UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS, INC., and
MERCK SHARP & DOHME CORP.
Petitioners

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. 2016-00710[1]

PETITIONER'S REPLY BRIEF

[1] Case IPR2017-00047 has been joined with this proceeding.

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I. INTRODUCTION: GENENTECH'S "UNCERTAINTY" AND "PREVAILING MINDSET" ARGUMENTS ARE CONTRARY TO THE CONTEMPORANEOUS EVIDENCE

Before addressing the instituted grounds, Patent Owners Genentech and City of Hope (collectively "Genentech") discuss at length their view of the state of art. Genentech argues that the "prevailing mindset" was a "one-polypeptide-per-host-cell approach" and that "uncertainty" in the field would have a prevented a POSA from expressing an antibody recombinantly. Paper 31, at 10-17. These arguments are incorrect and contradicted by contemporaneous facts.

The contemporaneous facts directly contradict Genentech's arguments. Before the work reflected in the '415 patent was ever made public, three separate groups, including the authors of Ochi I and Oi that Genentech relies upon to support its arguments, acted contrary Genentech's "uncertainty" and "prevailing mindset" arguments. Exs. 1012, 1040, 1111-12, 1147 & 1150.

As explained by three co-authors of Ochi I—and corroborated by their contemporaneous documents—there was no "prevailing mindset" against or uncertainty in expressing the heavy and light chains in a single host cell. Ex. 1091, ¶¶24-25; Ex. 1093, ¶¶14-15; Ex. 1094, ¶19. In 1982, the Ochi authors began to recombinantly express an antibody in one host cell. They first showed that an antibody light chain could be expressed recombinantly and assembled *in vivo* with a native heavy chain to form a functional antibody. Ex. 1091, ¶¶16-21; Ex. 1093,

¶¶10-13; Ex. 1094, ¶¶10-12. Far from creating uncertainty, the work on the light chain published in Ochi I validated their experimental protocols and motivated them to express a complete recombinant antibody. Exs. 1091, ¶21, 1093, ¶¶18-19, 1094, ¶17. Accordingly, the Ochi authors thereafter began work to express the heavy and light chains in a single host cell, and ultimately published Ochi II in October 1983 – months before the subject matter of the '415 patent was made public. The Ochi authors never contemplated using multiple host cells to express the heavy and light chains separately. Ex. 1091, ¶¶29-34; Ex. 1093, ¶¶18-19. As they explain, only the one-host-cell-approach allowed for *in vivo* assembly in a eukaryotic host cell, which was preferred. Ex. 1094, ¶14.

Genentech's citations to the work of others are out of context and do not reflect the state of the art in April 1983. For example, Genentech quotes Dr. Milstein's statements in 1981 – two years before the '415 patent's priority date. However, significant advancements were made in the two years following Dr. Milstein's work, including the Southern paper that further refined the pSV2 vector as a means of transducing eukaryotic host cells with multiple genes.

Beyond the testimony of the Ochi co-authors and the contemporaneous records from 1982-83, Merck relies on the rebuttal testimony of Roger Kornberg, who won the Nobel Prize for identifying DNA transcription mechanisms, including

those underlying the strong promoters described in Bujard, to show that Genentech's reading of this patent is incorrect.

In contrast to Merck's declarants, Genentech's declarants lack any particular knowledge regarding the subject matter of the '415 patent. Drs. Fiddes and Gentz, have never recombinantly expressed an antibody. Ex. 1116, 43:9-16; Ex. 1114, 88:6-25. Dr. Fiddes, the only declarant who opined that the '415 patent claims are not obvious, did not review the specification of the '415 patent in connection with this matter. Ex. 1113, 58:1-17; 25:10-19. Instead, he "just focused on the claim[s]" and therefore could not identify any problem solved by the '415 patent or any questions about its disclosure. *Id.*, 82:8-83:13; 36:17-37:8; *see also id*., 25:10-19; 259:12-18. Genentech's other expert, Dr. Gentz, was chosen because he worked in the Bujard lab. However, he had no involvement with the Bujard patent and does not know if the Bujard inventors ever tried to make antibodies using the techniques described in the patent. Ex. 1114, 88:10-89:24; Ex. 1115, 90:10-13, 116:11-117:15.

II. GROUND I: GENENTECH'S ARGUMENTS REGARDING THE COMBINATION OF BUJARD WITH RIGGS & ITAKURA SHOULD BE REJECTED

A. Genentech's Reading of Bujard Is Inappropriately Narrow

Genentech seeks to limit Bujard's disclosure to a discovery that "strong promoters can be stably cloned into a recombinant DNA construct if paired with a

'balanced' strong terminator."[2] Paper 31, at 25. However, Bujard does not simply disclose a research tool for identifying strong promoters. Paper 31, at 43; Ex. 2019, ¶243. Bujard teaches that strong promoters should be used on a single vector to optimize the commercial production of polypeptides, including antibodies. Ex. 1002, 1:18-45; 6:53-7:20; 5:11-27; Ex. 1090, ¶66.

1. Bujard Teaches A Method for Producing Antibodies

It is undisputed that Bujard teaches that a vector containing the balanced promoter and terminator can be used with a "wide a variety of structural genes" "for production of proteins," including antibodies. Ex. 1002, 4:14-15; 4:35-36; 5:12-28. Despite this explicit disclosure, Genentech's non-obviousness expert argues that Bujard's reference to "immunoglobulins" did not suggest the production of antibodies "given the size and complexity of antibodies." Ex. 2019, ¶204. Yet, by April 1983, proteins more complex than immunoglobulins had been recombinantly made by co-expressing different polypeptides in a single host cell. Ex. 1090, ¶¶114-115. For example, in 1982, scientists used a single vector to express aspartate transcarbamylase ("ATCase"), which is composed of six catalytic and six regulatory polypeptides, with a molecular weight of 300,000 Daltons—

[2] Genentech's repeated reference to Bujard's abandonment (Paper 31, at 25, 64) are legally irrelevant. *Eolas Techs. Inc. v. Microsoft Corp.*, 399 F.3d 1325, 1334 (Fed. Cir. 2005). Likewise with Genentech's allegation that Bujard is not a well known patent. Paper 31, at 28; *In re Carlson*, 983 F.2d 1032, 1037 (1992) (A POSA "is charged with knowledge of all of the contents of the relevant art.").

nearly twice the size of a typical antibody. *Id.*, ¶115; Ex. 2019, ¶43. Dr. Fiddes admits he did not consider this fact in rendering his opinions. Ex. 1113, 251:11-15.

Citing two factually distinguishable Board decisions, Genentech also argues that Bujard's identification of antibodies is "legally insufficient" because Bujard identifies antibodies in a "laundry list" of proteins. Paper 31, at 27. That is not the law. Less than four months ago, the Federal Circuit affirmed a Board obviousness determination where the patent at issue claimed a particular elastomer for use in a vascular stent and the only prior art disclosure of the specific elastomer was from a long list of elastomers that could be used in medical devices. *In re Ethicon, Inc.*, 844 F.3d 1344, 1349-50 (Fed. Cir. 2017); *see also In re Bode*, 550 F.2d 656, 661 (C.C.P.A. 1977) (A prior art reference "must be evaluated for all it teaches…").

Genentech alleges that Bujard's list of proteins could not result in a "novel method of producing antibodies." Paper 31, at 28. However, as the '415 patent itself admits, the techniques needed for recombinant antibody expression were known as of April 1983. Ex. 1001, 4:6-50. There are no special techniques needed to recombinantly express an antibody. Ex. 1090, ¶¶113, 125. The fact that Bujard explicitly confirms the general applicability of its method reinforces what a POSA would have already known – that recombinant DNA technology is useful for synthesizing a wide variety of proteins, including large proteins such as antibodies.

Likewise, Genentech alleges that the list of "proteins of interest" should be disregarded because it was copied from other patents. Paper 31, at 27-28. However, while a portion of Bujard's list overlaps with other patents, Bujard intentionally broadened the list to include "immunoglobulins, e.g. IgA, IgD, IgE, IgG and IgM and fragments thereof," which is not found in the patents cited by Genentech. *Compare* Ex. 1002, 4:32-34 *with* Exs. 2004, 2036-40, 2042-59; *see also* Ex. 1113, at 194-197. A POSA would thus conclude that the Bujard inventors specifically added antibody proteins to their list because their method is fully applicable to antibodies..

Finally, Genentech asserts that because Dr. Gentz personally "worked in Dr. Bujard's lab in the early 1980s [and] did not use Bujard's technique to co-express the subunits of a multimeric eukaryotic protein," a POSA would not have used Bujard for that purpose. Paper 31, at 29. However, Dr. Gentz did not join the Bujard lab until after the Bujard patent application was filed. He never discussed the patent with anyone in the Bujard lab or with co-inventors Stanley Cohen and Annie Chang. Ex. 1114, 24:18-25:18; 26:4-27:5. Dr. Gentz does not know if the Bujard inventors tried to make antibodies using the techniques described in the patent. Ex. 1115, 116:11-117:15.

2. Bujard Teaches the Use of Co-Expression of Multiple Genes of Interest in a Single Host Cell

Genentech argues that Bujard does not teach or suggest the co-expression of multiple genes of interest in a single host cell. Paper 31, at 24-25. In making these arguments, Genentech ignores Bujard's express language and the knowledge of a POSA. The Board should reject these arguments.

The Bujard vector allows for the co-expression of multiple genes of interest in a single host cell. The vector Bujard describes is generally comprised of four distinct sections: (1) a strong promoter, (2) a "DNA sequence of interest"[3], (3) a balanced terminator, and (4) a marker gene. Ex. 1002, 2:3-20; Ex. 1090, ¶78. The vector is then transformed into a host. *Id*. Bujard repeatedly emphasizes that one or more genes of interest may be present in the "DNA sequence of interest" section of the vector. Specifically, Bujard states that "[t]he promoter and terminator may be separated by more than one gene, that is, a plurality of genes, including multimers and operons." Ex. 1002, 3:46-48. Bujard also states that "one or more structural genes may be introduced between the promoter and terminator." Ex. 1002, 7:61-63. Dr. Gentz agrees that Bujard suggests the presence of multiple genes separating the promoter and terminator. Ex. 1115, 148:24-162:4; Exs. 1141-43.

[3] Bujard uses several terms to describe the DNA sequence of interest (e.g., the "gene of interest," and "the desired gene(s),"). Ex. 1002, Abstract, 8:6, 11:32.

(a) Genentech's Interpretation of "Multimer" Is Wrong

Genentech challenges the Board's finding that Bujard's reference to "multimers" is not limited to multiple copies of the same gene. IPR2015-01624, Paper 15, at 19 (explaining "multimers" refers to "genes encoding for proteins with more than one subunit"). Genentech ignores the context of the sentence containing "multimer," which states that "[t]he promoter and terminator may be separated by more than one gene, that is, a plurality of genes." Ex. 1002, 3:46-48. The remainder of the sentence identifies "multimers" and "operons" as examples of a "plurality of genes." *Id*. It is undisputed that operons commonly contain more than structural genes. Ex. 2019, ¶184; Ex. 1113, 223-224. Regardless of the meaning of "multimer," a POSA would understand this sentence to teach that genes encoding more than one protein of interest could be expressed by a single vector. The Board's preliminary finding that this sentence "suggests the incorporation of a plurality of structural genes encoding for the subunits of a multimeric protein" is correct. IPR2015-01624, Paper 15, at 18-19.

Moreover, Genentech's interpretation of "multimer" is wrong. Publications prior to and after April 1983 show that a POSA would have understood "multimers" to mean genes encoding multimeric proteins, including either multiple copies of the same gene ***or*** multiple distinct genes. Ex. 1090, ¶¶88-93. For example, the 1975 Dictionary of Biochemistry defines "multimer" as an

"[o]ligomer," which is defined as "[a] protein molecule that consists of two or more polypeptide chains, referred to as either monomers or protomers, linked together covalently or noncovalently." Ex. 1071, at 205, 220; Ex. 1090, ¶92. Thus, while a multimer ***can*** be multiple copies of the same gene, it can also mean multiple copies of different genes. Genentech's citations do not contradict this broad definition and oftentimes did not even use the word "multimer." Ex. 1114, 136:9-137:4, 140:6-13.

(b) Genentech's Interpretation of "One or More Structural Genes" Is Wrong

Genentech incorrectly interprets Bujard's teaching that "one or more structural genes may be introduced between the promoter and terminator" (Ex. 1002, 7:61-63), arguing that "structural genes" would have been understood to include a gene for the protein of interest and a marker, or alternatively multiple copies of the same gene. Paper 31, at 33, 35. Bujard is not so limited. Rather, the structure of the Bujard vector demonstrates that the marker is separate and distinct from the one or more structural genes. Ex. 1090, ¶¶78-80. However, Bujard teaches that the vector is organized with "***optionally a structural gene which may be a marker***; a balancing terminator; and ***optionally a marker*** allowing for selection of transformants containing the construct." Ex. 1002, 2:41-43 (emphasis added). Because the marker gene is optional, the "one or more structural genes" cannot be not limited as Genentech argues. Rather, the Bujard vector could

optionally be any combination of one ***or more*** genes of interest with or without a marker gene.

(c) The Use of Multiple Stop Codons Teaches The Inclusion of Multiple Genes of Interest

The Board was correct in previously finding that Bujard's reference to "a plurality of translational stop codons" in "one or more reading frames of the vector" as allowing "multiple structural genes to be translated into separate polypeptides." IPR2015-01624, Paper 15, at 19. Genentech argues that "[n]othing about having multiple stop codons suggests co-expressing multiple genes." Paper 31 at 37. This is wrong. Bujard describes the stop codons as "signal[ing] the end of the polypeptide chain" such that "[w]hen a stop codon is reached [during translation], the polypeptide chain is complete and detaches from the ribosome." IPR2015-01624, Paper 15, at 19 n.7. A POSA would understand Bujard's multiple stop codons to require multiple reading frames, translating different proteins. Ex. 1090, ¶¶104-107.

3. Bujard Teaches the *In Vivo* Assembly of a Multimeric Protein Encoded by More than One Gene in a Single Host Cell

Bujard is clear that there are at least two ways of obtaining the protein: (1) "as a single unit," or (2) "as individual subunits [ ] joined together in appropriate ways." Ex. 1002, 4:19-21. Genentech argues that this passage simply refers to a monomeric protein or a multimeric protein made in different host cells. Again,

there is no basis to read Bujard's disclosure here. Bujard teaches making multiple multimeric proteins from a single vector. Ex. 1090, ¶121. A POSA would understand that a multimeric protein assembled *in vivo* would be made as a single unit. *Id.* Likewise, there is nothing about "join[ing]" "individual subunits" "in appropriate ways" that suggests use of separate host cells. As shown in the references cited by Genentech, the prior art discloses *in vitro* assembly of insulin in which the A and B chains were made in a single host cell and then "joined together in appropriate ways." *Id.*, ¶¶119-121.

B. It would have been obvious to combine Bujard with Riggs & Itakura

The Board correctly determined that there is a reasonable likelihood that a POSA would have found it obvious to combine Bujard's teachings "with the in vitro assembly technique taught by Riggs & Itakura . . . to produce an immunoglobulin molecule." IPR2015-01624, Paper 15, at 18.

1. A POSA Would Have Been Motivated to Combine Bujard with Riggs & Itakura

Genentech is wrong that Merck has not set forth a "reasoned basis" for combining Riggs & Itakura with Bujard. As set forth in the Petition, there was a strong motivation to make antibodies, Bujard taught the use of recombinant DNA technology to make the antibody chains, and a POSA would have been highly motivated to select a known technique for assembling the chains into an antibody.

Both references are in the same field of endeavor and both are directed to the same general problem – joining the individual chains of a multimeric protein. Paper 2, at 36-37. Bujard itself expressly teaches to use "appropriate ways" to join the chains of a multimeric protein (Ex. 1002, 4:19-21) and Riggs & Itakura states that the antibody heavy and light chains "could be assembled in vitro." Ex. 1003, at 537-38. These undisputable facts are more than sufficient to establish a motivation to combine. *KSR Int'l Co. v. Teleflex Inc.,* 550 U.S. 398, 401 (2007) ("[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.").

Genentech's only argument for why a POSA would not have been motivated to combine Riggs & Itakura with Bujard is because the assembly technique of Riggs & Itakura is allegedly "incompatible" with antibodies based on the specific cleavage technique used for insulin. Paper 31, at 43-44. However, Genentech's cleavage argument ignores the explicit teaching in Riggs & Itakura that a POSA can use another "cleavage trick." Ex. 1003, at 532. Such alternative cleavage tricks were well known by April 1983 and required only minor modifications. Ex. 1090, ¶126. Dr. Foote admitted one could follow the explicit teachings of Riggs &

Itakura and find "another method of cleaving [the protein of interest]." Ex. 2020, 377:9-10.

2. The Board Correctly Found That Riggs & Itakura Does Not Teach Away

Genentech also challenges the Board's finding that Riggs & Itakura does not teach away from expressing the heavy and light chains in a single cell. Paper 31, at 45-47. According to Genentech, because Riggs & Itakura only discloses a two-cell-approach, it teaches away from a one-cell-approach. This is legally insufficient for teaching away. "A reference does not teach away… if it merely expresses a general preference for an alternative invention but does not criticize, discredit or otherwise discourage investigation in the invention claimed." *Galderma Labs., L.P. v. Tolmar*, 737 F.3d 731, 738 (Fed. Cir. 2013). Riggs & Itakura does not discuss or criticize a one-cell-approach at all. Nor does it discuss any advantages of the two-cell-approach.

3. A POSA Would Have Had a Reasonable Expectation of Success in Combining Bujard with Riggs & Itakura

Genentech argues that because of alleged "uncertainty" and "unpredictability," a POSA would not have had a reasonable expectation of success. Paper 31, at 49-52. Genentech misstates the law. "[T]he expectation of success need only be reasonable, not absolute" *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364-65 (Fed. Cir. 2007). Moreover, if the tools to make the invention

are within the basic grasp of a POSA, this is evidence of a reasonable expectation of success. *AstraZeneca LP v. Breath Ltd.*, 603 F. App'x 999, 1001-02 (Fed. Cir. 2015). The '415 patent states that all of the tools needed to recombinantly express the heavy and light chains were within a POSA's ability. Indeed, 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) and Genentech has stated unequivocally that the techniques for *in vitro* assembly of the heavy and light chains disclosed in the '415 patent are ***not inventive*** and not claimed by the '415 patent. Ex. 1149, 18:10-17.

Genentech's arguments regarding reasonable expectation of success are also factually incorrect. First, the difference in size between insulin and the antibody heavy and light chains is not significant with respect to *in vitro* assembly. The same *in vitro* assembly technique is used regardless of the size the polypeptide chains that are being assembled. Ex. 1090, ¶114.

Second, as the patent admits and as Genentech has conceded, *in vitro* antibody assembly techniques were well known in the art. Ex. 1001, 12:58-13:52; Ex. 1149, 18:10-17. There is no requirement for Riggs & Itakura to teach what is well known. *KSR*, 550 U.S. 418 (an obviousness analysis must consider "the background knowledge possessed by a person having ordinary skill in the art").

Third, Genentech argues that Bujard or Riggs & Itakura must disclose that antibodies can be assembled without helper proteins. Paper 31, at 51. Riggs & Itakura does just that: "Bacteria may then be used for the production of the antibody peptide chains, which could be assembled in vitro and used for passive immunization." Ex. 1003, at 537-38.

Finally, Bujard and Riggs & Itakura do not have to discuss the "complication of 'inclusion bodies'" to provide a POSA with a reasonable expectation of success. Paper 31, at 51-52. Genentech recognizes that it was known that recombinantly expressed proteins often appeared as inclusion bodies (*id.*), yet ignores that standard chemical means to denature inclusion bodies to isolate proteins was also well known in April 1983. Ex. 1090, ¶¶137-140.

III. GROUND 2: GENENTECH'S ARGUMENTS REGARDING THE COMBINATION OF BUJARD WITH SOUTHERN SHOULD BE REJECTED

Genentech asserts that "Bujard and Southern address fundamentally different issues, and there would have been no reason in April 1983 for a skilled artisan to even consider their teachings together." Paper 31, at 55. The Board correctly found that Southern teaches "the general applicability of its disclosed cotransformation technique by inserting *genes of interest* into vector DNAs designed to express neo or gpt," and that there is a "reasonable likelihood that the skilled artisan would have found it obvious to use Southern's two-vector technique

to express both the heavy and light immunoglobulin chains in a single host cell." IPR2015-01624, Paper 15, at 22.

A. Southern Discloses a Two-Vector Approach to Express Multiple Proteins of Interest in a Single Host Cell

Genentech contends that "Southern does not disclose or suggest the 'single host cell' or the two vector limitations absent from Bujard." Paper 31, at 53. Dr. Fiddes likewise states that Southern "does nothing more than provide a new vector for use in mammalian cells," and "does not provide additional inferences that would have suggested the use of multiple vectors to express distinct genes in a single host cell." Ex. 2019, ¶¶291, 293.

Dr. Fiddes is incorrect that Southern "provide[s] a new vector." Ex. 2019, ¶291. The vector described in Southern – Prof. Berg's pSV2 vector – was described in several prior publications co-authored by Prof. Berg, including Prof. Berg's Nobel Lecture. Exs. 1069, 1120. That work is expressly referenced in Southern. Ex. 1004, at 340. The pSV2 vector was designed to "introduce and maintain new genetic information in a variety of mammalian cells," including multiple genes of interest from a single vector. Ex. 1069, at 300. Before Southern was published, the expression of genes of interest using the pSV2 vector was well established. Ex. 1090, ¶149. Southern demonstrated the viability of a new selectable marker, the *neo* gene, and to then show that vectors containing the *gpt*

and *neo* selectable markers could be co-transformed into a single host cell. *Id.*, ¶¶146-49.

A POSA would have readily understood that the purpose of the double transformation with two different markers was not purely academic but rather to permit the two vectors to express different genes of interest in a single host cell – that is what the pSV2 vector was designed to do. *Id.* Indeed, the group led by Sherie Morrison applied this very double-transformation-technique to express an antibody heavy and light chain in a single cell no later than October 1983 – at least nine months before the subject matter of the '415 patent was publicly disclosed. Exs. 1111, 1112, 1145, 1150.

Genentech's argument that "Southern described the need for future experimentation regarding some undisclosed use for the two-vector approach" (Paper 31, at 59) again ignores that the pSV2 vector had ***already been used*** to express multiple genes of interest. The data in Southern showing that cotransformation of the pSV2-neo and pSV2-gpt vectors in a single host cell was the only experiment needed to demonstrate the viability of the two-vector approach. Moreover, contrary to Genentech's argument, the ten-fold reduction in the number of stable transformants reported by Southern for the co-transformation technique would have made the two-vector approach non-obvious. *Id.*, at 57. A POSA would understand that seeing ***any*** significant number of stable

transformants, which Southern clearly shows, indicates that the experiment was a success. Ex. 1090, ¶149. Moreover, the claims of the '415 patent do not require a particular level of antibody production per vector or per cell.

B. A POSA Would Have Been Motivated to Combine Bujard with Southern

Dr. Fiddes opines that a POSA "would not have been motivated from the combination of Southern and Bujard to co-express antibody heavy and light chains in a single host cell using separate plasmids." Ex. 2019, ¶306. This is wrong for several reasons. Southern and Bujard are both directed to a general method of recombinantly expressing proteins in a eukaryotic host cell. Ex. 1090, ¶151. Southern discloses a two-vector approach that is optimally suited for expressing in a single host cell a multimeric protein comprised of two or more polypeptides; thus, Southern teaches a direct and efficient way to independently express both the heavy and light chains in a single host cell. *Id.* A POSA would have readily recognized that Southern's dual vector system is the ideal platform for recombinantly expressing antibodies as taught by Bujard. *Id.*

Dr. Fiddes also opines that "Bujard focuses on bacterial expression systems," whereas Southern focuses on "a mammalian expression system," and thus "the pSV2 system described in Southern would not be expected to express eukaryotic genes of interest in a bacterial host cell." Ex. 2019, ¶¶287-88. Dr. Fiddes ignores Bujard's express teaching that it applies to mammalian cells:

"Higher cells, e.g., mammalian, may also be employed as hosts, where viral, e.g., bovine papilloma virus or other DNA sequence is available which-has plasmid-like activity." Ex. 1002, 6:34-37. The pSV2 vector disclosed in Southern uses a viral promoter, SV40, and the vectors Southern describes have "plasmid-like activity." Ex. 1004, at 327. Thus, Genentech is simply wrong that "Bujard and Southern are directed to different cell types … and different promoters." Paper 31, at 55. Because the teachings of Bujard are expressly applicable to mammalian host cells and viral-based vectors, a POSA would have had a strong motivation to combine Bujard with Southern. Ex. 1090, ¶¶154-155.

C. A POSA Would Have Had a Reasonable Expectation of Success in Combining Bujard with Southern

Once again relying on alleged "uncertainties" in the art, Genentech argues that a POSA "would not have had a reasonable expectation that functional antibodies could be produced using two of Southern's vectors in a single host cell." Paper 31, at 61, Ex. 2019, ¶¶307-17. Again, Genentech misstates the law, which does not require absolute certainty of success. *Supra*, p. 13-14.

Prior to April 1983, Ochi I showed that a functional antibody could be recovered when the light chain is expressed using the pSV2-neo vector and the heavy chain produced natively. Ex. 1021, at 341. Oi and Rice & Baltimore, both expressed light chain in a myeloid cell line using the pSV2-gpt vector. As explained by the authors of the Ochi I paper, these results validated the

experimental techniques needed to transform eukaryotic host cells and showed that a functional antibody could be assembled using a recombinantly expressed light chain. Ex. 1091, ¶¶26-30; Ex. 1093, ¶¶13-17.

Nothing about the larger size of the heavy chains would have created any uncertainty in the mind of a POSA. To the contrary, larger proteins had already been expressed using recombinant DNA technology. Accordingly, the results of Ochi I gave the Ochi authors confidence that that their work expressing both chains in a single host cell would be successful. *Id.*; Ex. 1094, ¶¶13-18. Contrary to Genentech's arguments, a detailed understanding of how immunoglobulin genes were regulated was not required to produce recombinant antibodies. Ex. 1091, ¶¶22-23.

D. Genentech's Arguments That Southern Cannot Invalidate Claims 1, 2, and 33 Are Wrong

Genentech argues that Bujard combined with Southern would not have rendered claims 1, 2, and 33 obvious because neither Bujard nor Southern allegedly teach antibody assembly. Paper 31, at 62. Bujard explicitly teaches that "immunoglobulins" can be made using its recombinant techniques and that the polypeptides can be assembled "in appropriate ways." Ex. 1002, 4:19-21. A POSA would have known how to assemble a heavy and light chain into a functional antibody using well-known *in vitro* assembly techniques—including those described in '415 patent. Ex. 1090, ¶163; Ex. 1021; Ex. 1031; Ex. 1040.

Additionally, the work of both Ochi I and Oi demonstrated the ability to transform the pSV2 vectors into lymphoid cells, which cells naturally assemble heavy and light chains into functional antibodies. Ex. 1090, ¶163; Ex. 1021; Ex. 1031; Ex. 1040. A POSA would have understood that by using a lymphoid host cells one could achieve *in vivo* antibody assembly. Ex. 1090, ¶163.

IV. GENENTECH'S SECONDARY CONSIDERATIONS EVIDENCE SHOULD BE GIVEN NO WEIGHT

Genentech failed to establish a nexus between the '415 patent and any secondary considerations evidence. That evidence should be given no weight. *Apple, Inc. v. Ameranth, Inc.*, CBM2015-00080, Paper 44, at *36-37 (Aug. 26, 2016) ("[T]o be accorded substantial weight, there must be a nexus between the merits of the claimed invention and the evidence of secondary considerations.").

A. Genentech Is Not Entitled to a Presumption of Nexus

Genentech's assertion that a presumption of nexus applies is wrong. Paper 31, at 64-65; Ex. 2033, ¶52. A presumption of nexus only applies if the claimed invention is coextensive with the commercially-successful product. A product is not coextensive with the patented invention when the invention is "only a component of a commercially successful [] process." *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988). Where the products are covered by multiple patents, the patentee is not entitled to a presumption of nexus. *Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d

1289, 1299 (Fed. Cir. 2010) (vacated on other grounds); *GrafTech Int'l Holdings, Inc. v. Laird Techs. Inc.*, 652 Fed. App'x. 973, 978-79 (Fed. Cir. June 17, 2016) (not entitled to nexus because Patent Owner submitted the same evidence in multiple IPRs to establish the commercial success of different patents and Patent Owner did not assert that the alleged commercial success resulted from the patented features).

Ms. Davis relies on a presumption that a nexus exists where the alleged commercially successful products practice the invention. Ex. 2033, ¶52. However, Genentech, as in *Therasense* and *GrafTech*, has previously stated that its products are covered by other patents—and in many cases argued that the commercial success is attributable to the other patents. Ex. 1092, ¶44. The same is true for the licensees' products. *Id.*, ¶45. Accordingly, a presumption of nexus does not apply.

B. Genentech Fails to Establish a Nexus Between its Licensing Program and the Challenged Claims

For Genentech's licenses to be relevant, Genentech must show a "nexus between the merits of the invention and the licenses themselves" and not just a desire to avoid the costs of litigation. *In re Antor Media Corp.*, 689 F.3d 1282, 1293-94 (Fed. Cir. 2012). Genentech has not made this showing. Each license covers at least one other Cabilly patent. Ex. 1092, ¶¶25-27. Genentech has never licensed the '415 patent on a standalone basis, and does not allocate royalties by

patent. *Id.*, ¶27. Because it relies solely on presumption of nexus to which it is not entitled, Genentech's evidence of nexus is insufficient. *Id.*, ¶28.

C. Genentech Fails to Establish a Nexus Between Any Alleged Commercial Success and the Challenged Claims

Genentech also fails to prove that any alleged commercial success was attributable to the alleged '415 patent. Relying on a presumption of nexus, Genentech offered no evidence that the commercial success resulted from use of any technology covered by any claim of the '415 patent. Additionally, Ms. Davis failed to consider other factors that contributed to the alleged commercial success of identified products. Ms. Davis did not apportion the alleged commercial success of the identified products to the '415 patent apart from Cabilly I or Cabilly III. Ex. 1092, ¶¶40-42, 48. Ms. Davis also did not consider the safety or efficacy, reputation of manufacturer of the drug or marketing efforts. *Id.*, ¶41.

D. There Was No Skepticism of Those Skilled in the Art

As described above, the prior art is clear that there was no skepticism that an antibody could be produced by and co-expressing its heavy and light chains in a single host cell. *See supra*, p. 1-2. Moreover, Genentech's reliance on Greg Winter's statements are misplaced because the cited testimony was limited to eukaryotic host cells and a specific antibody yield. Ex. 2023, ¶¶32, 59-60. The claims are not so limited. *Biomerieux, Inc. v. Patent Inst. for Envtl. Health Inc.*,

Appeal 2014-007983, 2015 WL 294327, at *15 (PTAB Jan. 20, 2015) (skepticism must be directed to "the full breadth of the claim").

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CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Petitioner's Reply Brief contains 5377 words as measured by the word processing software used to prepare the document, in compliance with 37 C.F.R. § 42.24(d).

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on April 7, 2017, the foregoing document is being served by E-mail by agreement of the parties to the following counsel of record:

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