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

U.S. Patent No. 6,331,415

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

Inter Partes Review No. 2016-01373

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 6,331,415 UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. §§ 42.100 *et seq*.

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Merck Sharp & Dohme Corp. ("Petitioner") requests *inter partes* review ("IPR") pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.100 *et seq*. of claims 1-4, 11-12, 14-20, and 33 (the "Challenged Claims") of U.S. Patent No. 6,331,415 (Ex. 1001), which issued on December 18, 2001 to Cabilly *et al*. and is assigned to Genentech, Inc. and City of Hope ("Owners"). Petitioner submits herewith the supporting declarations of Prof. Roger Kornberg, a Nobel Laureate in protein chemistry; Prof. Richard Lerner, a pioneer in recombinant antibody techniques who revolutionized means for making monoclonal antibody therapeutics; and Prof. Michael Wigler, the lead developer of the "Wigler method" of co-transformation, a seminal platform for eukaryotic protein production.

I. INTRODUCTION

The '415 patent relates to the production of immunoglobulins, or antibodies, using recombinant DNA techniques.[1] In broad terms, the '415 patent claims the production and assembly of immunoglobulin heavy and light chains using recombinant DNA techniques in a single host cell. However, recombinant DNA technology was a well-established means for producing complex eukaryotic proteins prior to the filing of the '415 patent. And the structure and function of immunoglobulins had been known for years prior to the '415 patent.

[1] For purposes of this Petition, the claim term "immunoglobulin" is interchangeable with "antibody." Ex. 1001, 1:23-24.

It is undisputed that the prior art U.S. Patent No. 4,399,216 ("the Axel patent," Ex. 1006), explicitly taught the use of recombinant DNA techniques to make antibodies in eukaryotic host cells. IPR2016-00383, Preliminary Response, 45 n.11. Owners have consistently sought to distinguish the prior art, including the Axel patent, based on the requirement in the Challenged Claims that the heavy and light chains be expressed in a single host cell. According to Owners, the "prevailing mindset" among persons of ordinary skill in the art ("POSAs") in April 1983 was that only one desired protein "of interest"[2] should be expressed in a single host cell. In other words, a POSA seeking to recombinantly express an immunoglobulin would have used two host cells, one expressing the heavy chain and the other expressing the light chain.

Owners' notion of a "prevailing mindset" is simply a fiction that was created years after the '415 patent was filed and is refuted by the prior art. Numerous prior art references, never previously cited to the Patent and Trademark Office ("PTO"), teach that multiple, different, eukaryotic proteins of interest can and should be recombinantly co-expressed in a single host cell. Significantly, Paul Berg, who was awarded the Nobel Prize in Chemistry for his development of recombinant DNA, provided a high-profile disclosure of this teaching.

[2] A "protein of interest" is any desired protein sought to be isolated from the host cell after it is recombinantly expressed. Ex. 1012, 49; Ex. 1009, ¶67.

In 1980, Prof. Berg developed a new expression vector for use in eukaryotic host cells—the pSV2 vector—which explicitly extended the Axel patent techniques to a wider variety of eukaryotic host cells. In Prof. Berg's publications, he describes how a single pSV2 vector can be used to co-express multiple proteins of interest. Likewise, Prof. Berg's Nobel Lecture, given in December 1980 and published in 1981, gives detailed teachings on how a single pSV2 vector can be used to "transduce several genes of interest simultaneously" and co-express several different eukaryotic proteins. The single vector would, of course, co-express the multiple proteins of interest in a single eukaryotic host cell.

Prof. Berg's publications directly refute Owners' arguments that the prior art "contains no suggestion to co-express multiple eukaryotic proteins of interest in a single host cell." IPR2015-01624, Owners' Response, 37 n.5. Significantly, researchers followed Prof. Berg's teachings and used the pSV2 vector to co-express heavy and light antibody chains together in a single eukaryotic host cell.

Apart from their inaccurate description of the "prevailing mindset," Owners cannot point to anything innovative in the '415 patent. The '415 patent simply uses known recombinant DNA techniques to attempt heavy and light chain co-expression. As presented in the Grounds below, the Challenged Claims are obvious in view of the prior art.

II. OVERVIEW OF THE '415 PATENT

A. The '415 Patent Specification

The '415 patent contains an extensive Background section detailing the prior art relating to both recombinant DNA technology and immunoglobulins, all of which was within the common knowledge of a POSA before April 1983. Ex. 1001, 1:12-4:50; Ex. 1008, ¶¶49-52; Ex. 1009, ¶39.

The '415 patent admits that "[r]ecombinant DNA technology has reached sufficient sophistication that it includes a repertoire of techniques for cloning and expression of gene sequences." Ex. 1001, 4:7-9. The '415 patent then lists the known techniques, including the use of DNA cloning, expression vectors and transformation of host cells, and states that this technology is "now in hand." *Id.*, 4:9-16. The specification makes no claim to have invented new recombinant DNA techniques.

With respect to immunoglobulins, the '415 patent states that "[t]he basic immunoglobin structural unit in vertebrate systems is now well understood." *Id.*, 3:17-18; Ex. 1008, ¶47. This basic structure includes two identical heavy chains and two identical light chains. Ex. 1001, 3:19-22. As shown in Figure 1 of the patent, the chains are covalently joined by disulfide bonds to form a "Y" shape:

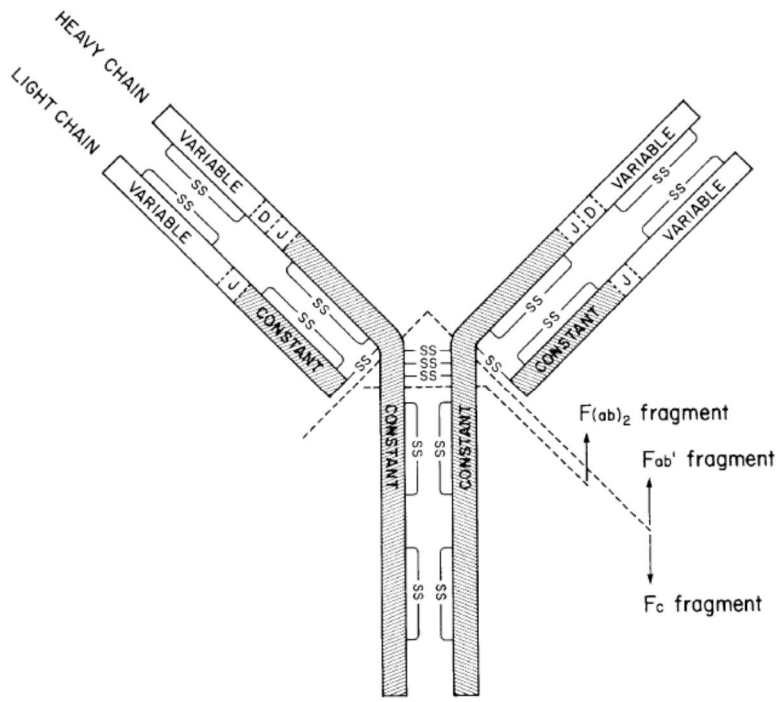


Fig. 1.

Id., 3:22-38. The heavy chain and light chain are encoded by separate DNA sequences. *Id.*, 1:48-51; Ex. 1008, ¶48; Ex. 1009, ¶46.

The recombinant DNA approach recited in the '415 patent for making immunoglobulins follows the same basic approach for any protein made recombinantly: (1) the genetic material encoding the heavy and light chains is identified and isolated (Ex. 1001, 11:28-12:3, 4:9-16); (2) the DNA encoding the heavy and light chains is inserted into one or more expression vectors (*id.,* 12:4-16); (3) the expression vector(s) is/are introduced into suitable host cell(s) by a process called "transformation" (*id.*, 12:23-30, 4:21-24); (4) the host cell(s) transcribe and translate the DNA, a process called "expression," to produce the

heavy and light chains (*id.,* 12:23-36, 4:24-29); and (5) the produced chains are recovered from the cell culture by methods known in the art so as to recover reconstituted antibody. *Id.,* 12:17-22, 12:36-56; 4:29-32; Ex. 1008, ¶¶49-52; Ex. 1009, ¶40. Indeed, the specification does not identify any aspect of using recombinant DNA technology to produce immunoglobulins that is novel.

Regarding the use of a single host cell, the '415 patent states that co-expressing the heavy and light chains in a single host cell is merely a design choice, setting forth three "options" for recombinantly expressing the heavy and light chains: 1) transforming two different host cells, one with a light chain expression vector and the other with a heavy chain expression vector; 2) transforming a single host cell with two different vectors each containing the gene for the heavy or light chain; and 3) inserting the genes for the heavy and light chains in a single vector and thus a single host cell. Ex. 1001, 12:23-36; Ex. 1008, ¶146; Ex. 1009, ¶¶41-42. The specification does not specify a preference for any of these options. *Id*.

B. The Challenged Claims

Claims 1-4, 11-12, 14-20, and 33 are at issue in this Petition. Among the Challenged Claims, claims 1, 15, 18, and 33 are independent. Claims 1 and 33 are directed to methods of producing immunoglobulins; claim 15 is directed to a vector; and claim 18 is directed to a transformed cell.

All of the Challenged Claims relate to expressing DNA encoding the heavy and light chains in a single host cell. The challenged method claims require that a single host cell "independently" express the heavy chain and light chain so that the heavy and light chains "are produced as separate molecules." Ex. 1001, 28:48-49; 30:40; Ex. 1009, ¶¶43, 48. The method claims also require assembly of the separate heavy and light chains into an immunoglobulin tetramer. Ex. 1001, 28:36; Ex. 1008, ¶55; Ex. 1009, ¶46; Ex. 1011, 46. This can occur either via *in vitro* assembly, in which the cell is lysed and the separate chains are assembled by chemical means or via *in vivo* assembly, in which the host cell uses its natural cellular machinery to assemble and secrete a complete immunoglobulin. Ex. 1001, 12:50-55; Ex. 1008, ¶55; Ex. 1009, ¶46; Ex. 1012, 29, n.8.

C. Construction Of The Challenged Claims

Petitioner submits that, for purposes of this IPR, no construction of any claim term is needed. Petitioner proposes that the claim terms take on their ordinary and customary meaning that the terms would have to a POSA in April 1983.

D. The Prosecution History Of The '415 Patent

The application that issued as the '415 patent did not initially include any claims having limitations directed to expressing the heavy and light chains in a single host cell. During prosecution, Owners provoked an interference with U.S. Patent No. 4,816,397 ("the Boss patent"), by copying the Boss patent's claims

reciting that limitation. Ex. 1013, 6-7. The copying of those claims was the first time that Owners added claim limitations directed to co-expression in a single host cell. *Id.*

1. Interference With The Boss Patent

On February 28, 1991, the PTO declared an interference between claims 1-18 of the Boss patent and the substantially identical claims 101-120 in the '419 application. Ex. 1014. The PTO awarded priority to Boss, holding that Owners had not established an actual reduction to practice before the Boss patent's British priority date. *Cabilly v. Boss*, 55 U.S.P.Q.2d 1238 (Bd. Pat. App. & Int. 1998). Genentech filed an action under 35 U.S.C. § 146, and, following a confidential settlement of the § 146 action, priority of invention was ultimately awarded to Owners. Ex. 1015.

2. Ex Parte Reexamination Of The '415 Patent

a. Rejections Over The Axel Patent

In 2005, the PTO received separate requests seeking *ex parte* reexamination of the '415 patent that were merged into a single proceeding. During the reexamination, the PTO repeatedly rejected the claims of the '415 patent on obviousness-type double patenting grounds ("ODP") based on the claims of the '415 patent's parent, the Cabilly '567 patent (Ex. 1016), in combination with various prior art references, including the Axel patent, Rice & Baltimore (Ex. 1017), and Ochi I (Ex. 1018). Exs. 1010, 1019, 1020, and 1021.

The ODP rejections that relied on the Axel patent were based on the Examiner's interpretations that Axel discloses the co-transformation and co-expression of heavy and light chains in a single host cell and thus makes up the "missing" teaching in the Cabilly '567 patent to produce both the heavy and light chains in one host cell. Ex. 1019, 5; Ex. 1021, 28-30; Ex. 1010, 51. The Examiner maintained these positions throughout the reexamination, and ultimately issued a Final Office Action on that basis, among others. Ex. 1021, 29-30.

b. Owners' Arguments In Response To The Rejections

i. Owners Concoct Their "Prevailing Mindset" Argument

To overcome these rejections, Owners argued that POSAs would not have thought to co-express both the heavy and light chains in a single host cell because the "prevailing mindset" among POSAs in April 1983 was that only one "polypeptide of interest" should be expressed per host cell. Ex. 1023, 8. According to Owners, no prior art reference, including the Axel patent, taught co-expressing two different proteins of interest in a single host cell, and thus a POSA would have expressed the heavy and light chains in separate host cells. *Id.*

Owners submitted ***seven*** Rule 132 expert declarations regarding the alleged "prevailing mindset." Ex. 1024, 85-87. According to Owners' declarants, the "prevailing mindset" would have led a POSA "to break down a complex project, such as production of a multimeric eukaryotic protein, into more manageable steps

(*e.g.*, produce each constituent polypeptide of the multimer in a separate host cell)."[3] Ex. 1023, 6-7.

In making these arguments, Owners repeatedly took advantage of the one-sided nature of the *ex parte* reexamination process, arguing that the PTO ***must*** accept the veracity of Owners' declarations: "The Examiner committed serious legal error by repeatedly substituting his own interpretations of the cited references for the well-reasoned opinions of qualified experts…. Relevant § 1.132 declaration evidence from a qualified expert is entitled to particular deference by the Office." Ex. 1024, 86.

As discussed below, Owners' one-sided declarations do not accurately reflect the thinking of a POSA in 1983. Numerous prior art references taught co-expressing more than one "protein of interest" in a single host cell, and by 1983, vectors had been designed with the specific goal of enabling the encoding of multiple genes of interest on a single vector for co-expression of several proteins of interest in a single host cell.

ii. Owners Attempt to Re-Interpret the Meaning of "Antibody" in the Axel Patent

Owners also challenged the ODP rejections in view of the Axel patent on a second basis—by advocating an interpretation of the word "antibody" that is

[3] A "multimeric" protein is a multi-protein complex that is composed of more than one distinct constituent or subunit. Ex. 1011, 37; Ex. 1009, ¶7.

unsupported by the intrinsic record and contrary to its plain meaning. Ex. 1024, 52. Owners' declarants reinterpreted the word "antibody" to mean only the heavy chain ***or*** light chain, and not a complete antibody tetramer. Ex. 1025, ¶67; Ex. 1026, ¶42.

Based on these one-sided expert declarations, Owners convinced the PTO to issue a reexamination certificate. Ex. 1027, 4. However, as explained below, the expert declarations submitted by Owners do not accurately describe the Axel patent's teachings. As explained by one of the co-inventors of the Axel patent, the word "antibody" in the Axel patent refers to the heavy ***and*** light chains. Ex. 1070, ¶¶24-26. And, consistent with the ordinary meaning of "antibody" in 1983, POSAs would have understood the teaching in the Axel patent to refer to the assembled antibody tetramer, and not just the heavy or light chain. Ex. 1008, ¶106; Ex. 1009, ¶¶81-82.

III. PERSON OF ORDINARY SKILL IN THE ART

A POSA as of April 1983 would have had a Ph.D. or M.D. in molecular biology or a related discipline, such as biochemistry, with at least 1-2 years of postdoctoral experience, or an equivalent amount of combined education and laboratory experience. Ex. 1008, ¶¶37-39; Ex. 1009, ¶¶31-33. A POSA would also have experience in expressing proteins using recombinant DNA technology. *Id.* A POSA would also have experience with protein chemistry, including the

chemistry of immunoglobulins and antibodies. *Id.*

IV. IDENTIFICATION OF THE CHALLENGE (37 C.F.R. §§ 42.104(b))

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

Ground 1: Claims 1, 3-4, 11-12, 14-17, 19, and 33 of the '415 patent are obvious under 35 U.S.C. § 103 based on the combination of the Mulligan Papers (Exs. 1002 and 1003) and the Axel patent (Ex. 1006).

Ground 2: Claims 1, 3-4, 11-12, 14-17, 19, and 33 of the '415 patent are obvious under 35 U.S.C. § 103 based on the combination of the Mulligan Papers (Exs. 1002 and 1003) and the Axel patent (Ex. 1006) in further view of the Nobel Article (Ex. 1004).

Ground 3: Claims 1, 3-4, 11-12, 14-17, 19, and 33 of the '415 patent are obvious under 35 U.S.C. § 103 based on the combination of Mulligan Papers (Exs. 1002 and 1003) and the Axel patent (Ex. 1006) in further view of the Builder patent (Ex. 1007).

Ground 4: Claims 1, 2, 11-12, 14, 18-20 and 33 of the '415 patent are obvious under 35 U.S.C. § 103 based on the combination of Southern (Ex. 1005) and the Axel patent (Ex. 1006).

Ground 5: Claims 1, 2, 11-12, 14, 18-20 and 33 of the '415 patent are obvious under 35 U.S.C. § 103 based on the combination of Southern (Ex. 1005) and the Axel patent (Ex. 1006) in further view of the Builder patent (Ex. 1007).

A detailed explanation of Petitioner's invalidity grounds is provided in Section VI below. 37 C.F.R. § 42.104(b)(4). Additional explanation and support for each ground of rejection is set forth in the accompanying Declarations of Richard A. Lerner, M.D. (Ex. 1008) and Roger D. Kornberg, Ph.D. (Ex. 1009).

V. THE PRIOR ART

A. The State Of The Prior Art

1. Recombinant DNA Technology Was Well Understood Prior To April 1983

Owners have argued that recombinant DNA techniques were "not well understood" by April 1983. IPR2015-01624, Owners' Response, 12. This argument is misleading when arguing for the patentability of the Challenged Claims. By April 1983, the techniques to recombinantly express complex proteins of interest were well understood and in use in laboratories around the world. Ex. 1008, ¶¶62-73; Ex. 1009, ¶¶55-66. In 1982, Prof. Tom Maniatis published his well-known textbook *Molecular Cloning: A Laboratory Manual*. Ex. 1055. This textbook describes the laboratory protocols needed to clone and recombinantly express proteins, including techniques for cloning eukaryotic genes, transforming host cells and analyzing recombinant protein expression. Ex. 1008, ¶64.

Moreover, Paul Berg was awarded the Nobel Prize in Chemistry in 1980 for his earlier work on recombinant DNA technology, indicating that its applications were then well accepted and its significance appreciated in the scientific community. Ex. 1009, ¶64; *see also* Ex. 1001, 4:7-9.

By 1983, several basic platforms for recombinantly expressing desired proteins had been disclosed and validated. One notable example is the work of Stanley Cohen and Herbert Boyer, reflected in U.S. Patent No. 4,237,224, filed in 1974. Ex. 1028. It discloses a simple yet powerful methodology for inserting heterologous DNA of interest into a host cell using a vector with DNA coding for a selectable marker. *Id.*, 3:3-24; Ex. 1008, ¶67; Ex. 1009, ¶58. The use of a selectable marker solved the problem of identifying and isolating successfully transformed host cells from nontransformed cells, as the cells are grown in conditions such that only cells that have acquired the selectable marker survive. *Id.*

Although Profs. Cohen and Boyer's platform was hugely influential, it had one significant disadvantage—it used prokaryotic host cells. Prokaryotic host cells lack the cellular machinery to properly process a eukaryotic protein once expressed. Ex. 1006, 2:32-3:18; Ex. 1008, ¶68; Ex. 1009, ¶59. Likewise, prokaryotic host cells have difficulty purifying eukaryotic proteins, sometimes

leading to unworkably low or non-existent protein production. Ex. 1006, 3:7-13; Ex. 1008, ¶68; Ex. 1009, ¶59.

To overcome the disadvantages of prokaryotic host cells, researchers sought to develop platforms to express eukaryotic genes in eukaryotic host cells. Ex. 1008, ¶69; Ex. 1009, ¶¶60-62. One of the first groups to do so was led by Prof. Michael Wigler. *Id.*; Ex. 1070, ¶¶9-15. Similar to the Cohen and Boyer approach—but using eukaryotic host cells—Prof. Wigler co-transformed DNA encoding a selectable marker along with DNA encoding one or more proteins of interest, thereby allowing selection of successful transformants. Ex. 1070, ¶¶9-15; Exs. 1032-1034. By designing a generally applicable platform that allowed for the expression in eukaryotic host cells, Prof. Wigler solved the problems resulting from the expression of eukaryotic proteins in a prokaryotic host cell. Ex. 1008, ¶70; Ex. 1009, ¶63; Ex. 1070, ¶19. Prof. Wigler's work is the subject of the Axel patent (Ex. 1006), on which he is a co-inventor. *See* Section V.B.1.

Although a significant advance, the platform disclosed in Prof. Wigler's early publications used mutant host cells, which significantly limited the variety of eukaryotic host cells that could be used. To overcome this limitation, Paul Berg developed a new expression vector—the pSV2 vector—and two new selectable markers that could be used in normal eukaryotic host cells. Ex. 1008, ¶¶71-72. Prof. Berg's work created a platform that expanded the range of eukaryotic host

cells and that also provided a simple means for co-transforming multiple genes of interest in a single eukaryotic host cell. Ex. 1009, ¶¶64-66; Ex. 1009, ¶¶89-92. Again, Prof. Berg's work has been widely adopted and has been used to produce a number of eukaryotic proteins of interest in a single host cell, including immunoglobulins. Prof. Berg published his work on the pSV2 vector in several journal articles and in his Nobel Article, each of which is described in detail in Section V.B.

2. The Actual "Prevailing Mindset" In 1983 Was That Recombinant DNA Technology Could Be Used To Produce Multiple Proteins Of Interest In A Single Host Cell

These seminal advancements demonstrate the correct "prevailing mindset" of the scientific community in 1983—that recombinant DNA technology provided a powerful method and practical means to manufacture multiple different genes of interest. Ex. 1008, ¶¶74-81; Ex. 1009, ¶¶55-66. Regardless of the platform, it was recognized that recombinant DNA technology could be applied to produce multiple proteins of interest and that a single host cell was the most practical means by which to do so. *Id.* Prof. Berg stated that "appropriately modified genes or clusters of genes from any source" could be inserted into a single pSV2 vector and co-expressed with a selectable marker. Ex. 1002, 1427. And similarly, Prof. Wigler concluded in 1980 that his "cotransformation system allows the

introduction and stable integration of virtually any defined gene into cultured eucaryotic cells." Ex. 1006, 31-33; Ex. 1070, ¶22.

Owners repeatedly have argued in prior proceedings that there was a "prevailing mindset" that only one recombinant protein of interest should be expressed per host cell. There has never been such a "prevailing mindset." As explained by Petitioner's experts, POSAs recognized that using a single host cell to express multiple genes of interest has a number of advantages over using multiple host cells. Ex. 1008, ¶¶74-81; Ex. 1009, ¶¶55-66. Using only one host cell mimics the way multimeric proteins are synthesized naturally and is more efficient than using multiple host cells. *Id.*

Owners have also argued that the prior art "contains no suggestion to co-express multiple eukaryotic proteins of interest in a single host cell." IPR2015-01624, Owners' Response, 37, n.5. However, Prof. Berg's pSV2 vector was designed and developed for the express purpose of expressing multiple eukaryotic proteins of interest in a single host cell. In his Nobel Article, Prof. Berg described his work "develop[ing] a new group of transducing vectors that can be used to introduce and maintain new genetic information in a variety of mammalian cells." Ex. 1004, 300. Discussing these vectors, Prof. Berg noted the ability of a "single DNA molecule" (*i.e.*, a vector) to express "several genes of interest":

> Additional 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 <u>several genes of interest simultaneously</u>***."

Id. (emphasis added). If one DNA molecule, *i.e*. one vector, expresses several genes of interest, it would necessarily express them in single host cell. Ex. 1008, ¶76; Ex. 1009, ¶87, 95. A POSA would understand that "several genes of interest" means different genes of interest contained on one vector, not multiple copies of the same gene. Ex. 1008, ¶77; Ex. 1009, ¶¶90-93.

Prof. Berg expressed similar views in his articles describing the development of the pSV2 vector. In those prior art publications, Prof. Berg explained that the pSV2 vector was specifically designed with multiple "restriction sites" to permit expression of one or more DNA segments in addition to the DNA encoding a selectable marker noting that "it should be emphasized again that pSV2…contain[s] suitable restriction sites for recombination with ***one or more additional DNA segments***," *i.e.* one or more genes in addition to the selectable marker. Ex. 1002, 1427 (emphasis added). The expression of the "one more additional DNA segments" from one vector would necessarily take place in a single host cell. Ex. 1008, ¶77; Ex. 1009, ¶93. A POSA would understand that the phrase "one or more additional DNA segments" refers to either a single gene of

interest or two or more different genes of interest (in addition to the DNA selectable marker), not multiple copies of the same gene on one vector. *Id.*

Given the obvious benefit of using a single host cell rather than two host cells, Prof. Berg developed a second way of expressing two proteins of interest in a single host cell—transforming a single host cell with two vectors. Expanding upon his earlier work, Prof. Berg developed a second selectable marker that could be used in the pSV2 vector and then demonstrated that two pSV2 vectors, each containing a different selectable marker, could be inserted in the same host cell. Ex. 1005, 336-337. Using this technique, a single host cell could be grown in conditions selecting for both selectable markers, thereby allowing different proteins of interest on two different vectors to be expressed in the same host cell. *Id.*

Profs. Cohen and Boyer also recognized that multiple genes encoding different proteins of interest could be inserted into a single vector. Ex. 1028, 5:64-65 ("The [foreign] DNA fragment may include one or more genes or one or more operons"). Profs. Cohen and Boyer's patent contains several other references to inserting multiple genes into a single vector. *Id.*, 9:12-14; 13:64-14:39; 17:4-30.

Consistent with those teachings, multiple research groups had co-expressed two protein chains using a two-gene-one-vector construct prior to April 1983, further demonstrating the lack of a "prevailing mindset." The multimeric protein

aspartate transcarbamoylase ("ATCase") is made up of twelve subunits, six catalytic subunits encoded by the *pyrB* gene and six regulatory subunits encoded by the *pyrI* gene. Ex. 1050, 4020. Prior to April 1983, separate researchers used the well-known vector pBR322 (the vector later used in the '415 patent) to co-transform a single host cell with the *pyrB* and *pyrI* genes and then co-expressed the catalytic and regulatory subunits to recombinantly produce the ATCase multimer in a single host cell. Ex. 1050, 4022-4023; Ex. 1008, ¶¶80, 151; Ex. 1009, ¶¶121, 158; Exs. 1051-54. These prior art publications establish that co-expression of two proteins to form a large and complex heterologous multimeric protein had been done in a single cell by 1983. *Id.*

3. The Techniques For *In Vitro* Recovery And Reconstitution Of Complex Eukaryotic Proteins Were Well-Known In The Prior Art

By April 1983, the techniques needed to recover and reconstitute recombinantly-expressed proteins were well-known. Ex. 1008, ¶¶82-88; Ex. 1009, ¶¶122-125. These techniques are performed outside the host and are therefore referred to as *in vitro* assembly. The same basic techniques of *in vitro* assembly do not vary by protein and work the same for simple, monomeric proteins and complex, multimeric proteins, such as antibodies. Ex. 1009, ¶129-133. Likewise, the techniques are the same whether multimeric proteins are recovered from a single host cell or separate host cells. Ex. 1009, ¶¶135-39.

The first step for *in vitro* assembly is recovering the recombinantly-expressed protein from the host cell. It was known that recombinantly-expressed proteins often appeared as insoluble clumps known as inclusion bodies. Ex. 1009, ¶¶124-25. To recover the proteins within an inclusion body, the prior art taught to lyse the cell and then to recover the proteins by dissolving them in a strongly denaturing solution, such as guanidine hydrochloride. Ex. 1007, 7:59-68; 12:63-13:50; Ex. 1009, ¶125.

The next step of the *in vitro* assembly process is to renature the proteins. Again, the renaturation process was known in the prior art, which contains numerous examples of renaturing *in vitro* the heavy and light chains to form a functional immunoglobulin. Ex. 1007, 15:68-18:45; Ex. 1008, ¶¶84-86; Ex. 1009, ¶¶124-133; Ex. 1040; Ex. 1065, 10:56-11:6; 24:66-25:24. Although these prior art references did not use recombinantly-expressed heavy and light chains, a POSA would have readily understood that these same techniques could be applied to recombinant heavy and light chains. Ex. 1008, ¶¶85, 88; Ex. 1009, ¶¶134-39.

The ’415 patent does not purport to teach anything new about *in vitro* assembly. *Id.* To the contrary, the specification explicitly states that prior art reconstitution methodologies were followed. Ex. 1001, 13:34-52. Although the ’415 patent experiment failed to follow all of the known steps (*e.g.*, binding and control studies), the steps it did employ were conventional denaturing and

renaturing chemical techniques. Ex. 1008, ¶¶86-88; Ex. 1009, ¶¶142-43; Ex. 1001, 12:58-13:52; 25:8-62.

4. By April 1983, The Limitations Of Hybridoma Technology Were Well-Known

In IPR2016-00383, the Board acknowledged that the specification of the '415 patent states that monoclonal antibodies produced from hybridomas suffer from a number of disadvantages. IPR2016-00383, Institution Decision, 3. Although hybridomas were known to be a reliable source of small quantities of antibody DNA, by April 1983, POSAs were aware of the problems with using hybridoma techniques to produce monoclonal antibodies. Ex. 1008, ¶¶89-97.

Accordingly, researchers recognized prior to April 1983 that recombinant DNA technology provided a far more versatile and superior platform for producing protein therapeutics, including human antibodies. Ex. 1008, ¶¶95-96; Ex. 1009, ¶115. POSAs knew in 1983 that, unlike hybridomas, recombinant DNA technology could be used to create synthetic/recombinant DNA sequences from multiple animal sources to make new and therapeutically-desirable antibody structures, such as chimeric antibodies. *Id*. In fact, Owners previously acknowledged that a "significant need … existed in 1983 for an alternative way to produce antibodies." IPR2016-00383, Preliminary Response, 24-25.

B. Overview Of The Cited Prior Art

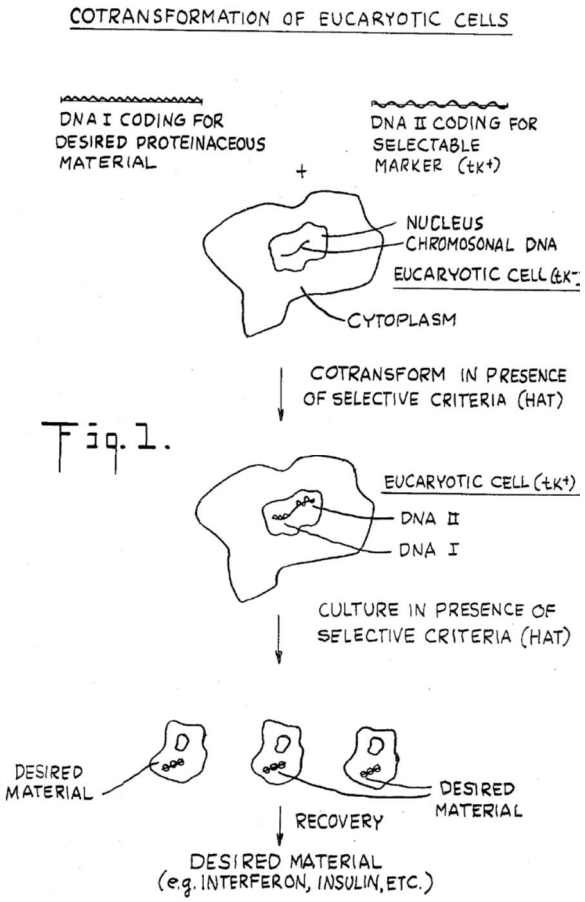
1. The Axel Patent Teaches That Antibodies Can Be Recombinantly Expressed In Eukaryotic Host Cells

The Axel patent (Ex. 1006) was filed on February 25, 1980 and issued on August 16, 1983. It qualifies as prior art under 35 U.S.C. § 102(e). As discussed above in Section II.D.2, the Axel patent was cited during the reexamination in connection with the PTO's double patenting rejections. The Axel patent has never been cited in a rejection under 35 U.S.C. §§ 102 or 103.

The Axel patent describes the efforts of Prof. Wigler and others to develop his co-transformation technique. Ex. 1070, ¶16-17. The patent states that it "relates to processes for inserting DNA into eucaryotic cells, particularly DNA which includes a gene or genes coding for desired proteinaceous materials for which no selective criteria exist." Ex. 1006, Abstract; Ex. 1070, ¶18. The Axel patent teaches that using eukaryotic host cells has a number of advantages over prior prokaryotic platforms, including the "ability to use unaltered genes coding for precursors" of eukaryotic proteins and that these precursors "can be further processed or converted within the eukaryotic cell to produce the desired molecules of biological significance." Ex. 1006, 2:36-41.

The eukaryotic platform described by the Axel patent introduces two DNA sequences into a single host cell, a process the patent refers to as "cotransformation." *Id.*, 4:23-28. The first DNA sequence, referred to as "DNA

I," codes for a "desired proteinaceous material," *i.e.* a protein of interest, while the second DNA sequence, referred to as "DNA II," codes for "a selectable phenotype not expressed by the cell unless acquired by transformation," *i.e*. a selectable marker. *Id.*, 4:64-66; Ex. 1070, ¶21. The co-transformed eukaryotic host cell is grown in conditions "such that the only cells which survive or are otherwise altered are those which have required [*sic*] the selectable phenotype." *Id.*, 4:68-5:2. This then allows the "desired materials" (the protein of interest) to be "recovered from the cells using techniques well known in the art." *Id.*, 6:21-23. Figure 1 of the Axel patent depicts this process:



Id., Fig. 1.

The Axel patent teaches that its co-transformation technique is generally applicable to a variety of eukaryotic proteins. *Id.*, 5:15-23; 6:19-43; Ex. 1070, ¶22. However, the Axel patent identifies seven types of proteins—"interferon protein, insulin, growth hormones, clotting factors, viral antigens, enzymes, and ***antibodies***"—as exemplary and explains that "the genes for [these proteins] may be inserted into and expressed using the cotransformation process." *Id.*, 5:24-28 (emphasis added). With the exception of viral antigens, each of these proteins are complex eukaryotic proteins that share certain characteristics (*e.g.*, they are naturally secreted by eukaryotic cells). Ex. 1008, ¶104; Ex. 1009, ¶71; Ex. 1070, ¶23. Accordingly a POSA would have understood that the Axel patent teaches that antibodies are among a specific and conscribed list of eukaryotic proteins that are particularly well-suited for the general co-transformation technique taught by the Axel patent. *Id.* The Axel patent also claims the production of antibodies using the co-transformation technique. Ex. 1006, claims 7, 23, 29, 37, 52, and 60.

As explained by Petitioner's declarants, a POSA would understand that if "DNA I" codes for "antibodies," as taught by the Axel patent, then "DNA I" would necessarily include the genes for the heavy ***and*** light chains. Ex. 1008, ¶106-107; Ex. 1009, ¶¶77-79; Ex. 1070, ¶¶24-26. Owners argued during the reexamination that a POSA would understand the Axel patent's reference to "antibody" as

meaning the heavy ***or*** light chain, but not both. This interpretation of "antibody" is not supported by any contemporaneous evidence and conflicts with the universally understood meaning of antibody to a POSA in 1983. *Id.* In fact, Owners recently acknowledged that the Axel patent "discloses antibodies as a protein of interest." IPR2016-00383, Preliminary Response, 45 n.11.

The Axel patent is one of the most successful biotechnology patents in history. The techniques it teaches were quickly adopted by the scientific community, as measured by citation trends of the Wigler publications and its use in both academic and industry laboratories. Ex. 1059, 688-89, 697; Ex. 1070, ¶29. Contemporaneous reports recognized the "Wigler method" as providing a universal framework for designing and producing "two or more" complex eukaryotic proteins. *Id.*, 697; Ex. 1058, 933; Ex. 1070, ¶3. Indeed, prior to the filing of the '415 patent, this technique was used to produce complex eukaryotic proteins. Ex. 1036 (producing ovalbumin polypeptide); Ex. 1037 (producing hypoxanthine phosphoribosyltransferase); Ex. 1038 (producing rabbit β-globin). Moreover, the Axel patent family has been widely licensed by the biotechnology industry, generating over $790 million in royalties, and was used to make numerous recombinant antibody drugs, including Humira® (adalimumab), Amevive® (alefacept), Zevalin® (ibritumomab tiuxetan), Enbrel® (etanercept) and Simulect (basiliximab). Ex. 1041, 591-93; Ex. 1059, 700 and Table 1; Ex. 1070, ¶30.

2. The Mulligan Papers Disclose An Improved Vector That Expresses Multiple Genes Of Interest And That Is Useful In A Wide Variety Of Eukaryotic Host Cells

The publication "Expression of a Bacterial Gene in Mammalian Cells" by R.C. Mulligan and P. Berg, Science, 209:1422-27 ("Mulligan 1980," Ex. 1002) was published on September 19, 1980. The publication "Selection for Animal Cells That Express the *Escherichia coli* Gene Coding for Xanthine-Guanine Phosphoribosyltransferase" by R.C. Mulligan and P. Berg, Proc. Natl. Acad. Sci. USA, 78, 4:2072-76 ("Mulligan 1981," Ex. 1003) was published in April 1981. Both Mulligan 1980 and Mulligan 1981 (collectively "the Mulligan Papers") qualify as prior art under 35 U.S.C. § 102(b). The Mulligan Papers were never cited to or considered by the PTO during prosecution or reexamination of the '415 patent.

The Mulligan Papers have the same authors—Dr. Richard Mulligan and Prof. Berg—and both papers cover the same subject matter—the development of an improved vector, the pSV2 vector, that expresses multiple genes of interest and that is useful in a wide variety of eukaryotic host cells. Ex. 1002, 1424.

The Mulligan Papers seek to improve upon the co-transformation technique described in the Axel patent. Ex. 1008, ¶¶71-72. Citing the Wigler publications that form the basis of the Axel patent, Mulligan 1981 explains that "[a] principal shortcoming of present selection systems is the necessity for specific mutant cell

lines as recipients of the transforming DNA." Ex. 1003, 2076 (citing Exs. 1032, 1034-1035 (three Wigler publications)). Mulligan 1981 notes that the "scarcity of such mutants among specialized cell types" limited the usefulness of the method. The Mulligan Papers sought to extend the applicability of the method taught in the Axel patent to a wide variety of eukaryotic host cells through the use of a new type of selectable marker that worked in normal cells. *Id.*

The Mulligan Papers use the *E. coli* gene *Ecogpt* (or *gpt*) as a selectable marker. This gene was chosen because eukaryotic cells lack this gene and thus "*Ecogpt* transformed cells, but not normal cells" will grow in certain conditions. Ex. 1003, 2072. The *Ecogpt* gene was then inserted into the new pSV2 vector, which contains an eukaryotic promoter derived from SV40. Ex. 1002, 1423-24, 1426. The Mulligan authors demonstrated that their new "pSV2-gpt" vector—containing *Ecogpt* as a selective marker—"may be useful for cotransformation of nonselectable genes," *i.e*. genes encoding proteins of interest. Ex. 1003, 2072.

Importantly, the Mulligan authors designed the pSV2 vector so that a single vector could simultaneously express multiple genes of interest: "To accommodate genes of interest, the vectors should contain suitably positioned restriction site for cloning appropriate DNA fragments." Ex. 1002, 1425. Figure of 4 of Mulligan 1980 shows that the pSV2 vector contains three restriction sites suitable for the insertion of genes coding for proteins of interest. *Id*., 1425-26. The Mulligan

Papers expressly teach that a single pSV2 vector can contain multiple genes of interest in addition to the selectable marker:

> [I]t should be emphasized again that pSV2 … contain[s] suitable restriction sites for recombination with ***one or more additional DNA segments***, for example, at the Eco RI, Pst I, and Bam HI site in the segment derived from SV40's late region. Accordingly, appropriately modified ***genes or clusters of genes*** from any source could be co-transduced with *Ecogpt* in acute transfection or by selection for stable *gpt* transformants.

Id., 1427 (emphasis added).

A POSA would understand that the "***additional*** DNA segments" refers to segments in addition to the DNA that encodes the selectable marker. Ex. 1008, ¶¶76-77, 114; Ex. 1009, ¶¶92-93. Thus, a POSA would know that the Mulligan Papers' reference to "one or more additional DNA segments" is teaching the use of a single vector for expression of multiple genes of interest, which necessarily involves the use a single host cell. *Id.*

Likewise, the presence of multiple different restriction sites means that more than one ***different*** gene can be inserted into the pSV2 vector. Ex. 1008, ¶¶113-14; Ex. 1009, ¶¶92-93. 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. Ex. 1008, ¶141; Ex. 1009, ¶153.

A POSA would understand that "genes or clusters of genes" refers to multiple ***different*** genes. Ex. 1008, ¶114; Ex. 1009, ¶¶96-98. In sum, a POSA reading this teaching would understand that the Mulligan Papers are not referring to placing multiple copies of the same gene into the vector, as Owners have argued with reference to other prior art teachings. Ex. 1008, ¶¶, 77, 106; Ex. 1009, ¶¶88-99.

The Mulligan Papers describe foundational technology. Mulligan 1980 has been cited 772 times. Likewise, Mulligan 1981 has been cited 1077 times. Ex. 1008, ¶115. The technology described by the Mulligan Papers has been widely adopted and used to recombinantly express a wide variety of proteins, including antibodies. Exs. 1042-1044. Indeed, prior to April 1983, three different research groups had used the pSV2-gpt vector described in the Mulligan Papers to recombinantly express antibody light chains (Exs. 1017, 1018, 1045), Ex. 1009, ¶¶113, 166, and the pSV2-gpt vector was used to express a complete antibody shortly thereafter. Ex. 1044; Ex. 1008, ¶¶128-134.

3. Prof. Berg's Nobel Article Explicitly Teaches The Expression of Multiple, Different Genes Of Interest From A Single Vector In A Single Host Cell

On December 8, 1980, Prof. Berg delivered his Nobel Lecture after receiving the Nobel Prize in Chemistry. Prof. Berg's Nobel Lecture was published in *Science* on July 17, 1981 ("the Nobel Article," Ex. 1004). The Nobel Article is therefore prior art under 35 U.S.C. § 102(b). The Nobel Article was neither cited to nor considered by the PTO during prosecution or reexamination of the '415 patent.

In his Noble Article, Prof. Berg describes his work developing the pSV2 vector explaining that the pSV2 vector was developed for use "in a variety of mammalian cells." Ex. 1004, 300. He explained that "[a]dditional DNA segments" that can be "inserted into the vector DNA's at any of several unique restriction sites." *Id.* Figure 5 of the Nobel Article identifies these restriction sites. *Id.*, 301; Ex. 1008, ¶¶116-17. Prof. Berg then explained that this design permits the expression of multiple genes of interest from a single pSV2 vector and thus a single host cell: "[C]onsequently, a single DNA molecule ***can transduce several genes of interest simultaneously***." *Id.*, 300 (emphasis added).

A POSA would have understood that the reference to "additional DNA segments" refers to DNA segments other than the selectable marker. Ex. 1008, ¶118. Likewise, a POSA would have understood the phrase "transduce several

genes of interest simultaneously" to be teaching that a single vector could be used to express multiple proteins of interest other than the selectable marker. Ex. 1008, ¶¶117-18; Ex. 1009, ¶¶103-105. A POSA would also understand that this phrase does ***not*** refer to expressing only multiple copies of a single gene, as Owners have argued with regard to other prior art teachings. *Id.* The purpose of having multiple different restriction sites is for introduction of multiple different genes of interest. *Id.*

4. Southern Discloses A Two Vector System With Distinct Selectable Markers

The publication "Transformation of Mammalian Cells to Antibiotic Resistance with a Bacterial Gene Under Control of the SV40 Early Region Promoter" by P.J. Southern and P. Berg, Journal of Molecular and Applied Genetics, 1:327-341 ("Southern," Ex. 1005) was published in July 1982. Therefore, Southern qualifies as prior art under 35 U.S.C. § 102(a). Southern was neither cited to nor considered by the PTO during prosecution or reexamination of the '415 patent.

The Southern paper reflects Prof. Berg's extension of the pSV2 platform described in the Mulligan Papers. Ex. 1009, ¶107. Southern utilizes the same pSV2 vector as was used in the Mulligan Papers but describes a new selectable marker, the bacterial gene *neo*, which allows normal eukaryotic cells to grow in the presence of the antibiotic G418. Ex. 1005, 328. The Southern authors inserted the

neo selectable marker gene into the pSV2 vector. *Id.*, 331. Southern then demonstrates that co-transformation with the *neo* selectable marker confers the expected selectivity and thus "cotransformation with neo as the dominant selection marker provides a way to introduce new genetic information into an extensive range of pro- and eukaryotic cells and organisms." *Id.*, 338.

Southern further demonstrates that the *neo* and *gpt* selectable markers are compatible with one another and thus can be used to insert two vectors into a single host cell: (1) a pSV2-neo vector that uses a *neo* selectable marker, and (2) a pSV2-gpt vector that uses a *gpt* selectable marker. *Id.*, 336-337. After co-transfection, the host cells were grown in conditions that selected for both the *neo* and *gpt* markers. *Id.* Thus, the only cells that survived were those that had been transformed with both vectors. *Id.*

By validating the ability to use two vectors with different selectable markers, the authors explained that the two vector system could be used to express two proteins of interest in a single host cell: "[c]otransformation with nonselectable genes can be accomplished by inserting genes of interest into vector DNAs designed to express *neo* or *gpt*. The schemes used to select for the expression of *gpt* and *neo* are complementary and experiments that exploit the possibilities of a double and dominant selection are now in progress." *Id.*, 339. A POSA would understand that the phrase "double and dominant selection" refers to a single host

cell grown in conditions selecting for both the *gpt* and *neo* markers where only host cells that express both *gpt* and *neo* and therefore contain both vectors will survive. Ex. 1008, ¶¶ 121-123; Ex. 1009, ¶¶109-110.

In a prior IPR, Owners argued that Southern was a work "in progress" and that its technology was still under development. IPR2015-01624, Owners' Response, 52-53. According to Owners, because Southern does not demonstrate the expression of any proteins of interest, it is of limited value. This argument ignores the fact 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. A POSA would understand that simply switching one selectable marker for another, as done in Southern, would not impact the ability of the pSV2 vector to express proteins of interest. Ex. 1008, ¶124; Ex. 1009, ¶111-112.

Indeed, Prof. Berg published a paper in September 1982 disclosing the use of the pSV2-neo vector to express the human interferon β_1 gene. Ex. 1042. Likewise, by April 1983, the pSV2-neo vector described in Southern had been used to recombinantly express immunoglobulin light chains. Exs. 1017-1018, 1045. And, shortly thereafter, two different research groups used the pSV2-neo vector to express the heavy and light chains in a single host cell. Exs. 1043-1044; Ex. 1008, ¶124. One group used a single pSV2-neo vector containing the genes for both the heavy and light chains and the other group used a double transformation

with the pSV2-neo and pSV2-gpt vectors to separately express the heavy and light chains on different vectors in a single host cell, as described in Southern. *Id.*

The technology in the Southern paper has been widely adopted. The Southern paper has been cited 3602 times, and the double transfection technique described in Southern is still used today. Ex. 1009, ¶125.

5. The Builder Patent Discloses Techniques For *In Vitro* Recovery And Reconstitution Of Recombinantly Expressed Proteins

U.S. Patent No. 4,511,502 ("the Builder patent," Ex. 1007) claims priority to an application filed on December 22, 1982 and is therefore prior art under 35 U.S.C. § 102(e). As explained in detail below, the Builder patent was cited during the reexamination of the '415 patent.

The Builder patent is directed to "recovering, in active form, proteins which have been produced in host cells, which are heterologous thereto, and which are at least partially deposited inside the cells as refractile bodies, *i.e*. clumps of insoluble protein." Ex. 1007, 2:3-9. The Builder patent describes a general process for recovering recombinantly-expressed proteins from a host cell (*id.*, 10:49-11:68), denaturing the proteins in a "strongly denaturing" solution (*id.*, 12:63-14:66) and then renaturing the proteins in a "weakly denaturing" solution (*id.*, 15:68-18:44).

During reexamination, the PTO cited the Builder patent as "teach[ing] a procedure for recovering, solubilizing and refolding" insoluble proteins found in

inclusion bodies. Ex. 1019, 10. Owners never disputed this characterization. Ex. 1011, 48-49.

C. Near Simultaneous Invention Of The Claimed Invention By Three Research Groups Working Independently

Simultaneous invention by others working independently weighs in favor of a finding of obviousness. *See* Section VI.F. Here, three separate groups—each unaffiliated with Owners and working independently—developed the claimed subject matter of the '415 patent within a span of less than six months. Ex. 1008, ¶¶128-134; Ex. 1009, ¶166. Each of these groups also performed their work before publication of Owners' work. *Id.*

Two of the groups directly followed the teaching of Prof. Berg to express different genes of interest from a single host cell. Those two groups utilized Prof. Berg's pSV2 vector to express both the heavy and light chains in a single host cell. First, on July 11, 1983, approximately three months after the '415 patent's priority date, a research group led by Atsuro Ochi and Marc Shulman communicated a paper (the "Ochi II paper") describing the same subject matter as claimed in the '415 patent. Citing Southern, the Ochi II paper describes inserting the DNA sequences for both the heavy and light chains in a single pSV2 vector and then expressing heavy and light chains in a single host cell. Ex. 1043, 6351-52; Ex. 1008, ¶129.

Second, a research group headed by Leonard Herzenberg obtained U.S. Patent No. 5,807,715 ("the Morrison patent"), which describes the production of functional immunoglobulins by transforming a single host cell with two different pSV2 vectors, one having DNA encoding the immunoglobulin heavy chain and the other having DNA encoding the immunoglobulin light chain. Ex. 1044, 8:20-67. The Morrison patent uses the pSV2-neo and pSV2-gpt vectors in a double transformation in single host cell as described in Southern. *Id.*; Ex. 1008, ¶¶130-32.

The Morrison patent claims priority to an application filed on August 27, 1984; however, during prosecution, the pending claims were rejected based on the Ochi II paper. The Morrison inventors swore behind Ochi II by submitting Rule 131 affidavits establishing that they invented the subject matter of the Morrison patent ***before*** Ochi II's October 1983 publication date. Exs. 1046-1047. The PTO accepted these Rule 131 affidavits and withdrew the rejection based on the Ochi paper. Ex. 1048. Thus, the Morrison inventors also developed the subject matter of the '415 patent within six months of the filing of the '415 patent and before the subject matter of the '415 patent was made public. Ex. 1008, ¶131.

Third, Celltech, Ltd. independently developed the subject matter of the '415 patent. This work resulted in the Boss patent (Ex. 1049), which claims priority to a UK patent application filed several weeks prior to the filing date of the '415 patent.

Ex. 1008, ¶133. As noted above, the '415 patent was involved in a patent interference proceeding with the Boss patent to address Celltech's independent and near simultaneous development of the subject matter of the '415 patent.

In addition to considerations regarding obviousness, the near simultaneous invention by three separate and independent groups (other than Owners) further evidences that there was no "prevailing mindset" that only one protein of interest should be expressed per host cell. The fact that three separate groups each used a single host cell to co-express both the heavy and light chains demonstrates that it was well known in April 1983 that a single host cell was the preferred choice for producing the heavy and light chains of an immunoglobulin. Ex. 1008, ¶134.

VI. EXPLANATION OF GROUNDS OF UNPATENTABILITY (37 C.F.R. § 42.104(b)(4))

A. Ground 1: The Mulligan Papers Combined With The Axel Patent Render Claims 1, 3-4, 11-12, 14-17, 19, And 33 Of The '415 Patent Obvious

Claims 1, 3-4, 11-12, 14-17, 19, and 33 are invalid as obvious based on the combination of the Mulligan Papers and the Axel patent. Among the claims at issue in this ground, claims 1, 15, and 33 are independent. Claims 1 and 33 are directed to a method for producing "an immunoglobulin molecule" in which DNA encoding both the heavy chain and light chain is transformed into a single host cell and then "independently express[ed]." Claims 1 and 33 are agnostic as to whether the DNA encoding the heavy and light chains is on one vector or two; however,

dependent claim 3 requires the use of a single vector that contains the DNA coding for the heavy and light chains. Independent claim 15 is directed to a single vector containing DNA that encodes both the heavy and light chains and that the DNA encoding the heavy and light chains are located at different insertion sites. Dependent claims 17 requires a host cell that is transformed with this vector.

The disclosure of the Mulligan Papers combined with the Axel patent renders the subject matter of claims 1, 3-4, 11-12, 14-17, 19, and 33 obvious. As discussed above, the Axel patent teaches the co-transformation and co-expression of genes coding for eukaryotic proteins in a eukaryotic host cell. Section V.B.1. The Axel patent explicitly teaches and claims that "antibodies" are among the eukaryotic proteins that can be made using the Axel patent's recombinant DNA methods. Ex. 1006, 2:32-36, 3:31-36, 5:24-28. Owners have argued that the Axel patent does not disclose expressing multiple genes of interest, *i.e*. the heavy ***and*** light chains, from a single vector. Ex. 1023, 6-8. These arguments are directly contradicted by the disclosure of the Axel patent because the teaching that "DNA I" can encode an "antibody" means that DNA I can encode both the heavy and light chains. Ex. 1008, ¶¶104-05; Ex. 1009, ¶¶81-83; Ex. 1070, ¶¶24-26.

In any event, the Mulligan Papers explicitly teach expressing multiple genes of interest on a single vector. The Mulligan Papers improve upon and extend the recombinant DNA techniques of the Axel patent to co-express multiple proteins of

interest in a single host cell. Citing to the work of the Axel inventors, the Mulligan authors explain that their intent was to expand the variety of host cells. Ex. 1003, 2072. To accomplish this goal, the Mulligan Papers describe a new selectable marker, *Ecogpt*, which can be used in a wide variety of eukaryotic host cells. *Id.*

The Mulligan Papers explicitly teach independent expression of multiple proteins of interest other than the selectable marker from a single vector: "In this regard it should be emphasized again that [the] pSV2 … vector[] contain[s] suitable restriction sites for recombination with one or more additional DNA segments." Ex. 1002, 1427. A POSA would recognize that these expression platforms were designed to independently express multiple, different proteins of interest from a single vector in a single host cell. Ex. 1008, ¶¶113-114, 139-141; Ex. 1009, ¶¶92-94.

Finally, once the heavy and light chains were expressed using recombinant DNA techniques, a POSA would have known how to recover and assemble the heavy and light chains using *in vitro* reassembly techniques to form "an immunoglobulin molecule," as required by claims 1 and 33. Ex. 1009, ¶¶123-133, 150. The Axel patent teaches that the proteins expressed using its co-transformation technique "may be recovered … using well known techniques." Ex. 1006, 6:26-27. As discussed above, those techniques were well known in the prior art. Finally, the '415 patent admits that these *in vitro* assembly techniques

were known in the art (Ex. 1001, 13:1-52) and "[a]dmissions in the specification regarding the prior art are binding on the patentee for purposes of a later inquiry into obviousness." *Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007).

There are numerous reasons why a POSA would have been motivated to combine the teaching of the Mulligan Papers and the Axel patent. Ex. 1008, ¶¶143-46; Ex. 1009, ¶¶114-121, 152-53. The first is simple common sense. *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1161 (Fed. Cir. 2007) (emphasizing that "the common sense of those skilled in the art" can be sufficient to "demonstrate[] why some combinations would have been obvious where others would not"). Both the Mulligan Papers and the Axel patent are directed to the same field. A POSA would know that the Mulligan Papers' teaching of an improved expression vector that can be used to stably integrate any number of genes into a eukaryotic host cell would be readily applicable to the Axel patent, which teaches a process of making antibodies through the stable integration of exogenous genes into a eukaryotic host cell. Ex. 1008, ¶¶144-45. Indeed, it would be a natural segue to apply the improvements of the Mulligan Papers to the teachings of the Axel patent. Ex. 1009, ¶94.

Second, the market forces provided a motivation to make therapeutic antibodies and recombinant DNA technology was the most viable option for

making such products. Ex. 1008, ¶¶96, 145; Ex. 1009, ¶115; Ex. 1001, 2:20-39; *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007) ("When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one.").

Third, the Mulligan papers extend the work of the Axel patent from mutant eukaryotic host cells to practically any type of host cell. The Mulligan Papers cite to the work which forms the basis of the Axel patent and state they improve upon the "principal shortcoming of present selection systems" by using a selectable marker that can be used in normal cells. Ex. 1003, 2076; *In re Kemps*, 97 F.3d 1427, 1430 (Fed. Cir. 1996) (finding it obvious to combine teachings of prior art to achieve claimed invention where one reference specifically refers to the other). Mulligan noted that Axel's limitations impeded "a variety of potentially interesting experiments." *Id.* Thus, a POSA would have understood that the teachings in the Mulligan Papers were to be applied the same type of "desired proteinaceous materials" identified in the Axel patent, including antibodies. A POSA would have been motivated to use the improved vector and selectable marker from the Mulligan papers to make the proteins described in the Axel patent, in particular antibodies. Ex. 1008, ¶¶144-45.

Consequently, common sense, the explicit teachings of the Axel patent and the Mulligan Papers, and the huge incentive to make therapeutic antibodies would

have led a person of ordinary skill in the art to use the pSV2 vector described in the Mulligan Papers to make antibodies in a single host cell. Ex. 1008, ¶¶143-45; Ex. 1009, ¶¶115, 152-53.

In the alternative, the subject matter of those claims are also obvious in based on the teachings of the Mulligan Papers and Axel because there was "market pressure to solve a problem and there [were] a finite number of identified, predictable solutions" for making monoclonal antibodies such that it would have been "obvious to try" making a recombinant antibody in a single host cell. *KSR*, 550 U.S. at 421. As discussed above, and as admitted in the Background section of the '415 patent specification, there was significant market demand for monoclonal antibodies for diagnostic and therapeutic purposes. Ex. 1001, 2:20-39. However, in 1983 the limitations of hybridomas for making such antibodies was known to a POSA. Ex. 1001, 2:40-66; Ex. 1008, ¶¶89-96; 146. This fact, combined with the Axel patent's explicit teaching that antibodies can be made using recombinant DNA techniques, would have motivated a POSA to use recombinant DNA technology to make antibodies. Ex. 1008, ¶¶95-96; Ex. 1009, ¶115.

Moreover, there were only three options for recombinantly expressing the heavy and light chains. Ex. 1008, ¶146; Ex. 1009, ¶¶41-42. Given the explicit teaching in the Mulligan Papers that multiple proteins of interest can be expressed from a single vector, it would been obvious to try the two-chains-in-one-vector

approach among the finite number of options available. Likewise, the combination of the Axel patent with Southern (Ground 4) would have made the two-vectors-in-one-cell approach obvious to try. Moreover, a POSA would have been additionally guided to these two "single cell" options, over the third, "separate cells" option, because it mimics the efficiency of nature and offers many practical advantages. Ex. 1008, ¶75; Ex. 1009, ¶¶117, 157 ("nature is the best teacher"), 179.

In addition, a POSA would have had a reasonable expectation that using a single pSV2-gpt vector as described in the Mulligan Papers to express both the heavy and light chains would be successful. Ex. 1008, ¶¶147-151; Ex. 1009, ¶¶154-55. Prior to April 1983, the techniques for co-transforming recombinant DNA genes and expressing multiple proteins had been well established. Indeed prior to April 1983, the pSV2 vector described in the Mulligan Papers had already been used to express eukaryotic proteins in eukaryotic host cells, including immunoglobulin light chains, and subsequent studies published shortly after April 1983 showed that POSAs used the pSV2 vector to express the heavy and light chains in a single host cell. Exs. 1017-1018, 1045.

Owners have previously argued that the size and complexity of the immunoglobulin molecule—a tetramer of approximately 150,000 Daltons—means that a POSA would not have had a reasonable expectation of successfully

expressing and reassembling the heavy and light chains in a single host cell. IPR2015-01624, Owners' Response, 10, 49-50. These arguments lack merit in view of the evidence that, before April 1983, proteins larger and more complex than an immunoglobulin had been successfully expressed using recombinant DNA techniques. Ex. 1008, ¶¶150-51; Ex. 1009, ¶¶156-58.

For example, a 1982 publication reported the co-transformation of two genes, *pyrB* and *pyrI*, in a single host cell using a single vector and the resulting expression of a multimeric protein. Ex. 1050 (explaining that *pyrB* and *pyrI* encode the multimeric protein ATCase, which is over twice as large as an immunoglobulin molecule (310,000 Daltons versus 150,000 Daltons) and has twelve subunits, not four). Ex. 1008, ¶¶80. Other prior art publications also reported co-expression of both protein chains to form the multimeric protein from a "two-gene-one-vector" construct. Exs. 1051-1054. Indeed, as explained by Profs. Lerner and Kornberg, it was widely thought in April 1983 that virtually any protein no matter how large or complex could be expressed using recombinant DNA technology. Ex. 1008, ¶151; Ex. 1009, ¶156. Thus, a POSA in April 1983 would not have been deterred by the size and complexity of an immunoglobulin and would have been motivated to apply the known art to target antibodies for recombinant production. *Id.*

A POSA would also have a reasonable expectation of success in recovering and assembling the heavy and light chains *in vitro* using well-established techniques. Ex. 1009, ¶¶150-51, 164-65. Owners have argued in the past that a POSA would not have reasonably expected to be able to assemble the heavy and light chains *in vivo*. However, setting aside the fact that the '415 patent provides no guidance whatsoever on *in vivo* assembly, Owners do not dispute that the Challenged Claims all cover assembly by any means, including *in vitro* assembly, which was well-known in the art. Ex. 1011, 46; Ex. 1012, 29, n.8.

Dependent claim 3 requires that the first and second DNA sequences are present in a single vector and dependent claim 4 requires that the vector be a plasmid.[4] Dependent claim 16 similarly requires that the vector be a plasmid. The pSV2-gpt vector described in the Mulligan Paper is a plasmid (Ex. 1003, 2073), as is the expression vector described in the Axel patent. Ex. 1006, 5:51-54; Ex. 1008, ¶152. Thus, the subject matter of claims 3, 4, and 16 is obvious for the reasons discussed above.

Dependent claims 11, 12, and 14 each depend from claim 1 and require, respectively, that the DNA sequences code for the complete heavy and light chains, that the DNA sequence coding for the constant region of the heavy or light

[4] The '415 patent states that "'plasmid' and 'expression vector' are often used interchangeably." Ex. 1001, 8:21-22.

chain be derived from the same source as the variable domain to which it is attached, and that the DNA sequences for the heavy and light chains are derived from one or more hybridomas. Ex. 1001, 29:6-21. The additional subject matter of each of these claims would have been obvious to a POSA in April 1983. The techniques for recovering mRNA and converting it into cDNA were well known in the prior art. Most notably, they are described in detail in Prof. Maniatis' well-known laboratory manual. Ex. 1055, Chapters 6-7.

A POSA seeking to recombinantly express an "antibody" as described by the Axel patent would have used these standard lab techniques to produce cDNA for the full length heavy and light chains. Ex. 1008, ¶153; Ex. 1009, ¶¶161-62. In addition, a POSA would understand that using these standard cloning techniques would result in the constant domain of both the heavy and lights chains being derived from the same source as the variable domains. *Id.* Finally, using hybridomas as a source of DNA for monoclonal antibodies would have been obvious to a POSA. *Id.* In 1983, hybridomas were a known source of monoclonal antibodies and several prior art references describe recovering mRNA encoding the heavy and light chains from hybridomas. Exs. 1056-1057. Converting this hybridoma mRNA into cDNA would have been routine in April 1983. Ex. 1008, ¶153; Ex. 1009, ¶¶161-62; Ex. 1057.

Dependent claim 19 requires that the host be a mammalian cell. Both the Axel patent, which focuses on CHO cells, and the Mulligan Papers, which use mouse 3T6 cells, disclose this limitation. Ex. 1006, 5:3-14; Ex. 1003, 2072, 2074.

B. Ground 2: The Mulligan Papers Combined With the Axel Patent In Further View Of The Nobel Article Render Claims 1, 3-4, 11-12, 14-17, 19, And 33 Of The '415 Patent Obvious

As described above, Prof. Berg's Nobel Article provides an additional explicit teaching that more than one different protein of interest could be expressed on a single vector in a single host cell. Section V.B.3. The Nobel Article disproves Owners' argument that the "prevailing mindset" in April 1983 was that only one protein of interest could be expressed per host cell.

Claims 1, 3-4, 11-12, 14-17, 19, and 33 of the '415 patent would therefore be obvious based on the combination of the Mulligan Papers in combination with the Axel patent in further view of the Nobel Article. All of the rationales described in Ground 1 are applicable to this ground with the additional teaching from the Nobel Article that two or more different proteins of interest could be expressed in a single host cell.

Common sense and the explicit teachings of the references would have led a POSA to combine the Nobel Article with the Mulligan Papers and the Axel patent because the 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, which, as noted above, was designed to extend the usefulness of the Axel patent's techniques. Ex. 1008, ¶¶158-159; Ex. 1009, ¶¶170. The Nobel Article explicitly teaches that the pSV2 vector can be used to express more than one protein of interest in a single host cell, and a POSA would have known that a multimeric protein, such as an immunoglobulin, would be particularly well-suited co-expression in a single host cell. *Id.*

The source of the teaching—the Nobel Prize acceptance speech related to the technology at issue here—would have provided strong motivation to proceed as Prof. Berg suggested when producing antibodies by these recombinant DNA techniques invented by Prof. Berg. Indeed, as discussed in Section V.C, researchers did exactly that using Prof. Berg's pSV2 vector.

C. Ground 3: The Mulligan Papers Combined With The Axel Patent In Further View Of The Builder Patent Render Claims 1, 3-4, 11-12, 14-17, 19, And 33 Of The '415 Patent Obvious

Although the '415 patent admits that the techniques for *in vitro* recovery and assembly of the heavy and light chains were known in the prior art, Owners have previously alleged that the assembly step of the Challenged Claims is non-obvious. Ex. 1011, 46; Ex. 1012, 29, n.8. To the extent the Axel patent's teaching to use "well known techniques" to recover the heavy and light chains is deemed insufficient (Ex. 1006, 6:26-27), claims 1, 3-4, 11-12, 14-17, 19, and 33 are

obvious based on the combination of the Mulligan Papers and the Axel patent in further view of the Builder patent.

As discussed above, the Builder patent teaches a general method for recovering recombinantly-expressed proteins from a host cell and assembling them *in vitro*. Ex. 1007, 2:3-14. The Builder patent describes the steps needed to recover an inclusion body from a host cell (*id.*, 10:49-11:68), denature the proteins recovered from the inclusion body (*id.*, 12:63-14:66), and renature the proteins (*id.*, 15:68-18:44). A POSA following these standard techniques would be able to recover and reassemble the heavy and light chains *in vitro*. Ex. 1009, ¶172.

A POSA would have been motivated to combine the Builder patent with the teachings of the Mulligan Papers and the Axel patent because the Builder patent explicitly states that it is directed to a general method of recovering recombinantly-expressed proteins. Recovering and assembling a recombinantly-expressed protein from an inclusion body is necessary before the protein can be used. A POSA would look at general methods, *e.g.* those described by the Builder patent, to recover and assemble *in vitro* the heavy and light chains. Ex. 1008, ¶¶162-63; Ex. 1009, ¶¶173-74. Likewise, a POSA would have had a reasonable expectation of success in applying the techniques of the Builder patent to assemble the heavy and light chains because it was well known that the steps for recovery and assembly of

proteins does not depend on the type of protein that is expressed and instead are generally applicable to any type of protein. *Id*.

D. Ground 4: Southern Combined With The Axel Patent Render Claims 1-2, 11-12, 14, 18-20 And 33 Of The '415 Patent Obvious

Claims 1-2, 11-12, 14, 18-20 and 33 are invalid as obvious based on the combination of Southern and the Axel patent. Among the claims at issue in this ground, claims 1, 18, and 33 are independent. As discussed above, claims 1 and 33 cover the use of both a single vector or two different vectors to make "an immunoglobulin molecule or an immunologically functional immunoglobulin fragment." Dependent claim 2 requires the use of two different vectors. Claim 18 is directed to a "transformed host cell" containing two vectors, one having DNA encoding the heavy chain and the second vector having DNA encoding the light chain.

The Axel patent is directed to a general method of using recombinant DNA techniques to express eukaryotic proteins in a single eukaryotic host cell. Ex. 1006, 3:20-42. The Axel patent explicitly identifies antibodies as one type of eukaryotic protein that can be expressed using the recombinant techniques of the Axel patent. *Id.*, 2:32-36, 3:31-36, 5:24-28. Likewise, Southern is directed to the same field of endeavor as the Axel patent—using recombinant DNA techniques to express eukaryotic proteins in eukaryotic cells. Ex. 1005, 327; Ex. 1008, ¶170.

Indeed, like the Mulligan Papers, Southern cites to the work of the inventors of the Axel patent and seeks to expand upon it. Ex. 1005, at 329.

In particular, 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. *Id.*, 336-337. The dual vector approach is a direct and efficient way to independently express both the heavy and light chains in a single host cell. As shown in Southern, the different proteins can be identified by growing the doubly transformed host cells in media that selects for both selectable markers. *Id.*; Ex. 1008, ¶¶123-124, 166; Ex. 1009, ¶¶177. The technique taught by Southern ensures that the heavy and light chains are independently expressed because the DNA encoding the heavy and light chains are on different vectors under the control of separate promoters. *Id*.

Finally, as discussed above in Ground 1, once the heavy and light chains were expressed using recombinant DNA techniques, the steps for reconstituting the heavy and light chains into a functional immunoglobulin were known in the art. Ex. 1009, ¶178. Indeed, the '415 patent admits these techniques were known in the art. Ex. 1001, 13:1-52.

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. Ex. 1008, ¶¶168-170; Ex. 1009, ¶¶179-80. First, is common sense. Southern discloses a two vector approach that is particularly well-suited to expressing more than one protein of interest in a single host cell. A POSA would have recognized that Southern's two vector approach was particularly well-suited for a multimeric protein such as an immunoglobulin. Ex. 1008, ¶168. Second, there was a strong market demand for therapeutic antibodies. Ex. 1008, ¶169. Third, both references relate to the same field of endeavor, and Southern cites to the work of the Axel inventors, stating that it is attempting to improve upon the method disclosed in the Axel patent. Ex. 1005, 327. A POSA would have therefore readily recognized that the platform taught in Southern is compatible with the teachings of the Axel patent and that Southern's platform should be used for the same type of "desired proteinaceous materials" identified in the Axel patent, including antibodies. Ex. 1008, ¶170; Ex. 1009, ¶180.

Likewise, a POSA would have reasonably expected that using two vectors to express the heavy and light chains in a single host cell would have been successful. Ex. 1008, ¶171; Ex. 1009, ¶181. By April 1983, the co-transformation and co-expression techniques described in both the Axel patent and Southern had been used to produce eukaryotic proteins. Exs. 1036-1038, 1042-1044. A POSA would have known that the heavy and light chains could similarly be recombinantly expressed. Ex. 1008, ¶171. Indeed, the pSV2-neo and pSV2-gpt vectors described

in Southern had already been used to express a light chain in a eukaryotic host cell (Exs. 1017-1018, 1045) and subsequent studies published shortly after April 1983 showed that the double vector system of Southern—a pSV2-gpt vector and a pSV2-neo vector—could be used to express the heavy and light chains in a single host cell. Ex. 1043-1044.

For the same reasons discussed in Ground 1, the limitations of claims 11-12 and 14 would have been obvious to a POSA seeking to recombinantly express an "antibody" as described in the Axel patent. Ex. 1008, ¶172.

Finally, the limitation of claims 19 and 20 is disclosed in both the Axel patent, which focuses on CHO cells as the preferred host cell, and Southern, which uses mouse 3T6 cells. Ex. 1008, ¶173.

E. Ground 5: Southern Combined With The Axel Patent In Further View Of The Builder Patent Render Claims 1-2, 11-12, 14, 18-20 And 33 Of The '415 Patent Obvious

As noted above in Ground 3, the Builder patent describes a general method for the recovery and assembly of recombinantly-expressed proteins *in vitro*. Ex. 1007, 2:3-14. 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 to recover and assemble the heavy and light chains, thereby rendering claims 1-2, 11-12, 14, 18-20, and 33 obvious. Ex. 1008, ¶174; Ex. 1009, ¶¶184-87.

F. The Near Simultaneous Invention Of The Claimed Subject Matter By Three Separate Research Groups Supports A Finding Of Obviousness

Each of the above Grounds is further bolstered by the near simultaneous invention subject matter of the '415 patent by three other research groups. The Federal Circuit has recognized that "[i]ndependently made, simultaneous inventions, made 'within a comparatively short space of time,' are persuasive evidence that the claimed apparatus 'was the product only of ordinary mechanical or engineering skill.'" *Geo M Martin Co. v. All Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010); *see also Ecolochem, Inc. v. Southern Cal. Edison Co*., 227 F.3d 1361, 1389 (Fed. Cir. 2000). In *Martin*, the Federal Circuit found that an independent invention made over a year after the patentee was "strong evidence" of obviousness. 618 F.3d at 1305-06.

As discussed in Section V.C, at least three separate research groups worked independently to arrived at the claimed subject matter within six months of each other. Significantly, two of these groups expressly followed the teachings of Prof. Berg, using his pSV2 vector to express multiple proteins of interest (the heavy and light chains) in a single host cell. The fact that multiple groups each independently arrived at the claimed invention is a strong indicator that the subject matter of the '415 patent was obvious as of April 1983.

G. Secondary Considerations Do Not Support A Finding Of Non-Obviousness

At this stage of these proceedings, Petitioner has no burden to identify and rebut secondary considerations. Rather, Owners must first present a *prima facie* case for such consideration, which Petition should then have the chance to rebut. *Sega of Am., Inc. v. Uniloc USA, Inc.*, IPR2015-01453, 2015 WL 1090311, at *10 (PTAB Mar. 10, 2015). For that reason, the Board typically rejects arguments against institution based on objective indicia, so that the Petitioner can have a fair opportunity to address any secondary indicia evidence on reply. *See, e.g.*, *Petroleum Geo-Services Inc. v. WesternGeco LLC*, IPR2015-01478, 2015 WL 1276718, at *22 (PTAB Mar. 17, 2015).

Nonetheless, Owners have argued in prior proceedings that secondary considerations support a finding of non-obviousness. In IPR2015-01624, Owners relied upon three secondary considerations to support their non-obviousness arguments: licensing by others, commercial success, and skepticism of others. IPR2015-01624, Owners' Response, 60-63. None of these secondary considerations supports a finding of non-obviousness.

1. Licensing Does Not Support Non-Obviousness

Owners' attempts to rely on licenses to the '415 patent are flawed. The Federal Circuit has noted that licenses are sometimes taken "because of business judgments that it is cheaper to take licenses than to defend infringement suits, or

for other reasons unrelated to the unobviousness of the licensed subject matter." *EWP Corp. v. Reliance Universal, Inc.*, 755 F.2d 898, 907-908 (Fed. Cir. 1985). Accordingly, Owners must establish nexus between the merits of the claimed invention and the licenses. *Iron Grip Barbell Co. v. USA Sports, Inc., 392 F.3d* 1317, 1324 (Fed. Cir. 2004).

Owner have not provided copies of the licenses, let alone shown that the licenses demonstrate alleged "widespread recognition of the patent as a groundbreaking invention." IPR2015-01624, Owners' Response, 61. The '415 patent has been involved in six lawsuits challenging its validity. In each case, Owners settled rather than have the validity of the '415 patent adjudicated. If Owners granted licenses to settle litigations at substantially lower rates than its non-litigation licenses, this would indicate that Owners' licensing revenues are not tied to the merits of the claimed invention.

2. Commercial Success Does Not Support Non-Obviousness

Owners reliance upon the commercial success of its licensees' products is similarly flawed. The Federal Circuit has recognized that "[t]he commercial success of a product can have many causes unrelated to patentable inventiveness." *Ritchie v. Vast Res., Inc.*, 563 F.3d 1334, 1336 (Fed. Cir. 2009). To make the required showing of a nexus, "[t]here must be proof that the sales were a direct result of the unique characteristics of the claimed invention—as opposed to other

economic and commercial factors unrelated to the quality of the patented subject matter." *In re Applied Materials, Inc*., 692 F.3d 1289, 1299-1300 (Fed. Cir. 2012).

Each of the products that Owners rely upon for commercial success is the result of years of independent scientific and clinical development by Owners' licensees. Owners have presented no evidence that the sales of these products was a direct result of the invention of the '415 patent as opposed to, for example, the innovation of the licensee, the therapeutic effects of these products, or the result of other patents covering those products.

3. There Was No Skepticism That Antibodies Could Be Produced Recombinantly

Owners have relied on alleged skepticism in past proceedings. However, in April 1983, there was no skepticism that the heavy and light chains could be co-expressed in a single host cell. Lack of skepticism is demonstrated by, among other things, the near simultaneous invention by three research groups working separately from Owners. *See* Section VI.F. Moreover, Owners' skepticism evidence relates almost entirely to whether the heavy and light chains could be assembled *in vivo* once expressed in the host cell. As discussed above, the claims at issue here do not require such *in vivo* assembly.

H. This Petition Is Not Duplicative Of Other IPRs Or Of Previous Arguments Presented During Prosecution

35 U.S.C. § 325(d) permits the Board to consider whether "the same or substantially the same prior art or arguments previously were presented to the Office." The Board's assessment is discretionary and has typically involved a consideration of whether the same prior art or arguments were presented to the PTO in a prior petition such that they raise identical or substantially identical patentability grounds. *HTC Corp. v. NFC Tech., LLC*, IPR2015-00384, Paper 11 at 9-11.

Here, there are no such concerns. The grounds presented in this petition are neither identical nor substantially similar to any ground that has previously been presented, during prosecution, reexamination, or in an IPR petition. Neither the Mulligan Papers nor Prof. Berg's Nobel Article have ever been cited to the PTO with respect to the '415 patent. As explained above, those references directly refute Owners' arguments that the prior art "contains no suggestion to co-express multiple eukaryotic proteins of interest in a single host cell." IPR2015-01624, Owners' Response, 37, n.5.

One reference cited in this petition, Southern, was cited in IPR2015-01624 and IPR2016-00383. However, Southern is being combined with different art in this petition and overcomes the deficiencies alleged by Owners for the combinations with Southern in those proceedings. Specifically, Owners criticized

the invalidity arguments in IPR2015-01624 because Southern was being combined with references that relate to prokaryotic host cells. *Id.* at 53-54. This petition does not suffer from these alleged infirmities and presents grounds that combine Southern with other references directed to eukaryotic host cells. Similarly, in IPR2016-00383, the Board denied institution because Southern did not overcome the deficiency in the primary reference, Salser, which failed to teach anything about antibodies. Here, Southern is being combined with the Axel patent, which unlike Salser, explicitly teaches that antibodies can be made using recombinant DNA techniques. Moreover, Southern is an extension of Prof. Berg's work reflected in the Mulligan Papers and the Nobel Article. Evaluating Southern in the context of these other related references provides important context that was not presented in prior proceedings and refutes Owners' arguments that Southern was a work in progress.

Beyond the significant differences between the prior art references presented in this petition and IPR2015-01624, Petitioner's experts are uniquely qualified to opine upon the state of the art in April 1983. Prof. Kornberg is a Nobel Laureate who specializes in protein chemistry and is an expert in protein expression and assembly. By 1983, he had been practicing in the field for several years. Prof. Lerner has devoted his career to the study of antibodies and has contributed to many key advances in the field. In 1983, he was Chairman of the Department of

Molecular Biology at the Scripps Research Institute. The opinions and judgment of these experts regarding the invalidity of the '415 patent claims in view of the prior art and their years of experience in the field presents substantial new questions of unpatentability for obviousness that are sufficient to justify institution of this petition.

The only other reference in Petitioner's grounds that was substantively discussed by the PTO in prior proceedings is the Axel patent, which was cited during the reexamination. Petitioner's reliance on the Axel patent here substantially differs from the arguments in the reexamination for a number of reasons.

First, as discussed above, Owners overcame the ODP rejections based on Axel based on their argument that the Examiner ***must*** accept the arguments presented in Owners' one-sided expert declarations. This is an important and appropriate factor to take into account when deciding whether to institute this Petition. The Board has previously recognized that "the *ex parte* nature of the reexaminations differs from the adversarial nature of an [IPR]" and instituted an IPR based on a prior art reference that had been previously presented during a reexamination proceeding *Microsoft Corp. v. Parallel Networks Licensing, LLC,* IPR2015-00483, Paper 10 at 15 (Jul. 15, 2015); *see also Research in Motion Corp. v. WI-LAN USA, Inc.*, IPR2013-00126, 2013 WL 8563788, at *11 (PTAB June 20,

2013) (instituting IPR based on prior art that had been considered during prosecution); *Conopco, Inc. v. Procter & Gamble Co.,* IPR2013-00505, 2014 WL 1253037, at *4 (PTAB Feb. 12, 2014) (same).

Second, this Petition relies on Axel in connection with a different legal ground of invalidity than the reexamination. In the reexamination, the Axel patent was exclusively relied on in connection with the PTO's ODP rejections. In contrast, this petition relies on Axel as part of an obvious argument under 35 U.S.C. § 103. The legal standards for these two inquiries are different. *Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1377 n.1 (Fed. Cir. 2003). The significant differences in legal standards combined with the different prior art combinations presented in this Petition demonstrate that its reliance on the Axel patent is not duplicative of PTO's consideration of Axel during reexamination.

VII. MANDATORY NOTICES (37 C.F.R. § 42.8)

A. Real Party-In-Interest Under 37 C.F.R. § 42.8(b)(1)

Pursuant to 37 C.F.R. § 42.8(b)(1), Petitioner certifies that Merck Sharp & Dohme Corp. is the real party-in-interest.

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

Pursuant to 37 C.F.R. § 42.8(b)(2), Petitioner states that four IPR petitions for the '415 patent have been filed: IPR2015-01624, IPR2016-00383, IPR2016-00460, IPR2016-00710. IPR2015-01624 was instituted by the Board on February 5, 2016 and remains pending. IPR2016-00460 was instituted and joined with IPR2015-01624

by the Board on June 8, 2016 and remains pending. IPR2016-00383 was denied institution by the Board on June 23, 2016. The Board has not issued an institution decision on IPR2016-00710, which remains pending.

C. Lead and BackUp Counsel and Service Information Under 37 C.F.R. § 42.8(b)(3)-(4)

Petitioner hereby designates lead and backup counsel as follows:

Lead Counsel	Backup Counsel
Raymond N. Nimrod (Reg. No. 31,987) QUINN EMANUEL URQUHART & SULLIVAN, LLP 51 Madison Ave., 22nd Floor New York, NY 10010 General Tel: (212) 849-7000 Direct Tel: (212) 849-7412 Fax: (212) 849-7100 raynimrod@quinnemanuel.com	Matthew A. Traupman (Reg. No. 50,832) QUINN EMANUEL URQUHART & SULLIVAN, LLP 51 Madison Ave., 22nd Floor New York, NY 10010 General Tel: (212) 849-7000 Direct Tel: (212) 849-7322 Fax: (212) 849-7100 matthewtraupman@quinnemanuel.com Katherine A. Helm (*pro hac vice* to be filed) SIMPSON THACHER & BARTLETT LLP 425 Lexington Avenue New York, NY 10017 General Tel: (212) 455-2000 Direct Tel: (212) 455-3647 Facsimile: (212) 455-2502 khelm@stblaw.com

Pursuant to 37 C.F.R. § 42.10(b), a Power of Attorney has been filed herewith. Petitioner consents to electronic service at the email addresses above. Petitioners will request authorization to file a motion for Katherine A. Helm to appear *pro hac vice*. Dr. Helm is an experienced attorney and has an established familiarity with the

subject matter at issue in this proceeding. Petitioners intend to file a motion seeking the admission of Katherine A. Helm to appear *pro hac vice* when authorized to do so.

VIII. IPR REQUIREMENTS (37 C.F.R. §§ 42.101, 42.104, AND 42.108)

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

Pursuant to 37 C.F.R. § 42.104(a), Petitioner certifies that the '415 patent is available for IPR and that Petitioner is not barred or estopped from requesting an IPR of the '415 patent on the grounds identified in this Petition. Petitioner further certifies that the prohibitions of 35 U.S.C. §§ 315(a)-(b) are inapplicable.

IX. PAYMENT OF FEES (37 C.F.R. § 42.15(a) AND § 42.103))

The required fees are submitted herewith in accordance with 37 C.F.R. §§ 42.103(a) and 42.15(a). If any additional fees are due during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 505708. Any overpayment or refund of fees may also be deposited in this Deposit Account.

X. CONCLUSION

Petitioner has demonstrated a reasonable likelihood that claims 1-4, 11-12, 14-20, and 33 of the '415 patent are obvious in view of the prior art. Accordingly, IPR of those claims is requested.

DATED: July 7, 2016

Respectfully submitted,

By *s/Raymond N. Nimrod*

Raymond N. Nimrod (Reg. No. 31,987)
raynimrod@quinnemanuel.com
Matthew A. Traupman (Reg. No. 50,832)
matthewtraupman@quinnemanuel.com
QUINN EMANUEL URQUHART
& SULLIVAN LLP
51 Madison Avenue, 22nd Floor
New York, NY 10010
Tel: (212) 849-7000
Fax: (212) 849-7100

Katherine A. Helm (*pro hac vice* to be filed)
khelm@stblaw.com
SIMPSON THACHER & BARTLETT LLP
425 Lexington Avenue
New York, NY 10017
Telephone: (212) 455-2000
Facsimile: (212) 455-2502

Attorneys for Petitioner Merck Sharp & Dohme Corp.

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), I hereby certify that the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 6,331,415 contains 13,999 words as measured by the word processing software used to prepare the document, in compliance with 37 C.F.R. § 42.24(a).

DATED: July 7, 2016

Respectfully submitted,

By *s/Raymond N. Nimrod*

Raymond N. Nimrod (Reg. No. 31,987)
raynimrod@quinnemanuel.com
QUINN EMANUEL URQUHART
& SULLIVAN LLP
51 Madison Avenue, 22nd Floor
New York, NY 10010
Tel: (212) 849-7000
Fax: (212) 849-7100

CERTIFICATE OF SERVICE

I hereby certify that true and correct copies of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 6,331,415 and Exhibits 1001-1074 were served on July 7, 2016 via EXPRESS MAIL to the attorneys of record for U.S. Patent No. 6,331,415 as evidenced on Public PAIR on July 7, 2016, namely:

JEFFREY P. KUSHAN, ESQ.
Sidley Austin LLP
1501 K Street, N.W.
Washington, D.C. 20005

and

SEAN JOHNSTON, ESQ.
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080

DATED: July 7, 2016

Respectfully submitted,

By *s/Raymond N. Nimrod*

Raymond N. Nimrod (Reg. No. 31,987)
raynimrod@quinnemanuel.com
QUINN EMANUEL URQUHART
& SULLIVAN LLP
51 Madison Avenue, 22nd Floor
New York, NY 10010
Tel: (212) 849-7000
Fax: (212) 849-7100