Transcriptional Elements Outside the Replication Region Can Interfere with Replication, Maintenance, and Stability of Co1E1-derived Plasmids*, Basic Life Sci. 30:45-52 (1985)

Patent Owners' Exhibit Number	Exhibit Name
2080	Expert Report of John Fiddes, Ph.D., *Bristol-Myers Squibb Co. v. Genentech, Inc. & City of Hope*, 2:13-cv-05400-MRP-JEM (C.D. Cal Nov. 10, 2014)
2081	Bruce Alberts et al., Essential Cell Biology, Chapter 1 (3rd ed. 2009)
2082	G. N. Godson et al., *Nucleotide Sequence of Bacteriophage G4 DNA*, Nature 276:236-47 (1978)
2083	Protein Structure, Boundless, https://www.boundless.com/biology/textbooks/boundless-biology-textbook/biological-macromolecules-3/proteins-56/protein-structure-304-11437 (last visited May 12, 2016)
2084	RCSB Protein Databank, Molecular Machinery: A Tour of the Protein Data Bank, Protein Data Bank, http://cdn.rcsb.org/pdb101/learn/resources/2014-mol-mach-poster.pdf (last visited May 10, 2016)
2085	Vectors: A Survey of Molecular Cloning Vectors and Their Uses, Chapter 1: The Plasmid, pBR322 (Rodriguez, R.L. and Denhardt, D.T. eds., 1988)
2086	Gilbert, *Expression of active polypeptides in E. coli*, Recomb. DNA Tech. Bull. 4(1):4-5 (1981)
2087	Jürg Meyer and Shigeru Iida, *Amplification of Chloramphenicol Resistance Transposons Carried by Phage P1Cm in Escherichia coli*, Molec. Gen. Genet. 176:209-219 (1979)
2088	Linscott's Directory of Immunological and Biological Reagents (2d ed. 1982-83)
2089	Annie Solomon, *Bence Jones Proteins and Light Chains of Immunoglobulins*, Scand. J. Immunol. 5:685-695 (1976)
2090	Deposition Transcript of James H. Sabry, M.D., *Sanofi-Aventis U.S. LLC v. Genentech, Inc.*, No. 2:15-cv-05685 (C.D. Cal) (Mar. 16, 2016) PROTECTIVE ORDER MATERIAL
2091	Deposition Transcript of Timothy R. Schwartz, *Sanofi-Aventis U.S. LLC v. Genentech, Inc.*, No. 15-cv-05685 (C.D. Cal) (Mar. 1, 2016) PROTECTIVE ORDER MATERIAL

Patent Owners' Exhibit Number	Exhibit Name
2092	Karen Talmadge et al., *Eukaryotic Signal Sequence Transports Insulin Antigen in Escherichia coli*, Proc. Nat'l Acad. Sci. (USA) 77:3369-3373 (1980)
2093	Expert Report of Robert C. Rickert, Ph.D., *Bristol-Myers Squibb Co. v. Genentech, Inc.*, No. 2:13-cv-05400-MRP-JEM (C.D. Cal. Oct. 13, 2014) PROTECTIVE ORDER MATERIAL
2094	Sanofi, About Us, http://www.sanofi.us/l/us/en/layout.jsp?scat=EA904297-0D20-4FCA-AAAA-217EC9546F14 (last visited May 6, 2016)
2095	Sanofi, United States Securities and Exchange Commission Form 20-F (for fiscal year ended Dec. 31, 2015), *available at* https://www.sec.gov/Archives/edgar/data/1121404/000119312516493072/d246196d20f.htm
2096	Sanofi, Sanofi Key Facts and Figures, http://en.sanofi.com/our_company/key_facts_and_figures/key_facts_and_figures.aspx (last visited May 13, 2016)
2097	Sanofi, Products, http://www.sanofi.us/l/us/en/layout.jsp?scat=8D4FB6C09DD04C748C949859D8B2687B (last visited May 9, 2016)
2098	Regeneron Pharmaceuticals, Inc., United States Securities and Exchange Commission Form 10-K (for fiscal year ended Dec. 31, 2015), *available at* https://www.sec.gov/Archives/edgar/data/872589/000153217616000045/regn-123115x10k.htm
2099	Regeneron Pharmaceuticals, Inc., Corporate Fact Sheet (Feb. 2016), *available at* http://files.shareholder.com/downloads/REGN/2034285123x0x519844/F1BC3721-4078-424C-94A4-640192399E66/REGN_Final_Corporate_Fact_Sheet_1115.pdf
2100	Certificate of Third Amendment of Amended and Restated Certificate of Incorporation (Apr. 16, 2004), *available at* http://www.sec.gov/Archives/edgar/data/318771/000031877104000010/dna-ex3_5.htm
2101	Genentech, Visit Us, https://www.gene.com/contact-us/visit-us (last visited May 9, 2016)

Patent Owners' Exhibit Number	**Exhibit Name**
2102	Genentech, "Roche Completes Acquisition of Genentech" (Mar. 26, 2009), *available at* http://www.gene.com/media/press-releases/12007/2009-03-26/roche-completes-acquisition-of-genentech
2103	Genentech, About Us, http://www.gene.com/about-us (last visited May 9, 2016)
2104	Genentech, Genentech Fast Facts, http://www.gene.com/media/company-information/fast-facts (last visited May 9, 2016)
2105	Genentech, Company Information, http://www.gene.com/media/company-information (last visited May 9, 2016)
2106	City of Hope and Affiliates, Consolidated Financial Statements (years ended Sept. 30, 2015 and 2014), *available at* http://www.cityofhope.org/doc/1430376104234-wcc_031604.pdf
2107	City of Hope, Locations, http://www.cityofhope.org/about-city-of-hope/locations (last visited May 9, 2016)
2108	City of Hope, Who We Are, http://www.cityofhope.org/about-city-of-hope/who-we-are (last visited May 9, 2016)
2109	City of Hope, About Us, http://www.cityofhope.org/about-city-of-hope (last visited May 9, 2016)
2110	City of Hope, Form 990 (year ending Sept. 30, 2013)
2111	U.S. Patent No. 4,816,567
2112	Order Denying Plaintiffs' Motion for Summary Judgment on Double Patenting, *Eli Lilly and Co. and ImClone Systems LLC v. Genentech, Inc. and City of Hope*, Case No. 2:13-cv-07248-MRP-JEM (C.D. Cal. Mar. 5, 2015)
2113	U.S. Patent No. 7,923,221
2114	Appendix A to Declaration of Julie L. Davis, *Sanofi-Aventis U.S. LLC v. Genentech, Inc.*, IPR2015-01624 PROTECTIVE ORDER MATERIAL
2115	Appendix B to Declaration of Julie L. Davis, *Sanofi-Aventis U.S. LLC v. Genentech, Inc.*, IPR2015-01624 PROTECTIVE ORDER MATERIAL

Patent Owners' Exhibit Number	Exhibit Name
2116	Appendix C to Declaration of Julie L. Davis, *Sanofi-Aventis U.S. LLC v. Genentech, Inc.*, IPR2015-01624 PROTECTIVE ORDER MATERIAL
2117	Appendix D to Declaration of Julie L. Davis, *Sanofi-Aventis U.S. LLC v. Genentech, Inc.*, IPR2015-01624 PROTECTIVE ORDER MATERIAL
2118	Appendix E to Declaration of Julie L. Davis, *Sanofi-Aventis U.S. LLC v. Genentech, Inc.*, IPR2015-01624 PROTECTIVE ORDER MATERIAL
2119	Janssen Biotech, Inc., Our History, https://www.janssenbiotech.com/company/history (last visited May 9, 2016)
2120	Johnson & Johnson, United States Securities and Exchange Commission Form 10-K (for fiscal year ended Jan. 3, 2016), *available at* https://www.sec.gov/Archives/edgar/data/200406/000020040616000071/form10-k20160103.htm
2121	Sanofi, "Sanofi-aventis to Acquire Genzyme for $74.00 in Cash per Share Plus Contingent Value Right" (Feb. 16, 2011), *available at* http://en.sanofi.com/Images/28367_20110216_Deal_Genzyme_en.pdf
2122	Maryann P. Feldman et al., *Lessons from the Commercialization of the Cohen-Boyer Patents: The Stanford University Licensing Program*, In Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices 1797-1807 (A Krattiger et al., eds., 2007)
2123	Ann Gibbons, *Molecular Scissors: RNA Enzymes Go Commercial*, Science, New Series, 251:521 (1991)
2124	Lita Nelsen, *The Rise of Intellectual Property Protection in the American University*, Science, New Series, 279:1460-61 (1998)
2125	Frederic M. Scherer, *The Size Distribution of Profits from Innovation*, The Economics and Econometrics of Innovation, No. 49/50:495-516 (1998)
2126	Emily Waltz, *Industry Waits for Fallout from Cabilly*, Nature Biotechnology, 25(7):699-700 (2007)

Patent Owners' Exhibit Number	Exhibit Name
2127	Letter from Jay P. Siegel, M.D., FACP, to M. David MacFarlane, Ph.D. (Nov. 26, 1997), *available at* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm107740.pdf
2128	Laura Lorenzetti, "7 New Blockbuster Drugs to Watch in 2016," Fortune (Mar. 25, 2016), *available at* http://fortune.com/2016/03/25/new-blockbuster-drugs-to-watch/
2129	Ben Hirschler, "Seven $1 Billion-plus Drugs Seen Reaching Market in 2016", Reuters (Feb. 3, 2016), *available at* http://www.reuters.com/article/us-pharmaceuticals-blockbusters-idUSKCN0VC0CG
2130	Cabilly License Agreements PROTECTIVE ORDER MATERIAL
2131	Cabilly Settlement Agreements PROTECTIVE ORDER MATERIAL
2132	Cabilly Royalty Statements PROTECTIVE ORDER MATERIAL
2133	Karen Talmadge et al., *Bacteria Mature Preproinsulin to Proinsulin*, Proc. Nat'l Acad. Sci. (USA) 77:3988-3992 (1980)
2134	Nancy Lee et al., *Cloning with Tandem Gene Systems for High Level Gene Expression*, Nucleic Acids Res. 12(17):6797-6812 (1984)
2135	Transcript of Deposition of Dr. Jefferson D. Foote, *Bristol-Myers Squibb Co. v. Genentech, Inc. & City of Hope*, 2:13-cv-05400-MRP-JEM (C.D. Cal Jan. 9, 2015)
2136	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 May 12, 2016)
2137	Modified Default Standing Protective Order and Patent Owners' Certification of Agreement to Terms
2138	Modified Default Standing Protective Order (Redline)

Patent Owners' Exhibit Number	**Exhibit Name**
2139	Exhibit 17 to Deposition Timothy R. Schwartz, *Sanofi-Aventis U.S. LLC v. Genentech, Inc.*, No. 2:15-cv-05685 (C.D. Cal) (Mar. 1, 2016), Selected Historical Financial Data PROTECTIVE ORDER MATERIAL