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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

GENENTECH, INC. AND CITY OF HOPE,
Patent Owners

Case IPR2016-01373
Patent 6,331,415

PATENT OWNERS' PRELIMINARY RESPONSE

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes

Legislative Materials

I. INTRODUCTION

This proceeding involves one of the foundational inventions 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 an entirely new field—the therapeutic use of recombinant antibodies—and is protected by U.S. Patent No. 6,331,415 ("the Cabilly '415 patent") (Ex. 1001). Recognizing the importance of that invention, the world's most sophisticated biotechnology companies have paid well over a billion dollars to license it for use in making therapeutic antibodies for a wide range of diseases.

The Cabilly '415 patent has also been one of the most scrutinized patents in history. It has been challenged in two reexaminations, several IPRs, and multiple litigations—collectively involving hundreds of cited references. Yet, these many proceedings have failed to unearth any reference before the patent's April 1983 filing date disclosing the recombinant production of the different polypeptide chains of ***any*** multimeric eukaryotic protein as separate molecules in a single host cell—let alone a protein as large and complex as an antibody. The present petition is no different and should be denied for several reasons.

First, the Board should decline to institute under 35 U.S.C. § 325(d). For each proposed ground, Merck relies on Axel (Ex. 1006)—the only reference underlying Merck's proposed grounds that even mentions antibodies. But the

Patent Office previously confirmed the challenged claims over Axel, and recently instituted IPR2016-00710 based on art (Bujard, Ex. 2030) that the Board has found is "more specific and robust than the Axel reference." Indeed, even Dr. Richard Axel—lead inventor of the Axel patent—has supported the patentability of the Cabilly invention. (Ex. 2032.) Simply put, it would be wasteful to institute based on art found to be weaker than that already under consideration in IPR2016-00710.

Moreover, in its petition, Merck relies on Southern (Ex. 1005) for proposed Grounds 4 and 5, and asserts that Southern is the culmination of the work described in the Mulligan papers (Exs. 1002-03) and Nobel article (Ex. 1004) underlying proposed Grounds 1-3. But the Patent Office considered Southern during reexamination of the Cabilly '415 patent—despite Merck's claims to the contrary. And the Board also is presently considering Southern in IPR2016-00710, and recently declined to institute grounds relying on Southern in IPR2016-00383. Because Merck does not present any new interpretation of Southern here, the Board should decline to institute on any ground for this additional reason.

In addition, on October 11, 2016, Merck filed a separate petition (IPR2017-00047) addressing the same art and grounds presented in IPR2016-00710—including based on Bujard and Southern—and also requested to join IPR2016-00710. If joinder is granted, the earlier final written decision in that consolidated proceeding will estop Merck on any instituted ground in this proceeding under

35 U.S.C. § 315(e)(1). To prevent needless waste of agency and party resources, the petition should be denied for this reason as well.

Second, Merck's petition fails on the merits. Each of Merck's proposed grounds rests on Axel. But Axel is merely directed to generic recombinant DNA techniques, and only mentions the word "antibodies" in passing within a broad list of other proteins—without providing any teaching specific to antibodies. Given that bare disclosure, the Patent Office previously found that Axel failed to teach the Cabilly '415 invention, and Merck presents no reason for a different conclusion here.

The Mulligan papers, Nobel article, and Southern do not cure Axel's deficiencies. None of those references mentions antibodies or discloses co-expressing the different polypeptide chains of any multimeric eukaryotic protein in a single host cell—and certainly not one as large and complex as an antibody. Instead, Merck points to generic terms in the references such as "genes," "genes of interest," "clusters of genes," and "DNA segments." Such generalized terms do not teach the co-expression of antibody heavy and light chains in a single host cell, as required by every challenged claim. Indeed, following Merck's reasoning would lead to the untenable conclusion that the same generalized references teach the recombinant production of ***any protein*** by ***any means***.

Merck also contends that the prior art disclosure of vectors with multiple restriction sites teaches co-expressing the subunits of a multimeric eukaryotic protein in a single host cell. But vectors with multiple restriction sites have existed since at least the mid-1970s, and as of April 1983, scientists were using those different sites for purposes having nothing to do with such co-expression. Merck provides no explanation why a skilled artisan would have viewed the existence of multiple restriction sites as suggesting co-expression, as opposed to their actual established uses at the time.

Merck notes that the vectors described in the Mulligan papers, Nobel article, and Southern were widely known. But that only reinforces the non-obviousness of the challenged claims. Despite widespread knowledge and use of those vectors starting in 1980, Merck has failed to identify a single instance before April 1983 in which anyone (including the prolific authors of those publications and Merck's declarants in this proceeding) used the disclosed vectors—or any other vectors—to co-express different polypeptide units of ***any*** multimeric eukaryotic protein, much less an antibody, in a single host cell.

Merck's decades-later argument that its cited art suggests co-expressing antibody heavy and light chains in a single host cell is pure hindsight. That conclusion is confirmed by indisputable evidence that (i) at the time of the Mulligan papers and Nobel article, world-leading antibody scientists such as

Dr. César Milstein still were uncertain whether antibodies could even be produced recombinantly; and (ii) as of April 1983, extraordinarily-skilled antibody scientists such as Sir Gregory Winter remained skeptical given the perceived "uncertainty" and "unpredictability" of the underlying science.

Merck's hindsight-driven assertions also cannot be squared with other objective evidence—including the Cabilly '415 patent's extraordinary licensing revenues. Merck attempts to minimize the Cabilly inventors' achievement by pointing to supposed evidence of "simultaneous invention." But the subsequent success of a handful of extraordinarily skilled scientists does not demonstrate that the challenged claims would have been obvious to ordinarily skilled persons.

Institution should be denied.

II. PRIOR PROCEEDINGS

Through its original examination, reexamination, and IPRs, the Patent Office has already considered the Cabilly '415 patent at length—including in connection with Axel, which underlies each proposed ground. (Ex. 2005 at 4.) Indeed, Axel was the key reference considered during reexamination. Merck represents that its proposed grounds rely on other art and arguments not previously considered, but that is incorrect.

For example, Merck asserts that the Mulligan papers and Southern "were never cited to or considered by the PTO during prosecution or reexamination of the

'415 patent." (Paper 1 at 27, 32.) But the Patent Office considered Mulligan 1981 and Southern during reexamination, as shown on the face of the reexamination certificate. (Ex. 1001, Reexamination Certificate at 5-6; Ex. 2006 at 10, 12.)[1] Merck also ignores that the Board has considered proposed obviousness grounds relying on Southern and refused to institute. (IPR2016-00383, Paper 16 at 27-29.)

The Patent Office has also already concluded that Axel does not teach co-expressing antibody heavy and light chains in a single host cell. (Ex. 2005 at 4.) That conclusion was supported by declarations from several distinguished experts, who explained that the process described in Axel would have only been suitable to express a single gene together with a selectable marker. (Ex. 2007, Harris Decl. ¶¶ 20-30; Ex. 2008, McKnight Decl. ¶¶ 65-78; Ex. 2009, Botchan Decl. ¶¶ 48-62.) It also was confirmed by Dr. Axel's declaration filed in support of the patentability of the Cabilly invention. (Ex. 2032.)[2]

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[1] Mulligan 1980 was not cited, but its disclosure is similar to Mulligan 1981. Indeed, Merck's petition addresses both references collectively. (Paper 1 at 27-30.)

[2] Dr. Axel supported the patentability of U.S. Patent No. 7,923,211, which is a continuation of the Cabilly '415 patent and also involves co-expressing antibody heavy and light chains in a single host cell.

Merck portrays its obviousness arguments as different from the double-patenting challenge raised during reexamination. (Paper 1 at 23.) But Merck's petition rests on the same interpretation of Axel that the Patent Office previously rejected. (*Compare* Paper 1 at 39 ("[T]he Axel patent teaches the co-transformation and co-expression of genes coding for eukaryotic proteins in a eukaryotic host cell."), *with* Ex. 2005 at 4 ("Axel et al did not teach co-expression of two foreign DNA sequences ....").)

The same is true for Builder (Ex. 1007), which Merck cites in Grounds 3 and 5. The Patent Office considered Builder during reexamination and squarely held it "did not teach assembly of immunoglobulin tetramer" (Ex. 2005 at 6)—the very teaching Merck attributes to Builder here (Paper 1 at 50).

Similarly, Merck relies upon the Mulligan papers for their disclosure of vectors with multiple restriction sites and passing reference to "one or more additional DNA segments." (Paper 1 at 40.) But that generic reference to a plurality of "DNA segments" is no different from other references previously addressed by the Patent Office (*e.g.*, Axel) referring to "genes," "genes of interest," and other similarly generic terms.

The Patent Office did not previously consider the Nobel article. But Merck admits that reference merely describes Dr. Paul Berg's "work developing the pSV2 vector," which is the subject of the previously-considered Mulligan 1981 and

Southern references. (Paper 1 at 31; *id.* at 48-49 ("[T]he Nobel Article is by the same lead author as the Mulligan Papers and describes the same research as the Mulligan Papers, including the development of the pSV2 vector.").)

III. TECHNOLOGY BACKGROUND

A. As Of April 1983, There Were Numerous Perceived Challenges To Producing Eukaryotic Proteins Recombinantly.

Merck characterizes the task of producing a eukaryotic protein from recombinant DNA as known and predictable as of April 1983.[3] But those assertions are contrary to the actual state of the art. For instance, an article that Dr. Timothy Harris published in April 1983—*i.e.*, the same month the Cabilly '415 patent was filed—confirms the technology was still nascent: "[I]t is clear that not all the rules governing the expression of cloned genes have been elaborated and those rules that do exist are still largely empirical." (Ex. 2010 at 129.)

As the Harris article explained, there still were many perceived challenges with producing eukaryotic proteins recombinantly, including (i) the presence of introns (non-coding sequences) in eukaryotic genes; (ii) the different regulatory

[3] Prokaryotes are simple organisms, like bacteria, that lack a membrane-bound nucleus and maintain their genetic material as circular DNA in the cytoplasm. Eukaryotes are higher organisms that contain a nuclear membrane and distinct chromosomes with their genetic material. (Ex. 2014 at 11-12, 15, 20, Table 1-1.)

signals found in eukaryotic DNA; (iii) the different codon usage in eukaryotic genes; and (iv) factors "not well defined" affecting protein folding, solubility, and post-translational modifications. (*Id.* at 131-33, 173.)

Given these obstacles, only a few relatively small and simple eukaryotic proteins had been produced recombinantly by April 1983—as reflected in Harris's Table 2, which provided "an up to date summary of the higher eukaryotic proteins that have been expressed in *E. coli*." (*Id.* at 163-69, Table 2; Ex. 2007, Harris Decl. ¶ 16 (describing listed proteins as "relatively small polypeptides with simple tertiary structures").) In the now-terminated IPR2015-01624 proceeding, both parties' technical experts (Drs. Jefferson Foote and John Fiddes) confirmed that Harris had accurately described the uncertainties facing skilled artisans attempting to produce eukaryotic proteins recombinantly in April 1983. (Ex. 2011, Foote Dep. 76-79, 134-49; Ex. 2012, Fiddes Decl. ¶¶ 57, 72; *see* Ex. 2013, Silverstein Dep. 28 (Axel co-inventor admitting he "had a lot of trouble" with recombinant DNA techniques in early 1980s).)

Despite responding to other arguments that Patent Owners raised in that prior IPR proceeding, Merck says nothing about Harris—including why Dr. Harris would have described these perceived challenges and uncertainties as still existing in April 1983, if Merck's cited art had supposedly resolved them years earlier.

B. Before April 1983, Nobody Had Reported Recombinantly Producing Any Multimeric Eukaryotic Protein By Co-Expression In A Single Host Cell.

Before the Cabilly '415 invention, skilled artisans viewed recombinantly producing a ***multimeric*** eukaryotic protein (*i.e.*, one consisting of multiple polypeptide chains) as especially challenging. At that time, only one multimeric eukaryotic protein (insulin) was reported to have been produced recombinantly. (Ex. 2010 at 163-69, Table 2.) That insulin work involved either producing preproinsulin (a single polypeptide) or expressing the A and B chains in different host cells (*i.e.*, one polypeptide per host cell) and joining them afterward. (Ex. 1067; Ex. 2012, Fiddes Decl. ¶¶ 81-91; Ex. 2011, Foote Dep. 103, 109-11; Ex. 2015, Harris Decl. II ¶ 14.)

This insulin work reflected a basic reality of prior art recombinant eukaryotic protein techniques: all used ***one host cell per polypeptide***. Indeed, despite numerous proceedings challenging the Cabilly '415 patent, the record is devoid of a single example in which anyone produced a multimeric eukaryotic protein recombinantly via co-expression in a single host cell before April 1983. And numerous experts have consistently confirmed that, even today, they are unaware of anyone who did so before the Cabilly inventors. (Ex. 2011, Foote Dep. 114-15; Ex. 2012, Fiddes Decl. ¶¶ 127-28; Ex. 2015, Harris Decl. II ¶¶ 15-16; Ex. 2016, McKnight Decl. II ¶ 5; Ex. 2017, Rice Decl. ¶ 15.)

The present petition is no different. Merck points to pre-April 1983 experiments involving aspartate transcarbamoylase ("ATCase"). (Paper 1 at 19-20.) ATCase, however, is a ***prokaryotic*** protein, and the genes encoding its two polypeptide chains exist within a contiguous DNA sequence (*i.e.*, an operon). (Ex. 1050 at 4023.)[4] Co-expressing two prokaryotic genes that are naturally expressed from a single contiguous piece of DNA under the control of the same promoter provides no teaching or expectation that two different eukaryotic genes from different locations in the genome (*e.g.*, the genes encoding for antibody heavy and light chains) could be recombinantly expressed in a single host cell. (Ex. 2012, Fiddes Decl. ¶ 184.)

Merck asserts that there was a "prevailing mindset" that "recombinant DNA technology could be used to produce multiple proteins of interest in a single host cell" and that "a single host cell was the preferred choice for producing the heavy and light chains of an immunoglobulin." (Paper 1 at 16, 38.) But there can hardly be a "prevailing mindset" or "preferred choice" for an approach that ***no one*** had previously used. It would not have been obvious for a person of ordinary skill in

[4] Operons are naturally-occurring sequences of prokaryotic genes under the control of a single operator/promoter region. They are unrelated to whether multiple eukaryotic genes could be co-expressed. (Ex. 2012, Fiddes Decl. ¶ 184.)

April 1983 to select a single-host-cell-approach to produce an antibody when that technique had ***never*** been used to make ***any*** multimeric eukaryotic protein before.

C. As Of April 1983, A Skilled Artisan Would Have Viewed Producing An Antibody Recombinantly As Particularly Challenging.

A typical antibody consists of four polypeptide chains (two light chains and two heavy chains) joined together in a "Y"-shape:

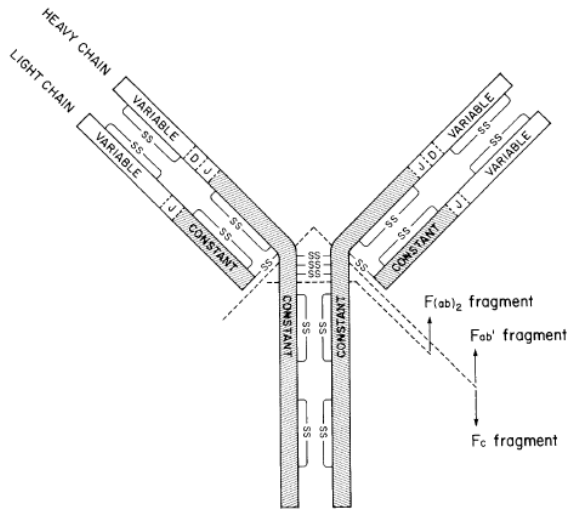
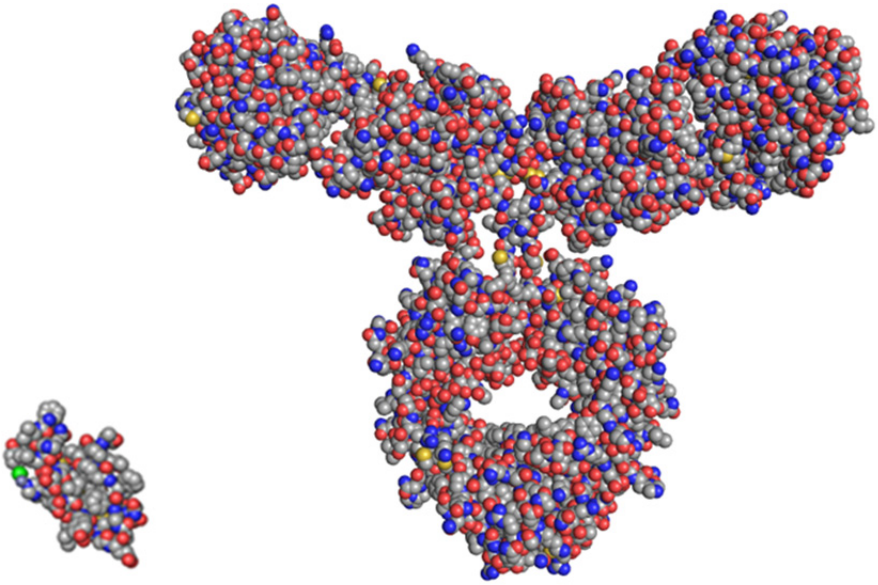


Fig. 1.

(Ex. 1001, Fig. 1.) Antibodies are significantly larger and more complex than other eukaryotic proteins made recombinantly as of April 1983. (Ex. 2011, Foote Dep. 107 (admitting no eukaryotic protein listed in Harris is as large as an assembled antibody).) For example, the immunoglobulin G ("IgG") isotype contains more than 1,300 amino acids, has a molecular weight of about 150,000

Daltons, and is joined together by 12 intra-chain and 4 inter-chain disulfide bonds. (Ex. 2012, Fiddes Decl. ¶¶ 39-45; Ex. 2011, Foote Dep. 86, 105-06.)

By contrast, insulin—the only multimeric eukaryotic protein produced recombinantly before April 1983—contains only 51 amino acids, has a molecular weight of about 5,800 Daltons, and is joined together by 2 inter-chain disulfide bonds and 1 intra-chain disulfide bond. (Ex. 2012, Fiddes Decl. ¶¶ 35-37; Ex. 2011, Foote Dep. 83, 116-18.) The larger size and complexity of an antibody (right) as compared to insulin (left) is illustrated in the molecular models below:



(Ex. 2012, Fiddes Decl. ¶¶ 43-45.)

As of April 1983, a person of ordinary skill would have viewed extending the recombinant techniques enabling insulin production to antibodies as a significant and unpredictable undertaking. Indeed, leading scientists expressed

great uncertainty at the time as to whether antibodies could be recombinantly produced. For example, in March 1981, an article reported then-recent comments from Dr. César Milstein—a future Nobel laureate and leading antibody scientist. Dr. Milstein speculated that antibodies might someday be produced using recombinant DNA techniques. (Ex. 2018 at 409-10.) However, he acknowledged that "there are very serious problems to be solved before such a scheme is carried out" and that "[t]he way to proceed from here is clouded by uncertainties and multiple possibilities." (*Id.* at 410.)

Merck ignores these observations from Dr. Milstein because they cannot be squared with Merck's hindsight-driven and unsupported storyline that Axel, the Mulligan papers, and the Nobel article all had already solved the same "very serious problems" and "uncertainties" that Dr. Milstein identified as still existing at the time.

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

- In 1982, Falkner & Zachau could not explain why they had failed to express antibody light chain, speculating that "something may be missing

from our systems" or "some as yet undefined factors provided in tissue-specific differentiation events may have a role." (Ex. 2019 at 288.)

- In December 1982, Dr. David Baltimore, a Nobel laureate, observed that "relatively little is known about the molecular mechanisms that control [antibody] gene expression." (Ex. 1017 at 7862.)
- In February 1983, Dr. Berg (co-author of the Mulligan papers and sole author of the Nobel article) and his co-authors published the Oi paper, in which these highly accomplished researchers could not explain why two cell lines failed to produce any detectable light chain from recombinant DNA. (Ex. 1045 at 827.)
- In March 1983, Ochi reported introducing the gene encoding for antibody light chain into cells already producing heavy chains, and could not explain why nearly all cell lines had no detectable antibody production or the observed "variability in gene expression." (Ex. 1018 at 341-42.)

This uncertainty and unpredictability continued through April 1983. Indeed, even Sir Gregory Winter—a world-leading antibody scientist—confirmed that he was "uncertain in the spring of 1983 about how to express recombinant antibodies," and that he still believed at the time that any solution "would be a major undertaking without any certainty of success." (Ex. 2020, Winter Rep. ¶ 61.) As Dr. Winter further explained:

- "[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." (*Id.* ¶ 31.)[5]
- "[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." (*Id.* ¶¶ 56-57.)
- "[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." (*Id.* ¶ 61.)
- "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. 2021, Winter Dep. 117-18.)

In IPR2015-01624, Dr. Foote—expert of the party challenging the Cabilly '415 patent, who worked in Dr. Winter's laboratory in the 1980s—agreed that

[5] All emphases are added unless otherwise indicated.

Dr. Winter had accurately described the uncertainty surrounding the possibility of recombinant antibody production as of April 1983. (Ex. 2011, Foote Dep. 173-80, 189-90.) Merck ignores these key admissions as well because they confirm that, as of April 1983, even persons of ***extraordinary skill*** continued to view the possibility of recombinant antibody production as an uncertain and unpredictable endeavor.

IV. THE CABILLY '415 PATENT

A. The Invention

The state of the art changed dramatically in April 1983 with the invention of the Cabilly '415 patent, which was the culmination of an effort by several 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 early advances in recombinant DNA technology, such as the production of somatostatin in 1977 (Ex. 1068) and human insulin in 1978 (Ex. 1067). In 1980, Dr. Riggs came to Genentech on sabbatical "to explore the possibility of producing antibodies in bacteria." (Ex. 2022, Riggs Decl. ¶ 3.) After his sabbatical, Dr. Riggs proposed a further collaboration with Genentech to pursue making antibodies recombinantly. (*Id.*)

At the time, Genentech was a small startup company with talented scientists, including molecular biologist Dr. Herbert Heyneker and protein chemist Dr. Ronald Wetzel. Together with Dr. Shmuel Cabilly, a post-doctoral fellow in

Dr. Riggs's lab, they worked over several years to develop recombinant techniques for producing antibodies. (*Id.* ¶¶ 4-6; Ex. 2023, Wetzel Decl. ¶¶ 4-11; Ex. 2024, Perry Decl. ¶¶ 2-14; Ex. 2025, Holmes Decl. ¶¶ 3-20; Ex. 2026, Rey Decl. ¶¶ 2-7; Ex. 2027, Mumford Decl. ¶¶ 2-13; Ex. 2028, Cabilly Decl. ¶¶ 3-9.)

By early 1983, the Cabilly inventors had successfully co-expressed the heavy and light chains of a monoclonal antibody in a single host cell, which they had folded and assembled into a functional antibody. (Ex. 2028, Cabilly Decl. ¶¶ 4-8.) That groundbreaking achievement was the first proof that antibodies could be produced recombinantly in a single host cell.

The challenged claims reflect the Cabilly inventors' novel single host cell approach. Claims 1, 3-4, 11-12, 14-17, 19, and 33 (Grounds 1-3) 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, 11-12, 14, 18-20, and 33 (Grounds 4 and 5) cover a process wherein the DNA encoding for heavy and light chains "are present in different vectors" (claim 2) or "[a] transformed host cell comprising at least two vectors" with at least one vector separately containing the DNA encoding for heavy and light chains (claim 18).

B. Industry Recognition

The industry has recognized the Cabilly '415 patent as a foundational invention; indeed, it has resulted in an entire new industry involving therapeutic

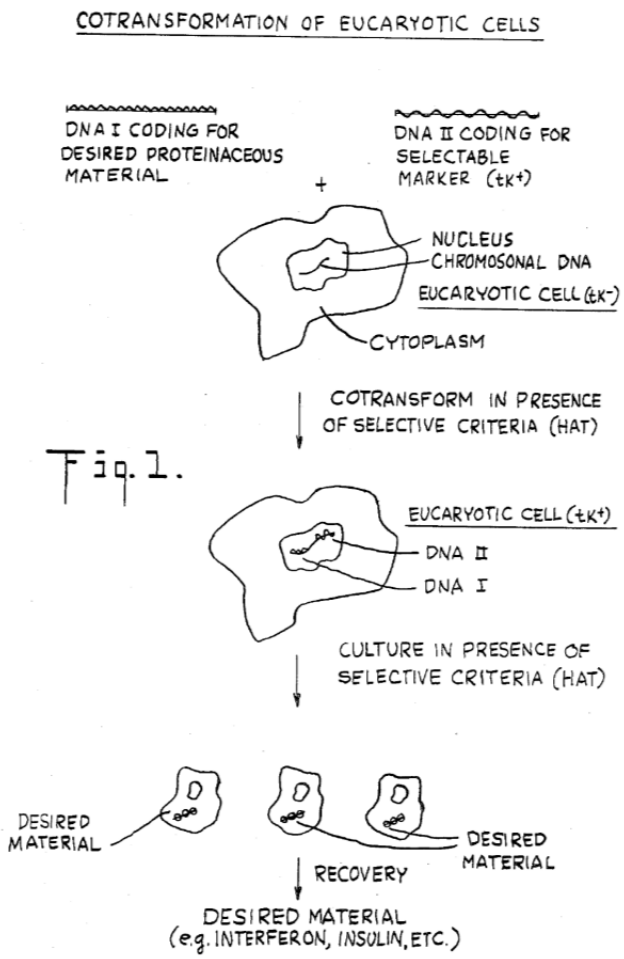
antibodies. More than seventy of the world's leading biotechnology companies have recognized this significance by licensing the Cabilly '415 patent, generating royalties well over a billion dollars. The patent has commanded these significant royalties because it provides a stable platform for manufacturing numerous highly successful drugs sold by Genentech and others.

Although the Cabilly '415 patent has enjoyed broad industry recognition and commercial success, its success was unexpected, even to extraordinarily-skilled persons—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. MERCK'S ASSERTED REFERENCES

A. Axel

Axel was filed in 1980 by scientists at Columbia University. The patent describes expressing a gene "coding for desired proteinaceous material" ("DNA I") with a selectable marker ("DNA II"):



(Ex. 1006, Fig. 1.) Axel identifies "antibodies" among a list of exemplary "proteinaceous materials" (*e.g.*, *id.*, 3:31-36), but includes no description or working examples disclosing how to make an antibody. In fact, Dr. Saul Silverstein—an Axel co-inventor—agrees it would have required "a great deal of experimentation" at the time to produce an antibody based upon Axel's disclosure. (Ex. 2013, Silverstein Dep. 78-79.) Dr. Axel himself also submitted a declaration in support of the patentability of the Cabilly invention. (Ex. 2032.) Merck has

failed to explain why Dr. Axel would have provided that opinion if his own work rendered the Cabilly invention obvious.

A 2005 reexamination request for the Cabilly '415 patent alleged that Axel discloses co-expressing antibody heavy and light chains in a single host cell—based upon Axel's bare reference to "antibodies" and generic statements referring to expressing "genes coding for desired proteinaceous materials." (Ex. 1006, abstract, 3:21-45; Ex. 2029 at 6 n.1.) In confirming the patentability of the challenged claims over Axel, the Patent Office concluded that "Axel et al did not teach a single host cell transformed with immunoglobulin heavy chain and immunoglobulin light chain independently" and "did not teach co-expression of two foreign DNA sequences." (Ex. 2005 at 4.)

B. Mulligan Papers

The Mulligan papers are two articles published in 1980 and 1981, which described a new selectable marker (*gpt*) for use in a mammalian expression vector. (*E.g.*, Ex. 1002 at 1423-24; Ex. 1003 at 2072.) Neither article mentions antibodies or describes co-expressing multiple genes encoding different polypeptide chains of a multimeric protein.

Before the Mulligan papers, techniques for recombinant DNA expression in mammalian hosts—such as those disclosed in Axel—involved specialized mutant cells. (Ex. 1002 at 1423; Ex. 1003 at 2076; Paper 1 at 27-28.) The Mulligan

authors sought to overcome that "shortcoming" by developing "vectors that could be introduced and maintained in a variety of cells." (Ex. 1002 at 1423.) The result of those efforts was the pSV2 vector, which contained *gpt* as a selectable marker for use in normal mammalian cell lines. (*Id.* at 1427; Ex. 1003 at 2076.)

The Mulligan papers indicate that the pSV2 vector has multiple restriction sites. Merck argues that a "POSA would understand that the reference to multiple restriction sites means that the DNA encoding the heavy and light chains (separate genes located on separate chromosomes) would be inserted at different sites to result in the 'independent expression' of the heavy and light chains produced 'as separate molecules' in a single host cell." (Paper 1 at 29-30.) But the record does not support that assertion.

For example, the Mulligan papers explain that the multiple restriction sites enabled better "efficiency" for expressing ***a single gene***—by allowing its insertion at different vector locations. (Ex. 1002 at 1427.) The Mulligan papers further state that multiple restriction sites allowed compatibility with a variety of ***different gene types***—with no suggestion to include multiple different genes in the same host cell. (Ex. 1003 at 2076 ("DNA segments containing the human globin (31), chick ovalbumin (32), or hormone gene (33) families can be inserted into the vectors and then into appropriate cells by using the *Ecogpt* function for selection.").)

Publications before April 1983 confirm that scientists at the time did not interpret the Mulligan papers' reference to multiple restriction sites as suggesting the Cabilly co-expression approach. For example, the February 1983 Oi article—which, like the Mulligan papers, came from Dr. Berg's laboratory—used the pSV2 vector to express only an antibody light chain, without mentioning any possibility of also co-expressing the heavy chain. (Ex. 1045 at 825.)

Similarly, in December 1982, Dr. Douglas Rice and Nobel laureate Dr. David Baltimore used the pSV2 vector to express antibody light chain, but not heavy chain (again without mentioning co-expression). (Ex. 1017 at 7862.) In fact, that work used ***two*** restriction sites (EcoRI and BamHI) to insert a ***single non-selectable gene*** into the vector. (*Id.*) That these highly skilled scientists used multiple restriction sites to insert only one non-selectable gene confirms that multiple restriction sites would not have inherently led a person of ordinary skill to co-express multiple non-selectable genes in a single host cell.

Indeed, despite touting wide citation to the Mulligan papers (Paper 1 at 30), Merck has not identified an example prior to April 1983 in which anyone used the pSV2 vector to co-express different polypeptides of ***any*** multimeric protein, much less an antibody. Merck's assertion decades later that ordinarily-skilled artisans would have interpreted the Mulligan papers as suggesting co-expression rests on hindsight.

C. Nobel Article

The Nobel article is a 1981 publication that reprinted Dr. Berg's Nobel Prize lecture. It did not report the results of any new research; rather, the article merely summarized prior work (including the subject matter of the Mulligan papers), and speculated about potential future applications for recombinant DNA, such as "[g]ene replacement as a therapeutic approach." (Ex. 1004 at 300-02.)

Like the Mulligan papers, the Nobel article does not mention antibodies or describe co-expressing genes encoding the different polypeptide chains of a multimeric protein in a single host cell. In fact, the only genes that the Nobel article discusses in connection with the pSV2 vector are selectable markers derived from "bacteria, their viruses, and simple eukaryotes." (*Id.* at 302.)

Merck focuses on the Nobel article's statement that "[a]dditional DNA segments can also be inserted into the vector DNA's at any of several unique restriction sites; consequently, a single DNA molecule can transduce several genes of interest simultaneously." (Ex. 1004 at 300; Paper 1 at 17-19.) But Merck cites no contemporaneous evidence that skilled artisans would have understood that generic reference to "several genes of interest" as suggesting co-expression of different polypeptide chains of a multimeric eukaryotic protein in the same vector.

Instead, the record confirms that a person of ordinary skill could have interpreted that passage as referring to co-expressing a marker gene with another

gene in the vector, consistent with how both contemporaneous references (including the Bujard patent at issue in IPR2016-00710, U.S. Patent No. 4,495,280) and later references equated a marker gene with a "gene of interest." (Ex. 2030, 2:33-47 ("[A] structural gene … may be marker."); Ex. 2031 at 49 ("The marker gene itself may be the gene of interest ….").) Alternatively, a person of ordinary skill could have interpreted that passage as referring to co-expressing multiple copies of the same gene in a vector, consistent with Axel's description of "cotransformation" involving multiple copies of the same genes to boost expression levels. (Ex. 1006, 3:43-67.)

Merck's argument that this isolated passage in the Nobel article necessarily suggests co-expressing the constituent polypeptides of multimeric proteins in a single vector also cannot be reconciled with the complete absence of (i) any contemporaneous document in which ***anyone*** treated the Nobel article as making that disclosure; or (ii) any document in which ***anyone*** prior to April 1983 used the pSV2 vector to co-express multiple polypeptide chains of a multimeric protein in a single host cell. Indeed, as discussed above, when Dr. Berg himself used the pSV2 vector prior to April 1983, he only included ***one*** non-selectable gene (encoding for a light chain) in the vector. (Ex. 1045.)

D. Southern

Southern is a 1982 publication describing further research from Dr. Berg's laboratory. Like the Mulligan papers and Nobel article, Southern does not mention antibodies or disclose any experiment co-expressing multiple eukaryotic genes in a single host cell. Instead, Southern's focus is a selectable marker (*neo*) for use in the pSV2 vector. (Ex. 1005 at 327-28.) Southern describes several experiments characterizing *neo*, including one in which a vector included *neo* and *gpt* 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 using a mixture of separate vectors containing *neo* or *gpt*. (*Id*.; Ex. 2012, Fiddes Decl. ¶¶ 280-85.)

Southern's last paragraph 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. 1005 at 339.) But "genes of interest" in that context refers to the fact that Southern discloses a general purpose vector for use with various different types of genes—not co-expressing multiple non-selectable genes in a single host cell. (*Id.* at 338 ("[V]ectors containing these markers provide a way to cotransduce other genes whose presence and/or expression can not be selected."); Ex. 2012, Fiddes Decl. ¶¶ 302-04.)

Southern's final sentence states that "[t]he schemes used to select for the expression of gpt and neo are complementary and experiments that exploit the possibilities of a double and dominant selection are now in progress." (Ex. 1005 at 339.) But nothing about the phrase "double and dominant selection" suggests co-expressing different eukaryotic genes encoding for the polypeptide chains of a multimeric protein. Rather, Southern itself explicitly states that the experiments conducted for "***[d]ouble selection***" only involved the *neo* and *gpt* ***selectable markers*** (Ex. 1005 at 337 (Table 3)), and never identifies results from any other tests supposedly "in progress."

Even though Southern was published in February 1982 and was widely known, Merck cites no publication prior to April 1983 in which the pSV2-neo vector was used to co-express multiple eukaryotic genes. Rather, just like the pSV2-gpt vector disclosed in the Mulligan papers, Southern's pSV2-neo vector was used only to express antibody light chain, but not heavy chain, prior to April 1983. (Ex. 1018 at 341.)

E. Builder

Builder is directed to recovery of proteins expressed in bacterial host cells, "which are at least partially deposited inside the cells as refractile bodies i.e. clumps of insoluble protein." (Ex. 1007, 2:3-9.) It describes only generalized

strategies and does not provide specific guidance concerning antibody assembly or even mention antibodies.

VI. PERSON OF ORDINARY SKILL

The Board should apply the definition of a person of ordinary skill used in prior proceedings. (IPR2015-01624, Paper 15 at 20 n.8.) Merck's proposal is similar, but also includes persons with an M.D. instead of a Ph.D. (Paper 1 at 11), which is overbroad and inconsistent with the patent's laboratory research focus. Nevertheless, for the reasons below, the Cabilly '415 patent would not have been obvious under either Merck's or Patent Owners' proposed definitions.

VII. CLAIM CONSTRUCTION

No claim terms require construction.

VIII. ARGUMENT

A. The Board Should Deny Institution Under 35 U.S.C. § 325(d).

Under 35 U.S.C. § 325(d), the Board may deny institution if "another proceeding or matter involving the patent is before the Office" or "the same or substantially the same prior art or arguments previously were presented to the Office." That is the case here.

The Board has already instituted IPR2016-00710, which challenges claims of the Cabilly '415 patent based on Bujard and Southern. Merck has now filed a copycat petition presenting the identical art, grounds, and arguments, along with a

motion seeking to join IPR2016-00710. (IPR2017-00047, Papers 2-3.) A final written decision in IPR2016-00710 is expected by September 2017, which would estop Merck's arguments in the present petition, if Merck is joined. 35 U.S.C. § 315(e)(1). It would make no sense to institute grounds in the present petition that will be estopped by a final written decision in other proceedings. For this reason alone, institution of all grounds should be denied under § 325(d). *See Toyota Motor Corp. v. Cellport Sys., Inc.*, IPR2015-01422, Paper 8 at 20-21 (P.T.A.B. Dec. 16, 2015) (denying institution due to mere possibility of estoppel from another earlier-filed proceeding because "instituting a second *inter partes* review may result in a significant waste of time and resources for the parties and for [the] Board"); *PNC Bank, N.A. v. Secure Axcess, LLC*, CBM2015-00039, Paper 9 at 20 (P.T.A.B. July 10, 2015) (same).

Regardless of how the Board treats Merck's copycat petition and joinder request, the substantive arguments in Merck's present petition further confirm that denial is warranted under § 325(d). The Patent Office has already considered hundreds of references asserted against the Cabilly '415 patent, and Merck's present petition just rehashes the same art and arguments that the Patent Office has already considered and/or is presently considering in other proceedings.

First, for each proposed ground, Merck relies on a single reference for supposed teachings specific to antibodies: Axel. But the Patent Office considered

Axel extensively during reexamination, and affirmed the Cabilly '415 claims over that reference—finding "Axel et al did not teach a single host cell transformed with immunoglobulin heavy chain and immunoglobulin light chain independently" or "co-expression of two foreign DNA sequences." (Ex. 2005 at 4.)

Moreover, the Board has already concluded that Axel is a weaker reference than Bujard, which is the subject of already-instituted IPR2016-00710 that Merck is seeking to join. (IPR2015-01624, Paper 15 at 16 ("We find Bujard's teachings to be more specific and robust than the Axel reference that was previously considered by the PTO.").)[6] For example, the Board determined that Bujard discloses: (i) "the plasmid vector may have the strong promoter and terminator separated by 'more than one gene, that is, a plurality of genes, including multimers and operons'"; and (ii) "the desirability of inserting 'translational stop codons … ' in one or more reading frames of the vector, which would allow for the multiple structural genes to be translated into separate polypeptides." (*Id.* at 10, 19.) Although Patent Owners respectfully disagree with the Board's preliminary conclusions concerning Bujard, Merck has not explained how Axel discloses anything more or different than Bujard.

[6] IPR2015-01624 was instituted on the same grounds involving Bujard that are pending in IPR2016-00710. IPR2015-01624 was terminated by settlement.

It would be wasteful to institute Merck's proposed grounds based upon the same Axel patent previously considered during reexamination, and that the Board has determined is less "specific and robust" than the Bujard patent currently at issue in IPR2016-00710. In addition, the fact that Merck has filed its own petition (IPR2017-00047) relying on Bujard provides a further basis for denying institution of all grounds under § 325(d). Even putting aside the statutory estoppel that would arise here from an earlier final written decision on Merck's copycat petition, institution here would unfairly permit Merck multiple opportunities to challenge the Cabilly '415 patent, contrary to the purpose of the AIA. H.R. Rep. No. 112-98, pt. 1, at 48 (2011), *reprinted in* 2011 U.S.C.C.A.N. 67, 78 (post-grant proceedings "are not to be used as tools for harassment … through repeated litigation and administrative attacks on the validity of a patent").

Second, for Grounds 4 and 5, Merck relies on Southern, which it represents was "neither cited to nor considered by the PTO during prosecution or reexamination of the '415 patent." (Paper 1 at 32.) But the reexamination certificate and file history confirm that Southern was, in fact, considered. (Ex. 1001, Reexamination Certificate at 6; Ex. 2006 at 12.)

The Board also recently declined to institute another petition that relied upon Southern in combination with another reference (Salser) that, like Axel, merely discloses generic recombinant DNA techniques. (IPR2016-00383, Paper 16 at 27-

29.) Merck argues it cured the deficiencies in the grounds raised in that petition. (Paper 1 at 59-60.) But Merck relies on Southern for the same supposed disclosure of co-expression with two vectors that was insufficient to demonstrate a reasonable likelihood of success in IPR2016-00383. (*Compare* Paper 1 at 52, *with* IPR2016-00383, Paper 16 at 28-29.) There is no reason for a different conclusion here.

The Board also is currently considering Southern in the recently-instituted IPR2016-00710, which involves a ground combining Southern with Bujard. And Merck has asserted the same ground and arguments based on Southern in its copycat petition (IPR2017-00047). The petitions in IPR2016-00710 and IPR2017-00047 rely upon Southern for precisely the same supposed teaching for which Merck relies upon Southern here. (*Compare* Paper 1 at 52, *with* IPR2016-00710, Paper 2 at 32-34, and IPR2017-00047, Paper 2 at 39-41.) It would make little sense to address Southern here too—particularly in combination with a reference (Axel) found less "specific and robust" than Bujard. (IPR2015-01624, Paper 15 at 16.) Grounds 4 and 5 should be denied for these additional reasons.

Finally, for Grounds 1-3, Merck represents that the Patent Office has never considered the Mulligan papers. (Paper 1 at 27.) Again, Merck is wrong. The reexamination certificate and file history identify the Mulligan 1981 paper as

considered. (Ex. 1001, Reexamination Certificate at 5; Ex. 2006 at 10.)[7] Further, Merck describes Southern as an "extension" of the work described in the Mulligan papers and the Nobel article. (Paper 1 at 32 ("The Southern paper reflects Prof. Berg's extension of the pSV2 platform described in the Mulligan Papers.").) Thus, Grounds 1-3 alternatively should be denied because they too rest on previously-considered references that are largely cumulative of other art presently under consideration.

B. Merck Has Not Shown A Reasonable Likelihood Of Success On Any Proposed Ground.

Merck does not assert any anticipation-based theory, and instead relies entirely on obviousness allegations involving a handful of references (with all but one ground involving ***three- or four-way*** combinations). Even if combined, those multiple references do not render any challenged claim obvious. Rather, they merely disclose general recombinant DNA techniques, and make reference to generic terms such as "genes," "genes of interest," "clusters of genes," and "DNA segments"—with no teaching of co-expressing the heavy and light chains of an

[7] The reexamination certificate and IDS identify the publication date for this reference as 1980, but the citation is to the same article from the *Proceedings of the National Academy of Science*.

antibody, or the polypeptide chains of any other type of multimeric eukaryotic protein, in a single host cell (or otherwise).

Merck resorts to expert declarations that, decades later, claim these generic statements somehow provided an obvious path to the challenged claims—due to a supposed "prevailing mindset" that ***any*** multimeric eukaryotic protein, including antibodies, could be produced in a single host cell. But Merck cannot square those claims with the record, which fails to identify ***any*** instance before April 1983 in which ***anyone*** had co-expressed in a single host cell the different polypeptide units of ***any*** multimeric eukaryotic protein—let alone a protein as large and complex as an antibody. No "prevailing mindset" existed with respect to something that had not been reported prior to the Cabilly invention.

Moreover, despite purporting to address certain arguments and evidence raised in now-terminated IPR2015-01624, Merck does not even attempt to address the evidence in that proceeding from two of the most highly regarded antibody scientists in the world (and from Dr. Foote, petitioners' own expert in that proceeding), who agreed that the speculative possibility of recombinant antibody production remained highly "uncertain" and "unpredictable" as of April 1983. (*See supra* pp. 13-17.)

In the end, only with the benefit of hindsight can Merck chart a path to the Cabilly inventors' specific solution. Because that is not a permissible basis for finding obviousness, the Board should reject each proposed ground.

1. Each proposed ground should be denied because Merck has presented no new arguments to overcome Axel's previously-determined deficiencies.

Each proposed ground rests on Axel—the only reference underlying Merck's proposed grounds that even mentions antibodies. But the Patent Office already confirmed the non-obviousness of the Cabilly '415 patent over Axel (and numerous other references) during reexamination, and Merck has not raised any new arguments to suggest a different outcome. The Board should deny institution of each proposed ground for this reason alone.

a) Axel does not disclose co-expression of multiple different eukaryotic genes.

Axel discloses a "co-transformation" technique involving two DNA sequences: (i) "DNA I coding for desired proteinaceous material"; and (ii) "DNA II coding for selectable marker." (Ex. 1006, Fig. 1.) Axel contains no teaching or suggestion that "DNA I" can comprise multiple different genes. The only context in which Axel refers to "DNA I" as multiple "genes" is when it describes the use of ***multiple copies of the same gene*** to increase yield of the desired protein. (*Id.*, 3:62-67, 6:44-47.) The Patent Office thus correctly concluded in reexamination

that "Axel et al did not teach co-expression of two foreign DNA sequences" encoding for different desired proteins. (Ex. 2005 at 4.)

Merck points to the fact that Axel specifically identifies "antibodies" in an exemplary list of "proteinaceous materials." (Paper 1 at 25-26, 39.) But the Patent Office already considered that argument and reached the opposite conclusion: *i.e.*, that "Axel et al did not teach a single host cell transformed with immunoglobulin heavy chain and immunoglobulin light chain independently." (Ex. 2005 at 4.)

Merck attempts to discount that prior ruling because it arose in connection with a double patenting challenge, rather an anticipation or obviousness theory. (Paper 1 at 23.) But regardless of the underlying legal theory, the Patent Office considered whether Axel teaches co-expressing antibody heavy and light chains in a single host cell—and concluded that it does not. (Ex. 2005 at 4.) That finding applies with equal force here.

Merck suggests it would be unfair to adopt that prior finding here because Merck was not a party to that proceeding. (Paper 1 at 10.) But Merck does not identify any new or different spin on Axel's generic disclosures beyond those previously considered. And although Merck has submitted a new declaration from Axel co-inventor Dr. Michael Wigler (Ex. 1070), his declaration does not offer any opinion that the challenged claims would have been obvious; he simply repeats the same interpretation of Axel that the Patent Office previously considered and

rejected. (*Compare* Ex. 1070 ¶¶ 24-25, *with* Ex. 2005 at 4.) In such instances, the Board regularly treats *ex parte* reexamination rulings as persuasive in IPRs. *See*, *e.g.*, *Integrated Global Concepts, Inc. v. Advanced Messaging Techs., Inc.*, IPR2014-01028, Paper 13 at 9 (P.T.A.B. Dec. 22, 2014) (denying institution where "the Petition does not present any persuasive evidence to supplement the record that was before the Office during the [ex parte] reexamination"); *Omron Oilfield & Marine, Inc. v. MD/Totco*, IPR2013-00265, Paper 11 at 12-13 (P.T.A.B. Oct. 31, 2013) (accepting examiner's analysis from *ex parte* reexamination).

The Patent Office's determination that Axel does not disclose co-expressing antibody heavy and light chains in a single host cell is well-supported. Axel does not disclose ***any*** details on how to make an antibody, and a person of ordinary skill in April 1983 would therefore have had no reasonable expectation of success in obtaining an antibody based upon Axel's limited, generic disclosure. Indeed, one of Axel's co-inventors admits that producing an antibody from Axel's disclosure would have required "a great deal of experimentation" (Ex. 2013, Silverstein Dep. 78-79), and Dr. Axel himself filed a declaration supporting the patentability of the Cabilly invention (Ex. 2032). Merck has no basis (other than impermissible hindsight) to contend that a skilled artisan would have held a different view.

b) Axel's generic reference to "antibodies" provides no guidance on how to make an antibody.

As noted above, Axel is the only reference underlying Merck's proposed grounds that actually mentions antibodies. But Axel only includes "antibodies" in an exemplary list of "proteinaceous materials" (Ex. 1006, 2:32-36, 2:61-66, 5:24-28), without explaining how to make an actual antibody. That omission is critical given the state of the art in April 1983, which was fraught with challenges and uncertainties surrounding antibody expression. (*See supra* pp. 13-17.)

Merck offers no explanation how Axel's passing reference to antibodies could have resolved those uncertainties. Indeed, Merck cites no evidence that anyone has ***ever*** credited Axel with teaching or suggesting ***anything*** with respect to antibody production, outside of litigation decades later. Nor does it address the previously-submitted declaration of Dr. Axel supporting the patentability of the Cabilly inventors' work (Ex. 2032), or Axel co-inventor Dr. Silverstein's confirmation that Axel's disclosure was insufficient to allow a skilled artisan to produce an antibody "without a great deal of experimentation" (Ex. 2013, Silverstein Dep. 78-79). Merck's assumption that Axel's mere reference to "antibodies" would have led a skilled artisan to the challenged claims rests on hindsight.

2. Ground 1: Claims 1, 3-4, 11-12, 14-17, 19, and 33 would not have been obvious over the Mulligan papers in combination with Axel.

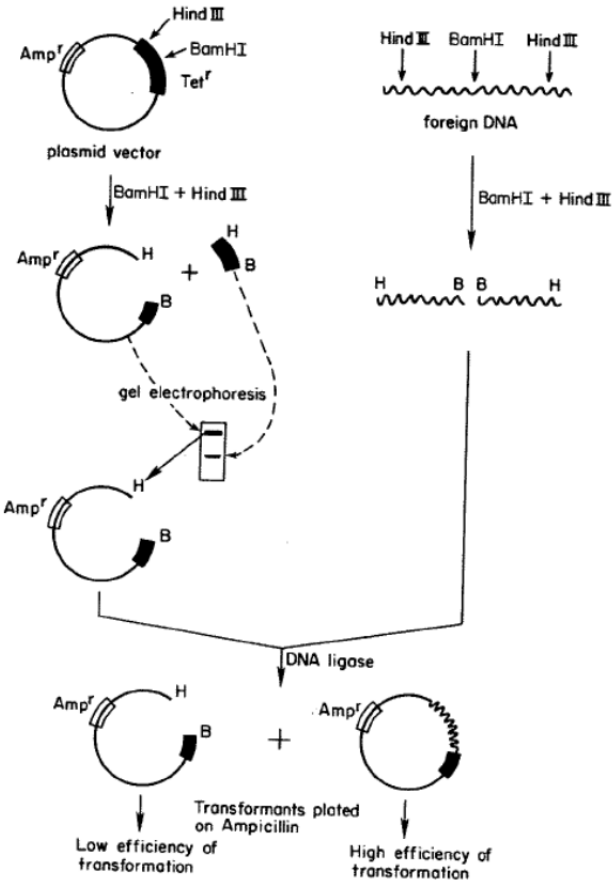
The Mulligan papers do not disclose the production of antibodies—or even mention them. Therefore, neither provides the teaching concerning co-expressing an antibody heavy and light chain in a single host cell that is lacking from Axel. That alone forecloses obviousness based on the Mulligan papers, and none of Merck's arguments change that result.

First, Merck points to the existence of multiple restriction sites in the pSV2 vector as suggesting co-expressing "multiple, different proteins of interest from a single vector in a single host cell." (Paper 1 at 40.) But Merck ignores that there were other reasons wholly unrelated to co-expression why it was useful in April 1983 for a vector to contain multiple restriction sites.

For example, it was well-known prior to April 1983 that multiple restriction sites could be used for "directional cloning," *i.e.*, to control the orientation of the inserted DNA. (Ex. 2033 at 13.) If a vector is cut using a single restriction enzyme, the inserted DNA could orient in two different directions because the cohesive ends could anneal to either DNA strand. However, if the vector is cut in two places using different restriction enzymes, the cohesive ends will be complementary in only one direction, making it possible to control the direction of the inserted DNA. (*Id.*)

Multiple restriction sites similarly allow control over the length of the inserted DNA and permit compatibility with a variety of DNA sequences. (*Id.* ("[D]ifferent combinations of enzymes can be used depending on the locations of restriction sites within [the] vector and the segment of foreign DNA."); Ex. 2034 at 91 ("We believe that the use of these six restriction enzymes and the 14 possible combination digests will provide not only the opportunity for cloning many interesting DNA fragments but also the further dissection of these DNAs into their component parts.").)

Using multiple restriction sites also was known to improve the efficiency of transformation with vectors containing the inserted DNA because a vector cut with two different restriction enzymes cannot self-anneal (which prevents it from entering cells without the inserted DNA). (Ex. 2033 at 13.) These two-enzyme techniques for inserting a single gene were described in molecular cloning textbooks prior to April 1983, including in the Maniatis reference that Merck cites:



(*Id.* at 14, Fig. 1.3.) Likewise, the Rice & Baltimore paper published in February 1983 used that two-restriction-site approach with "plasmid pSV2gpt, obtained from R. Mulligan[,]" to insert a single DNA fragment encoding for an antibody light chain. (Ex. 1017 at 7862.)

Multiple restriction sites also allowed scientists to insert a DNA fragment in different locations within the vector to optimize its expression. In fact, that is precisely how the Mulligan authors used them, *i.e.*, to control "the location of the inserted DNA segment in the vector." (Ex. 1002 at 1427.)

Moreover, the Mulligan papers were not the first to disclose vectors with multiple restriction sites; even the earliest vectors from the 1970s contained multiple restriction sites. (Ex. 2033 at 13 ("Most plasmid vectors carry two or more unique restriction enzyme recognition sites.") For example, the Cohen & Boyer patent filed in 1974, which Merck touts as a "notable example" of early recombinant DNA techniques (Paper 1 at 14), describes a vector with multiple restriction sites (EcoRI and BamHI) that were used to insert a single gene. (Ex. 1028, 15:4-17.)

The fact that Merck has cited ***no*** example of ***any*** multimeric eukaryotic protein produced by co-expressing separate molecules in a single host cell prior to April 1983—despite the fact that vectors containing multiple restriction sites had been known for years—confirms there is nothing about the presence of multiple restriction sites that would have led a skilled artisan to the Cabilly invention.

Second, Merck relies on Mulligan's statement that the pSV2 vector contains "suitable restriction sites for recombination with one or more additional DNA segments." (Ex. 1002 at 1427.) But Merck ignores that the Mulligan papers use the term "DNA segment" to refer to selectable markers. (*E.g.*, Ex. 1002 at 1427 (referring to "the *gpt* coding sequence" as "the inserted DNA segment").) Indeed, the passage quoted by Merck (Paper 1 at 18, 29, 40) is describing the possibility of identifying new ***selectable markers*** from "bacteria, their viruses, and simple

eukaryotes." (Ex. 1002 at 1427.) Using Mulligan's own terminology, a vector including a selectable marker and one non-selectable gene would have "one or more additional DNA segments."

Third, the Mulligan papers indicate that the "existence of several restriction sites" simply allows the vector to be used with a variety of different gene types—not to co-express multiple non-selectable genes in a single host cell. (Ex. 1003 at 2076.) The next sentence in Mulligan 1981 identifies various possible genes that could have been inserted using those restriction sites. (*Id.* ("DNA segments including the human globin (31), chick ovalbumin (32), or hormone gene (33) families can be inserted into the vectors and then into appropriate cells by using the *Ecogpt* function for selection.").)

Fourth, Merck points to the Mulligan papers' discussion of "genes or clusters of genes." (Paper 1 at 29-30.) During reexamination, the Patent Office considered similar generic references to a plurality of "genes" in Axel and found them insufficient to invalidate the challenged claims of the Cabilly '415 patent. (Ex. 2005 at 4.) The same result applies here, particularly where the cited passage specifically refers to using genes from "bacteria" as new selectable markers. (Ex. 1002 at 1427.) In that context, a person of ordinary skill would have understood the passage to refer to bacterial operons, which are naturally occurring "clusters of genes"—and not to genes encoding the different polypeptide chains of a

multimeric eukaryotic protein. (*E.g.*, Exs. 1050-53 (describing operons); Ex. 2012, Fiddes Decl. ¶ 184.)

Finally, Merck points to the prominence of the Mulligan papers and widespread use of the disclosed vectors. (Paper 1 at 30.) If anything, however, this evidence confirms the non-obviousness of the challenged claims. That Merck cannot identify a single instance before April 1983 in which anyone—including the highly-skilled Mulligan co-authors—used the teachings of the Mulligan papers to co-express genes encoding the different polypeptides of a multimeric eukaryotic protein in a single host cell only reinforces the validity of the challenged claims.

So too does the Oi paper cited in Merck's petition—co-authored by Dr. Berg in February 1983—which used the pSV2 vector ***solely*** to express antibody light chain, but ***not*** heavy chain. (Ex. 1045.) Other persons of extraordinary skill—such as Nobel laureate Dr. Baltimore—used the pSV2 vector in the same manner prior to April 1983. (Ex. 1017.) If a co-inventor of the pSV2 vector and other world-leading scientists did not use Mulligan's vectors to co-express both chains of an antibody in a single host cell before April 1983, even when studying antibodies, a person of mere ordinary skill would not have considered it obvious to do so.

a) A person of ordinary skill would not have combined the Mulligan papers with Axel.

Merck's conclusory assertion (Paper 1 at 41) that it would have been "common sense" to combine Mulligan with Axel is not legally sufficient to support institution. *See Arendi S.A.R.L. v. Apple Inc.*, __ F.3d __, 2016 WL 4205964, at *5 (Fed. Cir. Aug. 10, 2016) ("[O]ur cases repeatedly warn that references to 'common sense'—whether to supply a motivation to combine or a missing limitation—cannot be used as a wholesale substitute for reasoned analysis and evidentiary support …."). Merck argues that a skilled artisan would have been motivated to combine the Mulligan papers with Axel because the Mulligan papers explicitly state that they improve upon the "principal shortcoming" of Axel's technique (using mutant cells). (Paper 1 at 42; Ex. 1002 at 1427.) But Merck does not appear to rely upon Axel for any teaching other than its mere mention of the word "antibodies." (*E.g.*, Paper 1 at 42.) That is not an actual combination of teachings; it is merely hindsight-driven wordplay.

Merck also points to "market forces … to make therapeutic antibodies" as supposedly motivating the combination of the Mulligan papers with Axel. (Paper 1 at 41-42.) But the Mulligan papers do not mention antibodies, and Merck offers no explanation why those "market forces" would have motivated a skilled artisan to consider the Mulligan papers. Merck also ignores the already-available paths to

producing antibodies as of April 1983, such as using hybridomas—which, at the time, were being used extensively to produce monoclonal antibodies, and their uses were "expanding very rapidly," with "many commercial companies beginning to market them." (Ex. 2018 at 407; Ex. 2012, Fiddes Decl. ¶ 50; Ex. 2011, Foote Dep. 48-49; Ex. 1001, 1:64-2:11.)

b) A person of ordinary skill would have had no reasonable expectation of success given the uncertainties surrounding antibody production.

Even if combined, the Mulligan papers and Axel would not have led a skilled artisan to the Cabilly '415 invention for the reasons detailed above. Merck alternatively contends that it would have been obvious to extend those references to produce an antibody recombinantly in a single host cell based on Rice & Baltimore, Ochi, and Oi. (Paper 1 at 44 (citing Exs. 1017-18, 1045).) But these references show the opposite: even persons of ***extraordinary*** skill at that time—such as Nobel laureates Dr. Baltimore (Ex. 1017) and Dr. Berg (Ex. 1045)—used the vector solely to express only one antibody chain.

The same references also highlight the significant uncertainty that a person of ordinary skill would have faced at the time surrounding the production of even a ***single antibody chain*** from recombinant DNA:

- Rice & Baltimore acknowledged that "relatively little is known about the molecular mechanisms that control Ig gene expression." (Ex. 1017 at 7862.)
- Ochi explained that "[t]he mechanisms responsible for the regulation of the expression of rearranged immunoglobulin genes are poorly understood." (Ex. 1018 at 340.)
- Oi had no explanation why antibody light chain expressed successfully in certain cell lines, but not others. (Ex. 1045 at 829.)

Merck ignores these disclosures, along with statements from leading scientists such as Drs. Milstein and Winter—who, as discussed above, were still questioning whether antibodies could be recombinantly produced given the state of the art.[8]

Merck argues that the large size and complexity of an antibody would not have influenced a skilled artisan's expectation of success. (Paper 1 at 44-45.) But ***no*** multimeric eukaryotic protein—regardless of size and complexity—had been produced as of April 1983 by co-expressing its different polypeptide chains as

[8] Rice & Baltimore, Ochi, and Oi (Exs. 1017-18, 1045) were considered during reexamination of the Cabilly '415 patent. (Ex. 1001, Reexamination Certificate at 2.) Merck's petition simply rehashes previously rejected arguments concerning these references.

separate molecules in a single host cell. A person of ordinary skill would not have had a reasonable expectation of success in pursuing the claimed co-expression approach for antibodies when those techniques had not been proven to work with even simpler eukaryotic proteins. (Ex. 2012, Fiddes Decl. ¶¶ 57-80.)

Merck asserts that "proteins larger and more complex than an immunoglobulin had been successfully expressed using recombinant DNA techniques." (Paper 1 at 45.) But the only example that Merck cites is ATCase, a ***prokaryotic*** protein expressed from ***a single contiguous piece of DNA***. (Ex. 1050 at 4023.) The production of a ***multimeric eukaryotic*** protein such as an antibody in a single host cell would have been more challenging. (*See supra* pp. 8-17.) The cited publications describing ATCase (Exs. 1050-54) are irrelevant because they address a fundamentally different problem than the challenged claims.

c) Axel does not disclose the recovery and assembly of functional antibodies.

As of April 1983, the only multimeric eukaryotic protein that had been produced recombinantly was insulin. (*See supra* p. 10.) Despite its relatively small size and simple structure, however, the process at the time for recovering and assembling insulin was still challenging. (Ex. 1067 at 106 ("The efficiency of correct joining has been variable and often low.").) Given this backdrop, before the invention of the Cabilly '415 patent, a person of ordinary skill would have had

no reasonable expectation that conventional techniques could be extended successfully to the recovery and assembly of antibodies.

Axel does not change that result. It provides no guidance on how to recover or assemble an antibody produced from recombinant DNA. The only passage that Merck cites on this issue merely states that proteins may be recovered "using well known techniques." (Ex. 1006 at 6:26-27.) That generic statement would not have provided a reasonable expectation of success, especially given the potential challenges to reassembling a protein as large and complex as an antibody.

Merck argues that Axel's description is sufficient because the Cabilly '415 patent's written description also rests on techniques known in the art. (Paper 1 at 40-41.) But part of the Cabilly invention was recognizing that recombinant antibodies could be recovered and assembled by adapting existing techniques. (*E.g.*, Ex. 1001, 10:44-49, 14:20-35.) Merck cannot use the inventors' own discovery to provide a reasonable expectation of success. *See InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1351 (Fed. Cir. 2014) (criticizing using patent's disclosure as roadmap to support obviousness).

d) The invention of the Cabilly '415 patent would not have been obvious to try.

Merck also has failed to support its assertion that the challenged claims would have been obvious to try. (Paper 1 at 43-44.)

First, the Cabilly '415 patent's co-expression approach was not an "identified" solution to the problem of producing antibodies. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) (obvious to try requires "a finite number of identified, predictable solutions"). 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. Merck cannot contend that an approach no one had reported using as of April 1983 was an "identified" solution.

Second, the recombinant production of antibodies was not among a "finite" number of options a skilled artisan could have pursued starting from the Mulligan papers and Axel. The Mulligan papers do not even mention antibodies. And although Axel mentions "antibodies" in a broad (and non-limiting) exemplary list of "proteinaceus materials," it provides no guidance on how to make an antibody. As a result, even Axel's own co-inventors have confirmed that it would not have been possible to make an antibody starting from Axel "without a great deal of experimentation" (Ex. 2013, Silverstein Dep. 78-79), and have supported the patentability of the Cabilly invention (Ex. 2032).

Merck argues there are only a finite number of ways to make antibodies recombinantly. (Paper 1 at 43-44.) But that is irrelevant because Merck never explains why a skilled artisan would have chosen at the time to make an antibody, as opposed to countless other possible proteins, based on the generic disclosure of

the Mulligan and Axel references. Under Merck's flawed reasoning, it apparently would have been obvious to try producing ***any*** protein product recombinantly.

Third, co-expressing antibody heavy and light chains in a single host cell was not a "predictable" solution given the many actual and perceived uncertainties at the time relating to recombinant antibody production. (*Supra* pp. 13-17.) Merck never explains how the Cabilly inventors' solution was predictable as of April 1983, and does not even address this requirement under *KSR*. (Paper 1 at 43-44.)

3. Ground 2: Claims 1, 3-4, 11-12, 14-17, 19, and 33 would not have been obvious over the Mulligan papers in combination with Axel and in further view of the Nobel article.

As Merck acknowledges (Paper 1 at 48), Ground 2 is similar to Ground 1. The Board thus should deny institution for the same reasons discussed above for Ground 1.

In addition, the Nobel article does not mention antibodies. It therefore does not disclose the teaching of co-expressing antibody heavy and light chains in a single host cell that is absent from Axel and the Mulligan papers. Nor does the Nobel article purport to disclose any new research; it simply summarizes the work that Dr. Berg previously reported, including in the Mulligan papers, and speculates about future applications for that technology. (Ex. 1004 at 300-02.)

The only added teaching that Merck attributes to the Nobel article is the statement that "[a]dditional DNA segments can also be inserted into the vector

DNA's at any of several unique restriction sites; consequently, a single DNA molecule can transduce several genes of interest simultaneously." (*Id.* at 300.) That passage does not suggest the claimed co-expression approach of the Cabilly '415 patent for several reasons.

First, the statement that "a single DNA molecule can transduce several genes of interest simultaneously" is not describing any work that had actually been done. Rather, consistent with the forward-looking discussion of Dr. Berg's Nobel lecture, the statement is mere speculation about potential future applications for recombinant DNA technology. Such speculation would not have provided a reasonable expectation of success for any of those potential future applications; indeed, the Nobel article speculated that gene replacement therapy was on the horizon (*id.* at 302), even though it still does not exist today.

That is particularly true given that even leading scientists in the field, such as Drs. Milstein and Winter, had significant doubts concerning the production of recombinant antibodies prior to the Cabilly invention. (*See supra* pp. 13-17.) And in any case, there is nothing in the Nobel article's forward-looking statements that would have led to the production of antibodies (which are not mentioned), as opposed to any of the numerous other possible applications for recombinant DNA technology.

Second, beyond hindsight-driven statements made decades later, Merck has no evidence that the quoted passage is describing the co-expression of multiple different subunits of a multimeric eukaryotic proteins in a single host cell. For example, the Nobel article's description of co-transducing "several genes of interest simultaneously" covers vectors containing a marker gene plus an additional non-selectable gene inserted elsewhere. That interpretation is supported by the preceding sentence, which describes the marker gene used in Dr. Berg's vectors. (*Id.* at 300 ("Each of the vectors contains a marker gene ….").) A skilled artisan would have understood that a marker gene was sometimes called a "gene of interest." (Ex. 2030, 2:33-47 ("[A] structural gene … may be marker."); Ex. 2031 at 49 ("The marker gene itself may be the gene of interest ….").)

Alternatively, a skilled artisan might have understood that "several genes of interest" meant several duplicative copies of the ***same*** gene, as Axel describes. (Ex. 1006, 3:62-68.) Merck cannot base its obviousness theory on a combination involving Axel and then ignore what Axel says.

Likewise, Merck points to nothing in the Nobel article stating that "[a]dditional DNA segments" refers to inserting multiple different genes encoding for the different polypeptide chains of a multimeric protein. The preceding sentence makes clear that it does not; as used in the article, a "DNA segment" is something that can perform various functions in regulating gene expression—such

as a promoter or terminator—or can be a marker gene. (Ex. 1004 at 300 ("Each of the vectors contains … a ***DNA segment*** containing the SV40 early promoter and origin of replication (ori); another SV40 ***DNA segment*** that ensures splicing and polyadenylation of the transcript is located at the 3' end of the marker segment …."); *id.* ("To date, ***three marker DNA segments*** have been used in conjunction with the pSV2, pSV3, and pSV5 vector DNA's ….").) Merck cannot convert use of the general term "[a]dditional DNA segments" into the specific disclosure of co-expressing heavy and light antibody chains in a single vector.

Third, Merck has cited no publication prior to April 1983 using the pSV2 vector to co-express the genes for the different polypeptides of any multimeric eukaryotic protein, and certainly not for an antibody. The antibody references that Merck cites for their use of the pSV2 vector prior to April 1983—including Oi from Dr. Berg's own laboratory—expressed only antibody light chain. (Exs. 1017-18, 1045.) Merck's argument that a person of ordinary skill nevertheless would have pursued a co-expression approach cannot be reconciled with this real world evidence of how highly-skilled scientists at the time approached the issue.

4. Ground 3: Claims 1, 3-4, 11-12, 14-17, 19, and 33 would not have been obvious over the Mulligan papers in combination with Axel in further view of Builder.

Ground 3 relies on the same combination asserted for Ground 1 (Mulligan papers and Axel), in further view of Builder. The Board should deny institution of this ground for two reasons.

First, Merck has failed to meet its burden to establish that Builder is prior art. Builder was filed on June 1, 1984—well after the April 8, 1983 Cabilly '415 patent filing date. (Ex. 1007 at coversheet.) Merck asserts that Builder is prior art under § 102(e) because it "claims priority to an application filed on December 22, 1982." (Paper 1 at 35.) However, Merck has the initial burden of production to show that the patent is "entitled to the benefit of a[n earlier] filing date." *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008). Here, Merck "did not submit a copy of the [parent] application as an exhibit ... [and therefore] failed to demonstrate that there is a continuous chain from the [parent] application." *Ariosa Diagnostics, Inc. v. Illumina, Inc.*, IPR2014-01093, Paper 14 at 11 (P.T.A.B. Jan. 8, 2015).

Second, Builder does not mention antibodies, let alone disclose the recovery and assembly of a functional antibody. Instead, as Merck admits, and as the Patent Office has previously found, Builder merely discloses a generalized method for recovering expressed proteins. (Paper 1 at 50; Ex. 2005 at 6.) Builder thus does

not cure the deficiencies in Ground 1. The Board should deny institution of Ground 3 for the same reasons it should deny institution of Ground 1.

5. Ground 4: Claims 1-2, 11-12, 14, 18-20, and 33 would not have been obvious over Southern in combination with Axel.

a) Southern does not disclose the co-expression of antibody heavy and light chains in a single host cell.

Like the Mulligan papers, Southern does not disclose anything relating to the production of antibodies—or even mention antibodies. Southern therefore cannot cure the deficiencies that the Patent Office previously found with Axel: *i.e.*, that "Axel et al did not teach a single host cell transformed with immunoglobulin heavy chain and immunoglobulin light chain independently." (Ex. 2005 at 4.) Institution of Ground 4 should be denied for this reason alone.

Merck argues that "Southern teaches a technique by which two different genes, each encoding a distinct protein of interest, can be inserted into a single eukaryotic host cell using two different vectors, each with a different selectable marker." (Paper 1 at 52.) That is not what Southern discloses. In fact, the only experiments disclosed in Southern relate to selectable markers, not any eukaryotic protein. (Ex. 1005 at 336-37.)

Merck relies on the last paragraph of Southern, which speculates that "[c]otransformation with nonselectable genes can be accomplished by inserting genes of interest into vector DNAs designed to express neo or gpt." (*Id.* at 339.)

But as discussed above, the record confirms that persons of ordinary skill would have understood that statement at the time simply to mean that Southern's vectors could co-transform various non-selectable genes along with ***either*** a "neo or gpt" marker—not multiple non-selectable genes at the same time. (Ex. 2012, Fiddes Decl. ¶¶ 302-04.)

Merck also cites Southern's final sentence, which 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. 1005 at 339.) But Southern never disclosed any results from the tests supposedly "in progress." (Ex. 2011, Foote Dep. 386; Ex. 2012, Fiddes Decl. ¶ 305.) And in any case, there is nothing about "double selection" that requires co-expressing genes encoding for different polypeptide chains of multimeric eukaryotic protein. Indeed, Southern's "***[d]ouble selection***" experiments all involved ***two marker genes***—and ***no*** non-selectable genes. (Ex. 1005 at 337, Table 3.)

Merck notes that "Southern is an extension of Prof. Berg's earlier work that had already taught the use of the pSV2 vector to express proteins of interest." (Paper 1 at 34.) But Southern confirms that research left many unanswered questions. (Ex. 1005 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.").) Merck points to nothing in the prior art that resolves those many questions.

The scientific literature prior to April 1983 confirms that Merck's reading of Southern is pure hindsight. Each of the three research groups Merck cites for their use of the pSV2 vector—including Dr. Berg's laboratory in the Oi paper—produced only a single antibody light chain from one vector. (Exs. 1017, 1018, 1045.) Merck has not cited any example of anyone prior to April 1983 using two vectors to co-express genes encoding for different polypeptide chains of ***any*** multimeric eukaryotic protein. If ***extraordinarily-***skilled researchers including Dr. Baltimore (Ex. 1017) and Dr. Berg (Ex. 1045) did not apply Southern as Merck suggests, there is no reason to believe a person of ***ordinary*** skill would have either.

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

Merck restates the same arguments for motivation to combine that it offered for Ground 1 (Paper 1 at 52-53), and they fail for the same reasons.

Merck's conclusory assertion that such a combination is supported by "common sense" is legally insufficient. *Arendi*, 2016 WL 4205964, at *5. Nor

would a skilled artisan have "readily recognized that the platform taught in Southern is compatible with the teachings of Axel" simply because "Southern cites to the work of the Axel inventors." (Paper 1 at 53.) As with Ground 1, Merck does not point to any teaching in Axel that a person of ordinary skill would have supposedly been motivated to combine with Southern. On the contrary, Merck again relies on Axel for its mere mention of the word "antibodies"—not any teaching concerning how to make antibodies (which is absent from Axel).

Merck's assertion that the "market demand for therapeutic antibodies" (Paper 1 at 53) would have motivated the combination of Southern with Axel is also unsupported. Axel provides no guidance on how to make antibodies, and Southern does not mention antibodies. Merck's reliance on a desire to produce therapeutic antibodies therefore finds no support in the disclosure of those references. Merck's argument also ignores the other already-existing paths to producing therapeutic antibodies, such as using hybridomas. (*See supra* p. 46.)

c) Merck's remaining arguments fail for the same reasons addressed with respect to Ground 1.

Merck's other arguments for Ground 4 are similar to those presented in Ground 1. The Board should reject them for the same reasons.

Reasonable expectation of success. As with Grounds 1-3, Merck does not address the numerous uncertainties concerning recombinant antibody production

that a skilled artisan would have faced in April 1983. Merck argues that "[b]y April 1983, the co-transformation and co-expression techniques described in both the Axel patent and Southern had been used to produce eukaryotic proteins." (Paper 1 at 53.) But two of Merck's cited references post-date the filing of the Cabilly '415 patent. (Exs. 1043-44.) And none of Merck's cited prior art discloses co-expression of multiple eukaryotic proteins or a two-vector approach for any purpose. (Exs. 1036-38, 1042.) A skilled artisan in April 1983 would have had no reasonable expectation of success in overcoming the uncertainties surrounding recombinant antibody production, let alone in a single host cell when no one had previously produced ***any*** multimeric eukaryotic protein in that manner.

Recovery and assembly of antibodies. Merck restates its argument that it would have been obvious to recover and assemble a recombinantly-produced antibody because "the '415 patent admits these techniques were known in the art." (Paper 1 at 52.) But no multimeric eukaryotic protein as large and complex as an antibody had been produced recombinantly as of April 1983, and a person of ordinary skill thus would have had no reasonable expectation of success extending the one-host-per-protein techniques that worked only with difficulty for much simpler proteins (*i.e.*, insulin). (*Supra* pp. 8-17.) Merck may not rely on the Cabilly inventors' own discovery to invalidate the challenged claims.

Obvious to try. Merck provides no explanation why a two-vector approach would have been obvious to try beyond a single, conclusory sentence. (Paper 1 at 44 ("Likewise, the combination of the Axel patent with Southern (Ground 4) would have made the two-vectors-in-one-cell approach obvious to try.").) As discussed above, that unsupported assertion is legally insufficient, and none of the prerequisites to find obviousness to try are present here in any event. (*Supra* pp. 49-51.)

6. Ground 5: Claims 1-2, 11-12, 14, 18-20, and 33 would not have been obvious over Southern in combination with Axel in further view of Builder.

For Ground 5, Merck incorporates its analysis from Grounds 3 and 4. (Paper 1 at 54.) The Board should not institute Ground 5 for the same reasons explained above for Grounds 3 and 4—including because Merck has failed to establish that Builder is prior art, and because Builder does not support Merck's arguments concerning the recovery and assembly of antibodies (or even mention antibodies). (*See supra* pp. 55-56.)

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

The Federal Circuit has emphasized that real world evidence concerning a patented invention is a critical safeguard against hindsight reasoning—a risk especially acute here when the relevant analysis depends on the perspective of a

skilled artisan from April 1983. *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010) ("Secondary considerations 'can be the most probative evidence of non-obviousness in the record, and enables the ... court to avert the trap of hindsight.'"). Several objective indicia confirm that the path Merck seeks to draw from its generalized prior art to the specific co-expression approach of the Cabilly '415 patent is based on hindsight.

First, the Cabilly '415 patent is one of the most widely licensed patents in the industry, with over 70 licenses to world-leading biotechnology companies that have generated royalties well over a billion dollars. 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).

Merck discounts this evidence by suggesting that licenses may be taken because "it is cheaper to take licenses than to defend infringement suits." (Paper 1 at 56.) But the licensing revenues here greatly exceed the cost of any litigation and therefore provide strong evidence of non-obviousness. *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1353 (Fed. Cir. 2012) (royalties in excess of litigation costs "reflect the value of the claimed invention").

Second, the Cabilly '415 patent is a critical aspect of the manufacturing process for successful products from both Genentech and other companies. Merck does not dispute the commercial success of products embodying the Cabilly invention; it simply argues that products using the Cabilly invention are successful due to therapeutic properties and innovations unique to each embodying product. (Paper 1 at 58.) But any such properties and innovation would not have been possible without the Cabilly '415 patent—which first opened the door to recombinantly-produced therapeutic antibodies.

And a nexus to commercial success may exist even where a product is covered by multiple patents; proof of commercial success does not require proof that the patented invention is the sole reason for a product's success. *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1273 (Fed. Cir. 1991) ("It is not necessary ... that the patented invention be solely responsible for the commercial success, in order for this factor to be given weight appropriate to the evidence."). Here, the Cabilly '415 patent plays an important role in enabling the efficient and stable manufacture of numerous commercial products; indeed, that is precisely why so many companies in the industry have licensed it.

Third, as noted above, before April 1983, leading scientists were skeptical that an antibody could be produced using recombinant DNA. (*See supra* pp. 13-17.) The Cabilly inventors' success in the face of such skepticism—using a single

host cell approach not previously used for any other eukaryotic protein—underscores the non-obviousness of their invention. *See Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1367-68 (Fed. Cir. 2012).

Merck attempts to downplay this skepticism by pointing to evidence of supposed simultaneous invention. But as discussed further below (p. 65), relevant skepticism is from persons of ***ordinary*** skill. *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 885 (Fed. Cir. 1998). Here, the work cited by Merck—involving persons of ***extraordinary*** skill and resulting in two issued patents—only highlights the non-obviousness of the challenged claims.

Merck also argues that Patent Owners' evidence of skepticism relates "almost entirely" to the *in vivo* assembly of heavy and light chains, and not co-expression. (Paper 1 at 58.) But leading scientists such as Drs. Milstein and Winter had broader concerns relating to recombinant DNA techniques far beyond *in vivo* assembly. (Ex. 2018 at 410 ("The way to proceed from here is clouded by uncertainties and multiple possibilities."); Ex. 2020, Winter Rep. ¶ 61 (noting recombinant production of antibodies in April 1983 would have been "a major undertaking without any certainty of success").) And those concerns proved well-founded, as confirmed by the uncertainties that researchers (including authors of Merck's own cited references) faced as they struggled to get even one antibody chain to express prior to April 1983. (*See supra* pp. 13-17.)

These objective indicia of non-obviousness reaffirm that the challenged claims of the Cabilly '415 patent are not obvious.

D. Merck's "Simultaneous Invention" Argument Reinforces The Patentability Of The Challenged Claims.

Merck's "simultaneous invention" argument does not support institution.

First, "simultaneous invention" is only relevant if it reflects the "knowledge attributable to one of ***ordinary skill*** in the art." *Ecolochem, Inc. v. Southern Cal. Edison Co.*, 227 F.3d 1361, 1379 (Fed. Cir. 2000). Yet, the research groups that succeeded in making antibodies after the Cabilly inventors were ***extraordinarily skilled***—including Boss (Ex. 1049) and Morrison (Ex. 1044), who received patents for their work, "which sets them apart from the workers of *ordinary* skill." *Standard Oil Co. v. Am. Cyanamid Co.*, 774. F.2d 448, 454 (Fed. Cir. 1985) (emphasis in original). That those extraordinarily skilled artisans may have independently developed the invention several months later does not render it obvious. If anything, it underscores the Cabilly inventors' remarkable achievement in obtaining the invention first.

Second, the Board considered the same "simultaneous invention" argument in IPR2016-00383, and concluded it was insufficient to demonstrate a reasonable likelihood of success, including on obviousness grounds citing Southern.

(IPR2016-00383, Paper 16 at 30.) Merck does not provide any reason why the Board should reach a different conclusion here.

E. Merck's Proposed Grounds Are Duplicative.

All five proposed grounds repeat essentially the same obviousness argument based upon references describing the pSV2 vector in combination with Axel. Although Grounds 1-3 are directed to slightly different claims than Grounds 4-5, there is substantial overlap in the claims challenged by all five grounds (claims 1, 11-12, 14, 19, and 33).

Merck has not explained how its overlapping grounds are meaningfully different; rather, its petition repeatedly highlights similarities in the art and arguments presented across all grounds. (*E.g.*, Paper 1 at 48 (Ground 2: "All of the rationales described in Ground 1 are applicable to this ground …."); *id.* at 52 (Ground 4: "A POSA would have been motivated to combine the teachings of the Axel patent with Southern for several reasons, including all those set forth for Ground 1 above."); *id.* at 54 (Ground 5: "For the same reasons discussed in Ground 3, a POSA would have been motivated to further combine the Builder patent with Southern and the Axel patent as described in Ground 4 ….").) The Board should refuse to institute these duplicative grounds. *See, e.g.*, *Oracle Corp. v. Clouding IP, LLC*, IPR2013-00088, Paper 13 at 2-3 (P.T.A.B. June 13, 2003).

IX. CONCLUSION

The Board should deny institution of all grounds.

Respectfully submitted,

Date: October 17, 2016

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CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Patent Owners' Preliminary Response contains 13,961 words, as measured by the word processing software used to prepare the document and in compliance with 37 C.F.R. § 42.24(d).

Respectfully submitted,

Dated: October 17, 2016

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CERTIFICATE OF SERVICE

I hereby certify that, on October 17, 2016, I caused a true and correct copy of the following materials:

- Patent Owners' Preliminary Response
- Patent Owners' Updated Exhibit List
- Exhibits 2005-2034

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Patent Owners' Exhibit Number	**Exhibit Name**
2001	Declaration of Robert J. Gunther, Jr. In Support of Motion for Admission *Pro Hac Vice* (July 27, 2016)
2002	Declaration of Daralyn J. Durie In Support of Patent Owners' Motion for Admission *Pro Hac Vice* Admission (Aug. 4, 2016)
2003	Declaration of Joseph M. Lipner In Support of Motion for Admission *Pro Hac Vice* (Aug. 22, 2016)
2004	Declaration of David I. Gindler In Support of Motion for Admission *Pro Hac Vice* (Aug. 22, 2016)
2005	Notice of Intent to Issue Reexamination Certificate for U.S. Patent No. 6,331,415
2006	Information Disclosure Statement for Reexamination No. 90/007,542 (Nov. 28, 2005)
2007	Declaration of Dr. Timothy John Roy Harris, Reexamination Nos. 90/007,542 and 90/007,859 (Nov. 23, 2005)
2008	Declaration of Dr. Steven L. McKnight, Reexamination Nos. 90/007,542 and 90/007,859 (May 18, 2007)
2009	Declaration of Michael Botchan, Reexamination Nos. 90/007,542 and 90/007,859 (May 20, 2007)
2010	T.J.R. Harris, Expression of Eukaryotic Genes in E. Coli, in Genetic Engineering 4, 127-185 (1983)
2011	Deposition of Jefferson Foote, *Sanofi-Aventis U.S. LLC v. Genentech, Inc.*, IPR2015-01624 (Apr. 21, 2016)
2012	Declaration of John Fiddes, Ph.D., *Sanofi-Aventis U.S. LLC v. Genentech, Inc.*, IPR2015-01624 (May 13, 2016)
2013	Deposition of Saul J. Silverstein, *Bristol-Myers Squibb Co. v. Genentech, Inc.*, No. 2:13-cv-05400-MRP-JEM (C.D. Cal. Dec. 23, 2014)
2014	Bruce Alberts, et al., Molecular Biology of the Cell, Chapter 1 (1983)
2015	Second Declaration of Dr. Timothy John Roy Harris, Reexamination Nos. 90/007,542 and 90/007,859 (Oct. 26, 2006)
2016	Second Declaration of Dr. Steven L. McKnight, Reexamination Nos. 90/007,542 and 90/007,859 (June 3, 2008)
2017	Declaration of Dr. Douglas A. Rice, Reexaminations 90/007,542 and 90/007,859 (Oct. 26, 2006)

Patent Owners' Exhibit Number	**Exhibit Name**
2018	Milstein, *Monoclonal antibodies from hybrid myelomas*, The Wellcome Foundation Lecture, Proc. R. Soc. Lond. B 211, 393-412 (1981)
2019	Falko G. Falkner & Hans G. Zachau, E*xpression of Mouse Immunoglobulin Genes in Monkey Cells*, Nature, 298:286-288 (1982)
2020	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-MRPJEMx (C.D. Cal.) (Oct. 13, 2014)
2021	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)
2022	Declaration of Arthur Riggs, *Cabilly v. Boss*, Interference No. 102,572 (Oct. 28, 1991)
2023	Declaration of Ronald Wetzel, *Cabilly v. Boss*, Interference No. 102,572 (Oct. 28, 1991)
2024	Declaration of Jeanne Perry, *Cabilly v. Boss*, Interference No. 102,572 (Oct. 27, 1991)
2025	Declaration of William Holmes, *Cabilly v. Boss*, Interference No. 102,572 (Oct. 28, 1991)
2026	Declaration of Michael Rey, *Cabilly v. Boss*, Interference No. 102,572 (Oct. 28, 1991)
2027	Declaration of Michael Mumford, *Cabilly v. Boss*, Interference No. 102,572 (Oct. 28, 1991)
2028	Declaration of Shmuel Cabilly, *Cabilly v. Boss*, Interference No. 102,572 (Oct. 28, 1991)
2029	Request for Reexamination, Reexamination No. 90/007,859 (Dec. 23, 2005)
2030	U.S. Patent No. 4,495,280 (Bujard)
2031	Vile, *Selectable markers for eukaryotic cells*, Methods Mol. Biol. 8:49-60 (1992)
2032	Declaration of Dr. Richard Axel, U.S. Patent App. No. 08/422,187 (Aug. 26, 1999)
2033	T. Maniatis, et al., Molecular Cloning: A Laboratory Manual 11-14 (1982)

Patent Owners' Exhibit Number	**Exhibit Name**
2034	Bolivar, F., et al., *Construction and Characterization of New Cloning Vehicles, I. Ampicillin-Resistant Derivatives of the Plasmid pMB9*, Gene 2:75-93 (1977)