UNITED STATES DISTRICT COURT

CENTRAL DISTRICT OF CALIFORNIA

WESTERN DIVISION

BRISTOL-MYERS SQUIBB COMPANY, Plaintiff and Counter-Defendant, v. GENENTECH, INC., and CITY OF HOPE Defendants and Counter-Plaintiffs.	Case No. 2:13-cv-05400-MRP-JEM

EXPERT REPORT OF JOHN FIDDES, Ph.D.

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I. INTRODUCTION AND BACKGROUND

1. Genentech, Inc. and City of Hope have retained me as an expert consultant in the above-captioned case. I submit this report on their behalf pursuant to Federal Rule of Civil Procedure 26(a)(2).

2. In view of my education, training, skills, knowledge and experience, I have been asked to evaluate, and respond to, certain opinions regarding the validity of U.S. Patent No. 6,331,415 ("Cabilly II") and U.S. Patent No. 7,923,221 ("Cabilly III") expressed by Jefferson Foote, Ph.D., in an expert report dated October 13, 2014, filed in this case on behalf of Bristol-Myers Squibb Co. and Medarex, LLC (collectively, "BMS"). I expect to testify about my evaluations and responsive opinions, set forth herein.

3. If called to testify, to help make the complex science and the language associated with it understandable, I may also serve in a teaching capacity, explaining the basic principles referred to and the terminology used in this report, the report I address herein, as well as other documents and literature referenced herein. At this point in time, I have not prepared any demonstrative exhibits, illustrations, prototypes, models, animations or other such testimonial aids in support of my testimony, although I expect I may utilize such and will do so in accordance with the Court's orders.

4. I reserve the right to modify, amend and/or supplement the opinions expressed herein – especially to address any new arguments raised by BMS, directly or through its experts.

II. COMPENSATION

5. I am being compensated for my time spent working on this case at a rate of $450 per hour plus expenses. My compensation in this case is in no way dependent on its outcome.

III. PRIOR EXPERT TESTIMONY

6. I have not testified at a trial or deposition in the preceding four years.

IV. QUALIFICATIONS AND EXPERIENCE

7. If called to testify, I expect to describe my qualifications and experience that are relevant to the issues I address herein. My background is summarized below and in my *curriculum vitae* ("CV"), which includes a list of my publications and patents, both of which are attached as Exhibit A.

8. I received a Bachelor of Science degree in Biological Sciences (Molecular Biology) with First Class Honors from the University of Edinburgh, Edinburgh, Scotland in 1973. In 1977, I received my Ph.D. in molecular biology from Kings College, Cambridge University, Cambridge, England. My thesis advisor was Dr. Fred Sanger. The topic of my thesis was, "Sequencing of the bacteriophage ϕX174 and G4 genomes." From 1977 to 1980, I was a Postdoctoral Research Fellow at the University of California, San Francisco ("UCSF"), in the laboratory of Dr. Howard Goodman, where I worked on the human growth hormone, human chorionic somatomammotropin and human glycoprotein hormone genes. While I was focused on cDNA cloning and the cloning and structural characterization of genes encoding these human hormones, several of my colleagues focused on gene expression for the production of recombinant proteins, and I had frequent discussions with them on their research strategies.

9. After my post-doc at UCSF, I became a Senior Staff Investigator at Cold Spring Harbor Laboratory ("CSHL") in Cold Spring Harbor, New York, a position I held until January 1983. My research at CSHL focused on the structure, evolution and expression of the human glycoprotein hormone genes, specifically human chorionic gonadotropin and human luteinizing hormone, and on methods of making cDNA libraries suitable for immunological screening of expression products. I was also an instructor at the CSHL Advanced Cloning Course in the summers of 1982-1983.

10. Following my academic career, I entered industry and spent over twenty years in drug discovery and development in biopharmaceutical companies, as reflected in my CV. In January 1983, just shortly before the filing date of the Cabilly patents, I took a position at California Biotechnology Inc. (later called Scios Inc.) in Mountain View California, a biotechnology company interested in applying recombinant DNA technologies to the production of therapeutically useful proteins. Among other things, I was involved in the development of systems for the production of recombinant forms of basic fibroblast growth factor, and the isolation of cDNA and genomic clones for atrial natriuretic peptide, vascular endothelial growth factor variant and heparin-binding, EGF-like growth factor.

11. My last corporate position was at Genencor International Inc. in Palo Alto, California where I was Vice President Research, Health Care from 2003 to 2005. Since 2005, I have been an independent consultant on biopharmaceutical matters for a variety of organizations, including the California Antiviral Foundation and the Institute for One World Health.

12. Based on my academic and early industrial experience, I was well aware of the birth of recombinant DNA technology and experienced as well as followed the developments that led to the applications of the technology to the production of recombinant forms of medically and industrially important proteins. This, in my view, is the art to which the Cabilly patents pertain, and I believe I am well-positioned to understand and address the skills and mindset of a person of ordinary skill in this art circa 1982-83.

V. QUESTIONS PRESENTED

13. I have been asked to provide an overview of the state of the art of protein production using recombinant DNA technology as of April 1983, so as to express my opinion, responsive to that of Dr. Foote, on whether the inventions claimed in claims 15, 17 and 33 of Cabilly II (collectively, "the asserted claims") constitute inventive advances over the prior art Dr. Foote relies on, specifically, Cohen and Boyer, U.S. Patent No. 4,237,224 ("Cohen & Boyer") and Bujard *et al.*, U.S. Patent No. 4,495,280 ("Bujard"), alone or in combination with Riggs and Itakura, Am. J. Hum. Genet. 31:531-538 (1979) ("Riggs & Itakura").

14. As further discussed herein, my opinion is that the subject matter of the asserted claims of Cabilly II represents inventive advances over the references relied on by Dr. Foote.

15. I have also been asked to express my opinion on whether claims 20, 27, 43 and 46 of Cabilly III are obvious over claim 2 of U.S. Patent No. 4,816,567 ("Cabilly I") in combination with either Cohen & Boyer or Bujard alone or in further combination with Riggs & Itakura and thus to assess whether these claims are valid under the doctrine of obviousness-type double patenting ("ODP").

16. As further discussed herein, my opinion is that claims 20, 27, 43 and 46 of Cabilly III are not obvious from claim 2 of Cabilly I in combination with the art relied on by Dr. Foote and thus, not invalid under ODP.

VI. SUMMARY OF MY OPINIONS

17. As explained in detail below, my opinions expressed in this report with respect to Cabilly II may be summarized as follows:

- Claims 15, 17 and 33 are not anticipated by Cohen & Boyer.
- Claims 15, 17 and 33 are not anticipated by Bujard.
- Claim 33 is not obvious in view of Cohen & Boyer in combination with Riggs & Itakura.
- Claim 33 is not obvious in view of Bujard in combination with Riggs & Itakura.

18. As explained in detail below, my opinions expressed in this report with respect to Cabilly III may be summarized as follows:

- Claims 20, 27, 43 and 46 are not invalid under the doctrine of ODP in view of claim 2 of Cabilly I in combination with (1) Cohen & Boyer alone or (2) Cohen & Boyer plus Riggs & Itakura.
- Claims 20, 27, 43 and 46 are not invalid under the doctrine of ODP in view of claim 2 of Cabilly I in combination with (1) Bujard alone or (2) Bujard plus Riggs & Itakura.

19. A list of materials I have reviewed in preparation of this report is attached as Exhibit B.

VII. THE CLAIMS UNDER CONSIDERATION AND THEIR INTERPRETATION

20. I understand that before the validity (or infringement) of a patent claim can be judged, it must first be interpreted by the Court. As reflected in Exhibit B, I have

been provided a copy of the Court's Claim Construction Order ("Claim Constr. Or.") in this case and have reviewed it.

21. The claims of Cabilly II that I have considered are claims 15, 17 and 33, which read as follows:

> **15.** A vector comprising a first DNA sequence encoding at least a variable domain of an immunoglobulin heavy chain and a second DNA sequence encoding at least a variable domain of an immunoglobulin light chain wherein said first DNA sequence and said second DNA sequence are located in said vector at different insertion sites.
>
> * * *
>
> **17.** A host cell transformed with a vector according to claim **15**.
>
> * * *
>
> **33.** A process for producing an immunoglobulin molecule or an immunologically functional immunoglobulin fragment comprising at least the variable domains of the immunoglobulin heavy and light chains, in a single host cell, comprising:
>
> independently expressing a first DNA sequence encoding at least the variable domain of the immunoglobulin heavy chain and a second DNA sequence encoding at least the variable domain of the immunoglobulin light chain so that said immunoglobulin heavy and light chains are produced as separate molecules in said single host cell transformed with said first and second DNA sequences.

22. The claims of Cabilly III that I have considered are claims 20, 27, 43 and 46, which are reproduced below. Because all of these claims are dependent claims, the claims on which they depend (*i.e.*, claims 15, 25, 38 and 45) are also reproduced below:

> **15.** A method for making an antibody or antibody fragment capable of specifically binding a desired

antigen, wherein the antibody or antibody fragment comprises (a) an antibody heavy chain or fragment thereof comprising a human constant region sequence and a variable region comprising non-human mammalian variable region sequences and (b) an antibody light chain or fragment thereof comprising a human constant region sequence and a variable region comprising non-human mammalian variable region sequences, the method comprising coexpressing the heavy chain or fragment thereof and the light chain or fragment thereof in a recombinant host cell.

* * *

20. The method of claim **15** which results in the production of an antibody.

* * *

25. A method for making an antibody heavy chain or fragment thereof and an antibody light chain or fragment thereof each having specificity for a desired antigen, wherein the heavy chain or fragment thereof comprises a variable region sequence and a human constant region sequence, the method comprising culturing a recombinant host cell comprising DNA encoding the heavy chain or fragment thereof and the light chain or fragment thereof and recovering the heavy chain or fragment thereof and light chain or fragment thereof from the host cell culture.

* * *

27. The method of claim **25** wherein the host cell comprises a vector comprising DNA encoding the heavy chain or fragment thereof and DNA encoding the light chain or fragment thereof.

* * *

38. A method for making an antibody or antibody fragment capable of specifically binding a desired antigen, wherein the antibody or antibody fragment comprises (a) an antibody heavy chain or fragment thereof comprising a variable region sequence and a human constant region sequence and (b) an

antibody light chain or fragment thereof comprising a variable region sequence and a human constant region sequence, the method comprising coexpressing the heavy chain or fragment thereof and the light chain or fragment thereof in a recombinant host cell.

* * *

43. The method of claim **38** which results in the production of an antibody.

* * *

45. A replicable expression vector comprising DNA encoding an antibody heavy chain or fragment thereof and an antibody light chain or fragment thereof each having specificity for a desired antigen, the heavy chain or fragment thereof and the light chain or fragment thereof each comprising a variable region sequence and a human constant region sequence.

46. A recombinant host cell comprising the vector of claim **45**.

23. I understand that the Court has construed certain claim terms in Cabilly II. Specifically, "host cell" was construed to mean "a cell whose heritable DNA has been or will be altered by the inclusion of foreign DNA; the term includes the progeny of the originally transformed cell." Claim Constr. Or. at 18. Also, "transformed" was found to have its plain and ordinary meaning and that it "does not require a separate step of transforming." *Id.*

24. I understand that the Court has construed certain claim terms in Cabilly III. Specifically, "recovering the heavy chain or fragment thereof and light chain or fragment thereof" was found to have its plain and ordinary meaning. *Id.*

25. I further understand that the parties have agreed to the meaning of other terms within the claims of the Cabilly II and III patents. Specifically, the parties have

agreed that, in Cabilly II, "transformed host cell" means "a cell whose heritable DNA has been altered by the inclusion of foreign DNA; the term includes the progeny of the originally transformed cell." *Id.* at 4. Furthermore, "different insertion sites" was agreed to mean "in the vector, the DNA sequence encoding for at least the variable domain of the heavy chain is not contiguous to the DNA sequence encoding for at least the variable domain of the light chain, the former being separated from the latter by sufficient DNA sequence to ensure independent expression." *Id.* Lastly, "vector" was agreed to mean "a DNA construct comprising DNA foreign to the DNA host cell, which DNA construct is capable of effecting the expression of the foreign DNA." *Id.* at 5.

26. For Cabilly III, I understand that the parties have agreed that "recombinant host cell" means "a cell whose heritable DNA has been altered by the inclusion of foreign DNA; the term includes the progeny of the originally transformed cell." Claim Constr. Or. at 4. Furthermore, they have agreed that "coexpressing the heavy chain or fragment thereof and the light chain or fragment thereof" means "independently expressing the heavy chain or fragment thereof and the light chain or fragment thereof in the same host cell." Joint Claim Constr. And Prehearing Statement at 1-2. It was agreed that "host cell culture" has its plain and ordinary meaning. Claim Constr. Or. at 5. "Vector" was agreed to mean "a DNA construct comprising DNA foreign to the DNA host cell, which DNA construct is capable of effecting the expression of the foreign DNA." *Id.* Lastly, "replicable expression vector" was agreed to mean "a DNA construct comprising DNA foreign to the DNA host cell, which DNA construct is capable of effecting the expression of the foreign DNA." *Id.*

27. I understand that the Court has taken no position on the construction of the claim terms "immunoglobulin" (used in Cabilly II) and "antibody" (used in Cabilly III). Claim Constr. Or. at 2. I understand that the parties agree on the fact that all antibodies are also immunoglobulins. I use the terms interchangeably herein.

28. Lastly, I understand that the asserted process and method claims require not only the co-expression of heavy and light chains in a single host cell, but also that assembled immunoglobulins (in the case of Cabilly II) and assembled antibodies (in the case of Cabilly III) be produced.

VIII. RELEVANT LAW

A. 35 U.S.C. § 102: Novelty or "Anticipation"

29. I understand that Title 35 of the United States Code contains the statutory patent laws of the United States and that § 102 sets forth the novelty requirement. I have been informed that the subject matter of a valid claim must be new and that novelty (and hence, validity) is destroyed when a single prior art reference discloses, expressly or inherently, each and every element of the claimed invention. I have been further informed that such a prior art reference must not only disclose in an enabling manner all elements of a patent claim within its four corners to be novelty-destroying, but that it must also disclose those elements arranged as in the claim. Such a reference, I understand, is also said to be "anticipatory." I understand further that novelty/anticipation is judged as of a patent's priority date as understood by a person of ordinary skill in the art.

B. 35 U.S.C. § 103: Obviousness

30. I understand that the subject matter of a valid claim, in addition to being novel, must be non-obvious. I have been informed that 35 U.S.C. § 103(a) sets forth the standard for obviousness and states

> (a) A patent may not be obtained though the invention is not identically disclosed or described [in the prior art] if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

31. I also understand that, when evaluating whether the claims of a patent are obvious or not, one may (1) consider the inventions claimed in the asserted claims and the scope and content of the prior art; (2) compare the claimed inventions to the prior art and assess the differences; and (3) determine whether those differences would have been considered obvious to a person of ordinary skill in the art as of the priority date of the patent, which I have been asked to assume is the filing date of the application underlying Cabilly II, Serial No. 06/483,457, filed April 8, 1983.

32. Furthermore, I understand that obviousness is judged from the vantage point of a person of ordinary skill in the art as of April 1983, whom I have characterized in Section IX, below. I have been informed that I should assume that a person of ordinary skill in the art would have known of the teachings provided in all the relevant body of art.

33. I have been advised that the U.S. Supreme Court has commented that a person of ordinary skill in the art is not an automaton but rather possesses an ordinary level of creativity for problem-solving. However, I further understand, a person of

ordinary skill in the art is not an inventor and is not expected to solve problems with innovative approaches.

C. Obviousness-Type Double Patenting

34. It has been explained to me that so-called "obviousness-type double patenting" is a doctrine created by the courts, the purpose of which is to ensure that claims of commonly owned patents are patentably distinct, *i.e.*, that the subject matter claimed in one patent is not made obvious by the subject matter claimed in another co-owned patent. I have been informed that one of the policy concerns addressed by this doctrine is the prevention of a later-expiring patent, which claims an invention patentably indistinct from that claimed in an earlier-expiring patent, from, in effect, improperly extending the term of the patent monopoly.

35. I understand that the obviousness-type double patenting analysis requires that the claims of the later-expiring patent be compared to the *claims* of the earlier-expiring patent and not to the entirety of the teachings of the specifications, although the specification of the earlier expiring patent may be consulted, as necessary, for claim interpretation purposes.

36. I understand that this analysis includes basically three steps: (1) the interpretation of the claims of the earlier and later patent; (2) a comparison of the claims to identify differences, if any and (3) an assessment, in accordance with the principles of 35 U.S.C. §102 (anticipation) and §103 (obviousness) (described above), of whether the later claims are patentably distinct from the earlier claims.

IX. THE PERSON OF ORDINARY SKILL IN THE ART

37. In my opinion, the art area of the Cabilly II and III patents is the use of recombinant DNA technology for the production of proteins of interest in host cells, *i.e.*,

those cells engineered to contain, express and propagate genes they naturally do not harbor. Thus, the person of ordinary skill in this art in early 1983 would have had training in the then relatively new "genetic engineering" technologies. Such a person, in my view, would have had a Ph.D. in molecular biology or related discipline, such as biochemistry, microbiology or cell biology plus two to three years post-doctoral training and experience (whether in academia or industry) in the application of recombinant DNA technology to protein production. More often than not, in my view, the person of ordinary skill in the art in early 1983, whether in an academic setting or in industry, would have been pursuing the recombinant production of a protein of known or expected therapeutic or industrial utility.

38. The person of ordinary skill in the art, in my opinion, would not have been an immunologist, nor would otherwise have had extensive training about the immune response in humans and other animals. However, I believe that the person of ordinary skill in the art would have had a basic course in immunology or at least would have been knowledgeable about the structure and function of antibodies and would have had some familiarity with the genetics and other complexities of the immune system.

39. I base my ability to so characterize the person of ordinary skill in the art in early 1983 on my own personal experiences in academic and biotechnology industrial research at the relevant time.

X. THE STATE OF THE ART OF RECOMBINANT DNA-BASED PRODUCTION OF PROTEINS IN APRIL 1983

A. In April 1983, Co-expression Was a Novel, Non-Obvious Approach in Recombinant DNA Technology

40. Based on my personal experience and review of pre-April 1983 original research papers, I am aware of no instance in which the concept of co-expression in a

single host cell of two distinct exogenous genes encoding constituent polypeptide chains of a multimeric protein was articulated or implemented as a recombinant DNA ("rDNA") approach to the production of *any* multimeric protein, much less one as large and complex as an antibody. Consistent with the claim construction discussion above, by "exogenous genes", I mean genes that do not naturally exist in the host, but rather are heterologous or foreign to the host and have been introduced into it by recombinant means. By "co-expression", I mean the production in a single recombinantly engineered host cell of the individual polypeptide chains encoded by the introduced genes as separate protein molecules. By my read, the Cabilly patents were the first to have reported the co-expression approach for producing immunoglobulins from recombinant heavy and light chains made in a single host cell and to have demonstrated its successful practice.

41. To appreciate the ambitiousness of Cabilly *et al.'s* undertaking, and the significant advance in the art represented by their achievement, it is important to bear in mind the norms of the time.

42. As depicted in Fig. 1 of the Cabilly patents, and as would be known to a person of ordinary skill in the art in April 1983, an antibody is a multimeric protein composed of four constituent polypeptide chains. In a naturally occurring antibody, there are two identical "heavy" chains (or "H" chains) and two identical "light" chains (or "L" chains) that form what is schematically depicted as a Y-shaped molecule. A disulfide bond joins each L chain to a respective H chain, forming the "arms" of the Y, and three disulfide bonds join the two H chains at the top of the "stalk" of the Y. The heavy and light chains are so-called because they differ in molecular weight. By way of example, in antibodies of the immunoglobulin G ("IgG") isotype, the longer H chains, naturally

comprised of about 447 amino acids apiece, each have a molecular weight of about 50,000 Daltons, whereas the shorter L chains, naturally comprised of about 214 amino acids apiece, each have a molecular weight of about 25,000 Daltons. Thus, when the four chains are combined into the characteristic tetrameric form of an IgG antibody, the molecular weight of the resulting antibody is about 150,000 Daltons, strikingly larger than any other protein that had been made by rDNA techniques by April 1983.

43. Indeed, by April 1983, the vast majority of target recombinant proteins were relatively small compared to an antibody. The expression of eukaryotic genes in *E. coli*, a prokaryote and the best characterized and most widely used host cell of this era, was reviewed in Harris, *Genetic Engineering*, 4: 127-84 (1983). *See*, Table 2 for a summary of the types and sizes (molecular weights) of recombinant proteins expressed in *E. coli* prior to Cabilly *et al.'s* filing date. The successful recombinant production of proteins such as human insulin, growth hormone, interferons and β-endorphin, was widely hailed at the time because recombinant DNA technology had made possible vast quantities of medically important human proteins that were purer and expected to be safer and less expensive than their counterparts derived from human tissue (*e.g.* human growth hormone derived from the pituitaries of cadavers) or their surrogates derived from animals (*e.g.* porcine insulin derived from pigs). In the early 1980s, the recombinant production of known proteins with medical utility was considered a breakthrough and patents were regularly awarded for these efforts. *See, e.g.* U.S. Patent No. 4,517,294 (recombinant human antithrombin III); U.S. Patent No. 4,563,424 (recombinant somatostatin); U.S. Patent No. 4,530,901 (recombinant human interferon); U.S. Patent

No. 4,710,463 (recombinant hepatitis B viral ("HBV") antigens); and U.S. Patent No. 4,818,694 (recombinant herpes simplex virus ("HSV") proteins).

44. While *E. coli* was the predominant recombinant host cell in use in April 1983, strides were being made in the art to genetically engineer eukaryotic cells, including mammalian cells, for recombinant production of proteins. Examples of eukaryotic host cells and vectors and regulatory elements for use in them are disclosed in the Cabilly patents, *e.g.*, in Cabilly II at column 9, line 16-column 10, line 25.

45. For example, by April 1983, viral vectors had been the subject of significant study and development for introducing foreign DNA into mammalian host cells. Simian virus 40 ("SV40"), in particular, was a well-characterized virus at the time. SV40-derived viral vectors were in use in numerous laboratories world-wide for introducing and expressing genes encoding such proteins as human growth hormone, rat preproinsulin and proinsulin, human immune interferon and human fibroblast interferon in various mammalian host cells, including African Green Monkey Kidney cells, COS cells and human HeLa cells. *See, e.g.*, Pavlakis *et al.*, PNAS *78* (12): 7398-7402 (1981); Pavlakis and Hamer, Recent Progress in Hormone Research, 39: 353-385 (1983); Gruss and Khoury, PNAS *78* (1): 133-137 (1981); Horowitz *et al.*, J. Mol. Appl. Gen. *2*: 147-159 (1983); Lomedico, PNAS *79*: 5798-5802 (1982); Devos *et al.*, Nucl. Acids Res. *10* (8): 2487-2501 (1982); Fiers *et al.*, Phil. Trans. R. Soc. Lond. B *299*: 29-38 (1982); Gheysen and Fiers, J. Molec. Appl. Gen. *1*: 385-394 (1982); and Gray *et al.*, Nature *295*: 503-508 (1982). Other viral vectors, such as those derived from bovine papilloma virus ("BPV"), had been used by early 1983 for expression of human β interferon in C127 mouse cells. *See*, Mitrani-Rosenbaum *et al.*, Molec. Cell. Biol. *3* (2): 233-240 (1983).

46. As with the prokaryotic systems then in use, the target proteins in recombinant eukaryotic (mammalian) host cell systems were small in size relative to an antibody molecule.

47. What is perhaps more notable about the earliest recombinantly-made proteins is their lack of structural complexity. With one exception (insulin), discussed below, by April 1983, the proteins that had been produced in heterologous systems using recombinant DNA technology were all monomeric, *i.e.*, single chain proteins. In their native environments, such proteins were encoded by single genes. Not surprisingly, a "one-protein-of-interest-per-host-cell" approach was taken to produce these proteins recombinantly, because only one gene had to be introduced into a host cell to achieve this goal.

B. In April 1983, The One-Protein-Of-Interest-Per-Host-Cell Approach Would Have Been Followed By A Person of Ordinary Skill in the Art – Even For the Recombinant Production of a Multimeric Protein

48. In April 1983, the only multimeric protein that had actually been made in a heterologous host using recombinant DNA techniques was insulin, a small, dimeric protein.

49. Insulin, a polypeptide hormone that regulates glucose metabolism, is made in mammals in the pancreas. Cells in this organ express the DNA encoding insulin as a single polypeptide chain called "preproinsulin." A leader (or signal) sequence that facilitates secretion is cleaved from the polypeptide, leaving "proinsulin." Proinsulin, also a single polypeptide, is comprised of A and B chains separated by a C peptide. After folding, the C peptide is enzymatically cleaved out of the proinsulin molecule, leaving the A and B chains of insulin, which are held together by two disulfide bonds. The resulting insulin protein is a dimer (a "heterodimer" because the A and B chains differ in

amino acid sequence). The B chain of insulin contains 30 amino acids and the A chain contains 21. By way of contrast, as discussed previously, the heavy chain of an IgG antibody contains about 447 amino acids, while a light chain contains about 214. And a native antibody is a tetramer, not a dimer.

50. By April 1983, scientists at Genentech and City of Hope were considered to be among the leading recombinant DNA technologists in the world. Papers first-authored by David Goeddel, a Genentech scientist, were highly influential among the genetic engineering community, including persons of ordinary skill in the art in 1983. By April 1983, it was widely known that Goeddel *et al.* had successfully applied rDNA technology to the production of human growth hormone, human fibroblast interferon and human insulin.

51. Goeddel *et al.*, "Expression in *Escherichia coli* of chemically synthesized genes for human insulin", PNAS, 76(1): 106-110 (1979), is a paper that describes the cloning and expression of the A and B chains of human insulin using *E. coli* cells as hosts. The approach was to connect the bacterial gene encoding the *E. coli* enzyme, beta-galactosidase, to synthetic DNA encoding either the A or B chain of insulin. Each of these fused genes was inserted into a separate plasmid and each plasmid was transformed into separate *E. coli* cells. One type of cell expressed a fusion protein (a single polypeptide comprising beta-galactosidase attached to an insulin A chain) and the other type of cell expressed another fusion protein (a single polypeptide comprising beta-galactosidase attached to an insulin B chain). Each of these fusion proteins was recovered from the separate *E. coli* cultures and treated chemically, *in vitro*, to cleave off the beta-galactosidase portion of the polypeptide, leaving either A chains or B chains.

The chains were then subjected, separately, to oxidative sulfitolysis and then combined and reconstituted by reduction into dimeric insulin molecules.

52. A person of ordinary skill in the art wanting to make any multimeric protein in April 1983 would have paid close attention to Goeddel *et al.'s* statement at page 106 of the PNAS article, "We deliberately chose to construct two separate bacterial strains, one for each of the two peptide chains of insulin: the 21-amino-acid A chain and the 30-amino-acid B chain." This was the only published paper available in 1983 reporting the actual production of a multimeric protein (a simple small dimer) in a heterologous system, and there was no suggestion in it whatsoever of a co-expression approach. Rather, these leading genetic engineers expressed each of the A and B chains of insulin as a single polypeptide in a single host cell and subsequently recovered and joined them *in vitro* to make the dimer.

53. Others followed the Goeddel *el al.* approach. In Frank *et al.*, "Two Routes for Producing Human Insulin Utilizing Recombinant DNA Technology", Munch. Med. Wschr., 125, Suppl. 1: S14-S20 (1983), two Eli Lilly & Co. ("Lilly") scientists reviewed the company's approaches to making insulin recombinantly. The paper reports at S15, "The current method is to make the A and B chains in separate *E. coli* fermentations, while the second route is the production of proinsulin in a single *E. coli* fermentation and eventually to transform it to human insulin. At this point it should be emphasized that all the biosynthetic human insulin presently [*i.e.*, in 1983] being produced by Eli Lilly is derived from this chain combination procedure and that all clinical studies have been conducted with such insulin."

54. Thus, as of April 1983, according to this publication, Lilly was running two sets of commercial-scale fermentations to make A and B insulin chains in separate *E. coli* host cells, followed by *in vitro* reconstitution. The only process reported in Frank *et al.*, above, for making insulin in a *single* host cell was to make a *single* polypeptide, proinsulin, fused to an *E. coli* protein, and then chemically and enzymatically process it *in vitro* to make the dimeric insulin molecule. There is no suggestion in the paper whatsoever of co-expression of both A and B chains in a *single* host cell.

55. In my opinion, the Goeddel *et al.* approach to recombinant insulin production, and the adoption of it by a large pharmaceutical company like Lilly, would have had a profound impact on the person of ordinary skill in the art. That person would follow these leaders, even in 1983, as there had been no other reports of any other multimeric protein actually made in a heterologous system by recombinant DNA techniques. Thus, in my opinion, had a person of ordinary skill in the art set out to make a multi-chain protein in April 1983, he or she would have chosen the prevailing "one-protein-of-interest-per-host-cell" approach. Nothing in the published literature at this time, in my view, would have made obvious to a person of ordinary skill in the art what Cabilly *et al.* invented: the co-expression of heavy and light chains in a single host cell as an approach to producing immunoglobulins recombinantly.

56. Even a highly skilled scientist like 1980 Nobel Laureate Walter Gilbert made no mention of a co-expression approach to making insulin recombinantly in a 1981 article, Gilbert, Recombinant DNA Technical Bulletin *4*: 4-5 (1981). Rather, he recounted the approach, discussed above, "pioneered by Genentech, Inc." in which insulin is produced "by combining purified insulin A chains *produced by one strain of*

bacteria with insulin B chains *produced by a second strain of bacteria*" (emphasis added). He also described another approach developed in his laboratory in which a DNA sequence encoding proinsulin was expressed in *E. coli*. *See*, Talmadge *et al.*, PNAS *77*: 3369-3373 (1980) and Talmadge *et al.*, PNAS *77*: 3988-3992 (1980). In both the Genentech and Talmadge *et al.* approaches, only a single gene is recombined into a host cell, which, in my opinion, would have reinforced the prevailing one-protein-of-interest-per-host-cell approach – even for a multimeric protein.

C. Other Trends in the Art in 1983 Would Not Have Suggested Genetically Engineering Host Cells to Co-Express Antibody Heavy and Light Chains

1. Therapeutically useful monomeric proteins were still being actively pursued

57. One focus of genetic engineers in 1983 was on proteins of known therapeutic or industrial utility; the recombinant version of the protein was expected to replace the naturally-derived protein in an already-existing market. Thus, the early recombinant targets, like human growth hormone, insulin, interferon, urokinase and Factor VIII were already known to be therapeutically useful biological materials for which markets were established. Another focus was on proteins whose medical utility was clearly projected in April 1983, like tissue plasminogen activator, erythropoietin, and granulocyte-macrophage colony stimulating factor, and thus represented likely commercial targets to be pursued for recombinant production.

58. Although antibodies had been proposed in the literature as recombinant targets by April 1983, those proposals were speculative. For example, antibodies appeared in the patent literature in "laundry lists" of proteins one might produce recombinantly dating back to the 1970's (*See, e.g.* Cohen & Boyer, discussed below).

And yet, by April 1983, there were no publications reporting the production of antibodies using recombinant DNA technologies.

2. Hybridoma technology was in use in April 1983 for the production of monoclonal antibodies

59. In April 1983 the hybridoma approach pioneered by Drs. Kohler and Milstein in the 1970's was being used to make monoclonal antibodies. Continuously growing cell lines of B lymphocyte lineage, like myelomas, were fused with B lymphocytes producing antibody to an antigen of interest. The resulting "hybridomas" grew continuously in culture and continued to produce the desired antibody.

60. A person of ordinary skill in the art, would have been aware of this technology and would have perceived it as a viable approach to antibody production. The ongoing development of hybridoma technology would, in my opinion, have been another non-motivating factor influencing the person of ordinary skill in April 1983.

XI. CLAIMS 15, 17 AND 33 OF CABILLY II ARE NOT ANTICIPATED BY COHEN & BOYER

61. Dr. Jefferson Foote expresses the opinion in his report that claims 15, 17 and 33 of Cabilly II are anticipated by Cohen & Boyer. I disagree.

62. This is not to say, of course, that what is disclosed in Cohen & Boyer is not significant. On the contrary, this is the patent that disclosed their revolutionary methodology for introducing foreign DNA into microbial host cells where it would replicate and impart new "genotypical capability" to the host (col. 1, line 55).

63. The Cohen & Boyer approach was to take a DNA vector, such as a bacterial plasmid, and modify it so that it would contain DNA not normally present in the vector, but more importantly, DNA that would change the genetic make-up of the microorganism into which the modified vector would be introduced.

64. By way of illustration, a circular bacterial plasmid is enzymatically cut, at a single location, *e.g.*, with a restriction enzyme, to generate a linear DNA molecule. By any one of a variety of techniques, the ends of the linear DNA, if necessary, may be made compatible for joining ("ligating") them to another linear DNA molecule, foreign to the plasmid, thereby reforming a circular DNA that is a "hybrid" plasmid or plasmid "chimera" (col. 2, line 10). The hybrid plasmid so made is transformed into a microbial host cell where it can replicate and, under the right circumstances, express the newly introduced genetic material.

65. The work reflected in Cohen & Boyer was unquestionably ground-breaking, providing a practical approach to genetic recombination. Cohen & Boyer's methodology represents the very foundation of recombinant DNA technologies and remains, to this day, in widespread use. Nevertheless, Cohen & Boyer does not anticipate claims 15, 17 and 33 of Cabilly II.

66. Cohen & Boyer teaches that the foreign DNA molecule recombined with the vector DNA is itself a restriction fragment. That is, the foreign DNA to be introduced into the microbial host to change its genetic make-up is digested using a restriction enzyme to generate smaller DNA fragments. *See*, col. 4, lines 28-62. The resulting fragments may be separated by size and a single fragment is inserted into the vector. Any given fragment may contain no intact gene, one intact gene or more than one intact gene. Hence, the statement at col. 5, lines 64-65, "The DNA fragment may include one or more genes or one or more operons." The content of the fragment is not engineered, but rather the result of where the particular restriction enzyme cuts the foreign DNA.

67. Thus, to the extent that Cohen & Boyer discloses that the inserted DNA may contain more than one gene, the person of ordinary skill in the art would understand the patent to be teaching that such an insert contains genes that are naturally adjacent to one another in the foreign DNA prior to enzymatic digestion (as is the case for the trp operon exemplified in Example IV of Cohen & Boyer (*see*, col. 13, line 63-col. 14, line 39)) or near one another (as is the case of the inserted DNA encoding 18S and 28S ribosomal RNA exemplified in Example III of Cohen & Boyer (*see*, col.12 line 40-col. 13, line 63)).

68. The genes encoding the heavy and light chains of an immunoglobulin are not adjacent to one another, nor anywhere near each other such that they could reside on a single DNA fragment after a restriction enzyme digest. The heavy and light chain genes reside on separate chromosomes. There is no teaching in Cohen & Boyer to combine any genes located on different chromosomes into a single vector nor to transform a host cell with such a vector. Nor does Cohen & Boyer teach co-expression of heavy and light immunoglobulin chains in a single host cell. Thus, none of claims 15, 17, and 33 is anticipated by Cohen & Boyer.

69. Consequently, Dr. Foote is wrong at paragraph 66 of his report, where he states, "The Cohen & Boyer patent discloses a process for producing an antibody in a unicellular organism, *i.e.*, a single host cell, for example, a bacteria or yeast cell." In my opinion it does not, and the analysis Dr. Foote uses to reach this conclusion is flawed.

70. As reflected in his report at paragraphs 66-70 and the claim chart appended to his report as Exhibit C, to reach the conclusion that the asserted claims are anticipated, Dr. Foote has cobbled together (a) some generalized teachings that the DNA

inserted into the plasmid used to transform the host may contain more than one protein-encoding gene (*See, e.g.*, col. 9, lines 12-14: "By introducing one or more exogenous genes into a unicellular organism, the organism will be able to produce polypeptides and proteins [.]") with (b) some stray references to "globulins" and "antibodies", among many other "laundry-listed" target proteins (*See, e.g.*, col. 9, lines 28-34, where globulins/antibodies are listed among twenty or so proteins "of interest", but not among the numerous "directly useful" proteins listed in the preceding paragraph at col. 9, lines 20-27).

71. As indicated above, I have been informed that anticipation requires more than finding some elements of a claim here and there within a prior art reference and drawing some inferences based on hindsight; rather, an anticipatory reference has to disclose all the elements of the claim as arranged in the claim. I see no disclosure in Cohen & Boyer of elements as arranged in claims 15, 17 or 33 of Cabilly II.

72. Dr. Foote can point to no single part of Cohen & Boyer that discloses a method for producing an immunoglobulin molecule wherein a single host cell is engineered to contain DNA sequences encoding the constituent heavy and light chains and wherein the heavy and light chains are produced in such host cells as separate molecules as is claimed in claim 33. No such disclosure exists in Cohen & Boyer. Indeed, nowhere in this patent are heavy or light chains of an immunoglobulin mentioned, nor any approach to obtaining DNA sequences that encode them. Consequently, there is no disclosure of a vector containing heavy and light chain sequences as claimed in claim 15 nor a host cell transformed with such vector as claimed

in claim 17. In my opinion, Dr. Foote is reading far more into Cohen & Boyer than is warranted.

73. I note further that Dr. Foote's anticipation analysis of claim 33 rests in part on Example IV of Cohen & Boyer (*See*, paragraphs 69-70), but, in my opinion, that reliance is misplaced. Example IV does not pertain to recombinant immunoglobulin production as claimed in Cabilly II, but rather to restoring the ability of a mutant strain of *E. coli* to grow in the absence of tryptophan by introducing into the *E. coli* mutant a plasmid into which the *E. coli* trp operon had been inserted (*See*, Cohen & Boyer, col. 13, line 63 – col. 14, line 39).

74. The *E. coli* trp operon is a stretch of DNA in the *E. coli* chromosome containing multiple contiguous genes encoding enzymes that catalyze sequential steps in a pathway by which precursor compounds are converted into the amino acid tryptophan.

75. "Wild-type" *E. coli* cells naturally contain and can express all the enzymes encoded by the genes of the trp operon, allowing such cells to grow in the absence of tryptophan (as long as precursor compounds of the pathway are present). However, mutants that have lost the ability to produce one or more of the operon-encoded polypeptides also lose the ability to make tryptophan and their growth medium has to be supplemented.

76. In Cohen & Boyer's Example IV, a hybrid plasmid was constructed from the *E. coli* plasmid, ColE1, and a fragment of the bacteriophage ϕ80pt190, which contains a complete *E. coli* trp operon. A mutant *E. coli* host cell with a "ΔtrpE5" deletion was transformed with this plasmid. As stated in the patent at col. 14, lines 21-24, "ΔtrpE5" is a trp operon deletion entirely within trp E and removing most of the

gene." Thus, the mutant *E. coli* host cell used in this experiment was effectively missing a trp E gene but still contained the rest of the genes of the trp operon. Such host cells could not grow in the absence of tryptophan because the enzyme encoded by the E gene was not present to catalyze its step of the tryptophan pathway.

77. However, after transformation with the hybrid plasmid, *E. coli* cells were selected that were capable of growing in the absence of tryptophan. The introduction of the hybrid plasmid provided the genetic capability to the mutant host to produce the enzyme encoded by the trp E gene. The rest of the enzymes were also being produced, allowing the transformed cells to grow in the absence of tryptophan. Data are provided in Hershfield *et al*. PNAS 71 (9): 3455-3459 (1974), a paper that reports the Cohen & Boyer Example IV in greater detail, which indicate that all the genes of the introduced trp operon were being expressed in the recombinant host.

78. Thus, in Example IV of Cohen & Boyer, the genetic make-up of the *E. coli* host cell was altered by the introduction of only one gene, the trp E gene, a gene native to the host. The other genes on the introduced operon were also native to the *E. coli* host cell (and, in fact, already existed in the chromosomal DNA of the *E. coli* host). That the *E. coli* polypeptides were expressed and functional in an *E. coli* host was not, in my view, particularly remarkable because this is a homologous system, where genes native to the host are expressed and proteins native to the host perform their natural functions in the native environment. In fact, experiments utilizing the same bacteriophage ϕ80pt190 carrying the complete *E. coli* trp operon had previously shown that deletions in the trp E gene could be rescued by bacteriophage-mediated transduction (Deeb *et al.*, Virol. 31:289 (1967)).

79. The truly unique features of Cohen and Boyer's groundbreaking work were the use of a plasmid vector ColE1, a restriction enzyme EcoRI to digest both the plasmid vector and the ϕ80pt190 DNA, ligation of the digested plasmid vector and ϕ80pt190 DNA, followed by transformation of the host cell. In Example IV, the fact that the successfully introduced trp E gene functioned in *E. coli* was, therefore, not remarkable, given the earlier work of Deeb *et al.* I do not believe a person of ordinary skill in the art would have viewed this result as the same as Cabilly *et al.'s* showing that foreign antibody heavy and light chain DNA sequences could be expressed in a heterologous host and that the recombinantly produced polypeptide chains could be assembled into a functional antibody.

80. I also note that Dr. Foote's anticipation analysis of claim 15 rests in part on Example III of Cohen & Boyer (*see* the "§102 Invalidity Claim Chart" in Exhibit C to Dr. Foote's report), which he implies is relevant to the "different insertion sites" language of claim 15.

81. As indicated above, it is my understanding that "different insertion sites" in claim 15 was agreed to mean "in the vector, the DNA sequence encoding for at least the variable domain of the heavy chain is not contiguous to the DNA sequence encoding for at least the variable domain of the light chain, the former being separated from the latter by sufficient DNA sequence to ensure independent expression." Claim Constr. Or. at 4.

82. According to Dr. Foote's claim chart at C-3:

> [Cohen & Boyer] does not explicitly disclose whether the one or more genes are located at different insertion sites (non-contiguous). However, Example III teaches transcription of 18S and 28S rRNA in *E. coli*. It was

> known in the art that 18S and 28S rRNA [sic, ribosomal DNA] are non-contiguous and thus are located at different insertion sites.

83. There is an error in this entry on Dr. Foote's claim chart. It is not correct that Example III "teaches transcription of 18S and 28S rRNA in *E. coli*."[1] Cohen & Boyer report that the hybrid plasmid, CD4, contained inserted DNA that "annealed almost equally with both the 18S and 28S rRNA species" (col. 13, lines 9-10). However, in the minicell experiment reported at col. 13, lines 32-61, there is no showing that both 18S rRNA and 28S rRNA species were transcribed from the inserted DNA since no attempt was made to fractionate either the minicell-synthesized ^{3}H RNA or the *X. laevis* DNA into their respective 18S and 28S components.

84. Furthermore, for the reasons I discuss below, I do not believe a person of ordinary skill in the art in April 1983 would have considered the genes encoding 18S and 28S rRNA to be non-contiguous, nor would he or she view the CD4 construct of Cohen & Boyer's Example III to anticipate the vector claimed in claim 15 of Cabilly II.

85. By Cabilly *et al.*'s priority date, it was known that the DNA encoding rRNA in *Xenopus laevis* is present as a repeating unit. *See*, *e.g.*, Wellauer *et al.*, PNAS 71(7): 2823-2827 (1974). It was also known that the CD4 plasmid described in Example III of Cohen & Boyer, and further described in Morrow *et al.*, PNAS 71(5): 1743-1747 (1974), contained an entire ribosomal DNA repeating unit. *See*, Boseley *et al.*, Cell 17:19-31, at 20 (1979).

86. As shown in Fig. 6 of Wellauer *et al.*, *supra*, which is a map of one repeating unit of *X. laevis* ribosomal DNA, there are EcoRI cleavage sites that could

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[1] Ribosomal RNA or "rRNA" is a nucleic acid that forms part of the cellular machinery for translating messenger RNA ("mRNA") into proteins. Ribosomal RNA is transcribed from ribosomal DNA but is not itself translated into any protein.

potentially generate the DNA encoding 18S and 28S as separate restriction fragments, or, in the case of a partial digestion, as a single restriction fragment with both DNA sequences. At that time, obtaining partial restriction enzyme digests was common due to inhibitory impurities in DNA preparations, and there was no reporting in Cohen & Boyer of any attempt to demonstrate that a complete digest had been achieved. In either case, I do not believe a person of ordinary skill in the art would consider the genes encoding 18S and 28S rRNA to be distant from one another as is the case for genes encoding heavy and light chains of immunoglobulins. A person of ordinary skill would have understood the genes encoding 18S and 28S rRNA to be in close enough proximity to one another to be excisable by EcoRI on a single partial digestion fragment or on two contiguous restriction fragments. *See*, Fig. 6 of Wellauer, *et al.*

87. The complete sequence of the *X. laevis* ribosomal DNA genes is now available in GenBank (http://www.ncbi.nlm.nih.gov/nuccore/X02995.1). This sequence confirms the locations of the EcoRI sites. Also, the GenBank data show that the 18S and 28S genes are separated by only 1,100 nucleotides which is quite close and allowed Cohen and Boyer to clone both genes together. It is now known that a gene encoding 5.8S rRNA intervenes between the 18S and 28S genes, so the 18S and 28S genes are not adjacent. Nevertheless, the DNA encoding 18S, 5.8S and 28S rRNA form a repeating unit, much like an operon, that would be excisable as a single restriction fragment. In my opinion, partial digestion by EcoRI best explains the origin of the 18S and 28S-encoding DNA inserted into Cohen & Boyer's CD4 plasmid in Example III.

88. Thus, the CD4 plasmid of Cohen & Boyer's Example III is not analogous to the vector of claim 15 of Cabilly II. The genes for 18S and 28S rRNA inserted into the

CD4 plasmid naturally exist in very close proximity to one another in the source DNA. This is not the case for DNA sequences encoding heavy and light chains of immunoglobulins, which are distant from one another in natural sources. There is no teaching in Cohen & Boyer of engineering genes that are not proximate to one another into a plasmid vector, or transforming a host with such a vector, or producing proteins in such a host.

89. Lastly, I would note that the portions of the Cohen & Boyer patent that Dr. Foote cites in paragraph 77 of his report are incomplete quotes and do not support his assertion that Cohen & Boyer "discloses a novel recombinant plasmid having genes encoding for at least the variable regions of an immunoglobulin heavy chain and light chain." For example, whereas Dr. Foote quotes Cohen & Boyer as stating, "the plasmid must be able to accommodate…one or more genes", the full quote from Cohen & Boyer at col. 2, lines 58-60 states "First, the plasmid must be able to accommodate a replicator locus and one or more genes that are capable of allowing replication of the plasmid." By this statement I understand, as would a person of ordinary skill in the art understand, Cohen & Boyer to mean that the plasmid must retain all the functions needed for it to replicate in the host cell following transformation which is a different meaning from that implied by Dr. Foote's incomplete and inaccurate quote.

90. In summary, Cohen & Boyer does not disclose the subject matter claimed in claims 15, 17 and 33 of Cabilly II and, therefore, it is my opinion that these claims are not anticipated by Cohen & Boyer.

XII. CLAIM 33 OF CABILLY II IS NOT OBVIOUS IN VIEW OF COHEN & BOYER IN COMBINATION WITH RIGGS & ITAKURA

91. In paragraph 83 of his report, Dr. Foote states, "To the extent that Cohen & Boyer does not teach or disclose 'producing' an assembled 'immunoglobulin molecule', as required by [claim 33], solely from the co-expression of the heavy and light chains in a host cell, the Riggs & Itakura reference provides this teaching." Dr. Foote further states that, "[a] person of ordinary skill in the art would have also reasonably predicted that combining Cohen & Boyer with the *in vitro* techniques in Riggs & Itakura would have resulted in an assembled immunoglobulin molecule from its separate constitutive chains in the cell lysate" (Foote report at paragraph 85). I do not agree with this characterization of the combined teachings of these references or with Dr. Foote's conclusion.

92. Riggs & Itakura recount the Genentech/City of Hope approach to making insulin recombinantly that is also the subject of Goeddel *et al.* PNAS, 76(1): 106-110 (1979), which I discussed at length, above, in Section X.B. Briefly, this was the approach in which separate *E. coli* host cells were transformed with plasmids carrying either (1) a DNA sequence consisting of the bacterial gene encoding beta-galactosidase fused to a synthetic gene encoding the A polypeptide chain of insulin or (2) a DNA sequence consisting of the bacterial gene encoding beta-galactosidase fused to a synthetic gene encoding the B-polypeptide chain of insulin.

93. In my opinion, the combined teachings of Cohen & Boyer with Riggs & Itakura do not make obvious the co-expression of both a heavy and light immunoglobulin chain in a single host cell as claimed in claim 33. On the contrary, the combined teachings, in my view, would have reinforced in the mind of a person of ordinary skill that the constituent chains of a multimeric protein should be made as separate proteins in

separate microbial hosts. In other words, there is nothing about the combined teachings that would have made a person of ordinary skill in the art stray from the then-prevailing one-protein-of-interest-per-host-cell approach.

94. From the combined teachings of Cohen & Boyer and Riggs & Itakura, a person of ordinary skill in the art might also have concluded that for expression in a microorganism, it would be desirable to fuse the gene encoding the eukaryotic protein to DNA encoding a bacterial protein. This, too, is a different approach than the one taken by Cabilly *et al.*

95. Furthermore, the success with insulin would not have been considered predictive of whether the same approach would work for an immunoglobulin. This is because the heavy and light chains of immunoglobulins are different proteins than the A and B chains of insulin, and any eukaryotic protein newly expressed in *E. coli* would have been considered potentially vulnerable to damage in the foreign bacterial environment, *e.g.*, by proteolytic degradation. Prior to Cabilly *et al.'s* showing, it would not have been obvious to a person of ordinary skill in the art that heavy or light chains made recombinantly in *E. coli* would not be damaged, which, in turn, could affect their ability to be reconstituted as a functional molecule.

96. For the foregoing reasons, it is my opinion that Cohen & Boyer combined with Riggs & Itakura do not render obvious claim 33 of Cabilly II.

XIII. CLAIMS 15, 17 AND 33 OF CABILLY II ARE NOT ANTICIPATED BY BUJARD

97. According to Dr. Foote, Bujard discloses a process for producing immunoglobulins in a single host cell. (Foote Report at paragraph 71). By combining the laundry-listing of a variety of immunoglobulins among scores of other proteins of

interest (col. 5, lines 11-28) with a general statement that "[t]he proteins may be prepared as a single unit or as individual subunits and then joined together in appropriate ways" (col. 4, lines 19-21), Dr. Foote concludes, "Thus, the Bujard disclosure clearly differentiates between the production in a single host cell of single chains and tetrameric immunoglobulins." *Id.* I disagree. As with Cohen & Boyer, Dr. Foote has pieced together stray words and phrases from Bujard and has, in my opinion, applied hindsight to make the case that Bujard anticipates claims 15, 17 and 33 of Cabilly II.

98. In my opinion, Bujard is not an anticipatory reference. Nowhere in Bujard does one find the elements of the inventions claimed in claims 15, 17 and 33 as arranged in these claims of Cabilly II. Bujard does not disclose a vector containing a first DNA sequence encoding at least a variable domain of heavy chain and a second DNA sequence encoding at least a variable domain of a light chain located at different insertion sites (claim 15). Nor does it disclose a host cell transformed with such a vector (claim 17). Nor does it disclose a process for producing an immunoglobulin molecule by co-expressing such heavy and light chain-encoding DNA sequences in a single host cell as separate proteins (claim 33).

99. Bujard is an extension of the basic methodology disclosed in Cohen & Boyer, and in fact, Dr. Cohen is a co-inventor of the Bujard patent. Bujard *et al.'s* focus was on finding and using strong promoters to drive transcription of DNA sequences encoding a protein of interest introduced into a host cell by recombinant DNA techniques without interfering with expression of the marker used to select transformants. Bujard *et al.* discovered that strong promoters need to be balanced by strong terminators. Thus the invention provides methods and compositions for "preparing and cloning strong promoter

and terminator regulatory signals and utilization of the strong regulatory sequences in the transcription and expression of genes of interest." (col. 2, lines 28-32).

100. Bujard discloses a generic vector construct, with which to transform microorganism hosts, that contains four modular elements: (1) a strong promoter followed by (2) a DNA sequence of interest followed by (3) a balanced terminator followed by (4) a marker allowing for selection of transformants (col. 2, lines 8-13).

101. Elsewhere in the patent, Bujard *et al.* disclose that "the promoter and terminator may be separated by more than one gene, that is, a plurality of genes, including *multimers* and operons" (col. 3, lines 46-48 (emphasis added)).

102. Dr. Foote opines in paragraph 55 of his report that the term "multimers" has significance and would be understood by the person of ordinary skill in the art to mean "genes encoding multimeric proteins." His reasoning is as follows:

> A multimeric protein can be composed of all identical subunits or a mixture of two or more chemically distinct subunits. However, when a multimer is encoded by "a plurality of genes", as in the Bujard patent (col. 3:48), *with each gene making a different type of polypeptide, this can only be construed as the latter type, i.e., a protein with chemically distinct subunits*. While a construct with multiple repeats of the same gene could be accommodated by the language of the above-quoted passage, such a construct would be so implausible in 1981 that I do not believe that meaning was the inventor's intent. (emphasis added)

Foote Report at paragraph 55.

103. Construing "multimers" to mean genes encoding a multimeric protein is a key predicate to Dr. Foote's anticipation analysis and one with which I disagree.

104. In my opinion, the term "multimers" was used by Bujard to mean multiple repeating units of the same gene. *See, e.g.* Christie *et al.*, "Selective amplification of

variants of a complex repeating unit in DNA of a crustacean", PNAS, 77(5):2786-2790 (1980) ("Treatment of total DNA with *Hind III* nuclease produced an 8-base pair monomer and *multimers* to the size of an octamer.") (Abstract at 2786, emphasis added). At Cabilly *et al.'s* priority date in 1983, the term "multimers" would also have been understood by a person of ordinary skill in the art to mean multiple repeating units of the same gene that could be contained within a single restriction fragment. *See,* Frommer *et al.*, Nuc. Acids Res. 10 (2): 547-563 (1982) (describing restriction fragments that contained "adjacent multimers separated by an increment of 5 bp"); Israelewski, Nuc. Acids Res. 11 (20): 6985-6996 (1983) (describing "dimers and multimers" of a repeated sequence in rDNA of *C. thummi*).

105. A person of ordinary skill in the art would have understood Bujard's statement at col. 3, lines 46-48 that "the promoter and terminator may be separated by more than one gene, that is, a plurality of genes, including multimers and operons" to mean much the same thing as Cohen & Boyer's statement at col. 5, lines 64-65 that "[t]he DNA fragment [inserted into the plasmid] may include one or more genes or one or more operons." That is, the "plurality of genes, including multimers and operons" would be contained on a single restriction fragment excisable from some natural source of DNA.

106. At col. 7, lines 40-45, Bujard *et al.* state:

> *The methods for preparing the subject compositions will be conventional.* The various DNA fragments and sequences can be obtained from a variety of sources by restriction mapping and endonuclease cleavage to provide fragments having the desired intact sequence or gene. (emphasis added)

107. The foregoing passage of Bujard reinforces my view that any plurality of genes between Bujard's strong promoter and terminator was not engineered into the

vector from separate locations in the source DNA (as would be the case with sequences encoding immunoglobulin heavy and light chairs as discussed above), but rather, happened to be in close enough proximity to one another in the source DNA to be excisable by restriction enzyme digestion (as would be the case with repeating DNA units ("multimers") and bacterial operons). Consequently, I do not believe Bujard provides an anticipatory teaching of the vectors, host cells and method for producing an immunoglobulin by co-expressing heavy and light chains in a single host cell as claimed in Cabilly II.

108. I also do not believe that the Experimental section of Bujard provides "further evidence" of co-expression of multiple eukaryotic genes in a single host cell (Foote report at paragraph 74). In the experimental example of Bujard, two bacterial, *i.e.*, prokaryotic, genes (beta-galactosidase and *tet*) are inserted into a single plasmid. The gene for beta-galactosidase is located between the strong promoter and terminator, while the *tet* (for tetracycline resistance) gene is inserted after the terminator sequence. Thus, this construct is one in which there is a *single* gene encoding of *single* protein of interest (beta-galactosidase) situated on the same plasmid as a gene encoding a selectable marker (*tet*). This is *not* an example of *co*-expression in a single host cell of *two* eukaryotic genes encoding *two* proteins of interest (the constituent chains of a multimeric protein) as taught in the Cabilly patents.

109. Dr. Foote's reliance on Bujard's disclosure at col. 8, lines 12-17 that "the region between the promoter and terminator may be designed so as to provide for a plurality of restriction cleavage sites, allowing for the introduction and removal of DNA fragments without interruption of the remainder of the vehicle" as supporting his

anticipation analysis of claim 15 is similarly misplaced. According to Dr. Foote, when combined with Bujard's disclosure of immunoglobulins in a long laundry list of proteins of interest, this passage supposedly teaches the placement of genes encoding immunoglobulin heavy and light chains at different insertion sites on the same vector and, hence, anticipates claim 15 (Foote Report at paragraph 78). I disagree. One of ordinary skill in the art would have understood Bujard to be stating that a single restriction fragment to be inserted between the strong promoter and terminator may be generated from natural sources with any one of a variety of restriction enzymes. By designing multiple restriction sites into the region between the promoter and terminator, the plasmid has the ability to accommodate an inserted fragment resulting from any one of various restriction enzyme digests. This was a particularly important feature in the pre-PCR era of the early 1980s when the manipulation of genes was very dependent on the fortuitous positioning of restriction enzyme sites.

110. I do not view the disclosure of multiple restriction enzyme cleavage sites between the promoter and terminator in Bujard's plasmids as a teaching of a vector containing immunoglobulin heavy and light chain genes at different insertion sites, as claimed in claim 15, or of a host cell transformed with such a vector, as claimed in claim 17. Therefore, these claims are not anticipated by this or any other passage of Bujard.

111. Moreover, I disagree with Dr. Foote's position that Bujard's teaching that the "proteins may be prepared as a single unit or as individual subunits and then joined together in appropriate ways" (Bujard at col. 4, lines 14-21), "clearly differentiates between the production in a single host cell of single chains and tetrameric immunoglobulins" (Foote Report at paragraph 71). In my opinion, that passage stays true

to the prevailing one-protein-of-interest-per-host-cell paradigm that existed prior to the Cabilly co-expression approach. If the protein were monomeric, it would be prepared as a "single unit." If, however, the protein contained multiple "subunits," those subunits would be prepared individually (*i.e.*, *not* in the same host cell, but rather in separate hosts) and would be "joined together in appropriate ways". I note that the first protein of interest on Bujard's list is insulin (col. 4, line 32). Given that the Goeddel *et al* paper, discussed above in Section X.B., was published two years before Bujard was filed, I believe the reference to preparing subunits individually and subsequently joining them would likely guide the skilled reader not to co-expression but to expressing single protein chains in single hosts, followed by *in vitro* reconstitution, as was done to make insulin recombinantly.

112. I further disagree with Dr. Foote's position that Bujard "teaches *away* from production of light chains in one culture and heavy chains in another, to be combined chemically at a stage after their harvest and isolation" (Foote Report at paragraph 58, emphasis in original). Dr. Foote reasons that since an entry for "free heavy chains" was left off Bujard's laundry list of proteins of interest, which otherwise contained entries for several immunoglobulin isotypes and "free light chains" (*see*, col. 5, lines 11-28), a person of ordinary skill in the art would understand that producing a heavy chain in a host as the only recombinant protein was not preferred. Rather, from the listing of immunoglobulins by formula, *e.g.* IgG as γ2κ2 or γ2λ2, Dr. Foote opines that the person of ordinary skill "would understand that these heterotetramers (or 'fragments thereof') would be produced by co-expression of heavy and light chains within the same cell." (Foot Report at paragraph58).

113. One of ordinary skill in the art would not have viewed the omission of free heavy chains from a list with approximately one hundred proteins on it in the same way as Dr. Foote. I do not believe, as Dr. Foote asserts, that Bujard would be understood to describe co-expressing heavy and light chains in a single host cell as a recombinant approach to the production of immunoglobulins because it includes immunoglobulins and free light chains but not free heavy chains on a lengthy list of proteins.

114. One of ordinary skill in the art would have recognized that the laundry list of Bujard, spanning col. 4, line 32 to col. 6, line 6, is disorganized and redundant in many places. For example, insulin is mentioned in two places, as is albumin, and erythropoietin is mentioned three times. Thus, I do not believe that one of ordinary skill in the art would have ascribed the same significance to this omission as Dr. Foote does.

115. Bujard's list references several multi-subunit proteins in addition to immunoglobulins, including insulin, hemoglobin, histocompatibility proteins, and the glycoprotein hormones follicle stimulating hormone (FSH) luteinizing hormone (LH) and human chorionic gonadotropin (HCG).[2] However, all Bujard says about subunited proteins is that "[t]he proteins may be prepared. . . as individual subunits and then joined together in appropriate ways." (col. 4, lines 19-21). Given this teaching and the state of the art at the time, it is my view that a person of ordinary skill in the art, if motivated to make a multimeric protein on Bujard's list, would have tried the single-protein-of-interest-per-host-cell approach that had been used successfully for insulin. He or she

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[2] From the literature I have reviewed on hemoglobin (a tetrameric protein with two α subunits and two β subunits) and the glycoprotein hormones FSH, LH and HCG (each of which are dimers with an α subunit and a β subunit), I note that scientists working to produce these proteins recombinantly first reported co-expressing constituent polypeptide chains in a single host cell well after Cabilly *et al.*'s priority date. *See, e.g.*, Hoffman *et al.*, PNAS 87:8521-8525 (1990) (tetrameric human hemoglobin made recombinantly in *E. coli* by co-expression); and Reddy *et al.*, U.S. Patent No. 5,639,639 (disclosing co-expression approach for making HCG, LH and FSH recombinantly, claiming priority to November 2, 1983.)

would not have gleaned the co-expression approach of Cabilly *et al*. from the teachings of Bujard.

116. For all the foregoing reasons, it is my opinion that Bujard does not anticipate claims 15, 17 or 33 of Cabilly II.

XIV. CLAIM 33 OF CABILLY II IS NOT OBVIOUS IN VIEW OF BUJARD IN COMBINATION WITH RIGGS & ITAKURA

117. In my view, the combined teachings of Bujard and Riggs & Itakura are no different than the combined teachings of Cohen & Boyer and Riggs & Itakura, discussed previously in Section XII. Together, they reinforce the then-prevailing one-protein-of-interest-per-host-cell approach, the only approach that had been taken at that time with a multimeric eukaryotic protein, insulin. Assuming one of ordinary skill in the art had selected an immunoglobulin from Bujard's list to pursue as a recombinant target, he or she would, in my opinion, have followed the approach taken for insulin reported in Riggs & Itakura. Applying that approach to immunoglobulins, the person of ordinary skill in the art would have tried to produce heavy chains and light chains in separate host cells.

118. Furthermore, as discussed previously, the success with making insulin chains recombinantly in separate hosts and then joining the A and B chains *in vitro* would not have been viewed as predictive for other multimers, such as an immunoglobulin. That is, because immunoglobulin heavy and light chains differ significantly from insulin A and B chains, both physically (size) and chemically (sequence), a person of ordinary skill in the art would not have been confident that heavy and light chains made in a bacterial cellular environment would not have been damaged in some way that would have prevented production of a functional immunoglobulin molecule.

119. In summary, it is my opinion that Bujard in combination with Riggs & Itakura would not have made claim 33 of Cabilly II obvious to a person of ordinary skill in the art in April 1983.

XV. CLAIMS 20, 27, 43 AND 46 OF CABILLY III ARE NOT INVALID FOR OBVIOUSNESS-TYPE DOUBLE PATENTING IN VIEW OF CLAIM 2 OF CABILLY I IN COMBINATION WITH EITHER COHEN & BOYER OR BUJARD ALONE OR IN FURTHER COMBINATION WITH ITAKURA & RIGGS

120. As I understand Dr. Foote's ODP theory, he is of the opinion that claim 2 of Cabilly I, when combined with either Cohen & Boyer or Bujard, makes claims 20, 27, 43 and 46 of Cabilly III obvious. However, in the event Cohen & Boyer and Bujard do not teach assembled immunoglobulins (which they do not, as discussed above), he adds Itakura & Riggs into his obviousness combination.

121. Claim 2 is dependent on claim 1 of Cabilly I, and the language of those claims is as follows:

> 1. A method comprising
>
> (a) preparing a DNA sequence encoding a chimeric immunoglobulin heavy or light chain having specificity for a particular known antigen wherein a constant region is homologous to the corresponding constant region of an antibody of a first mammalian species and a variable region thereof is homologous to the variable region of an antibody derived from a second, different mammalian species;
>
> (b) inserting the sequence into a replicable expression vector operably linked to a suitable promoter compatible with a host cell;
>
> (c) transforming the host cell with the vector of (b);
>
> (d) culturing the host cell; and
>
> (e) recovering the chimeric heavy or light chain from the host cell culture.

2. The method of claim 1 wherein the first mammalian species is human.

122. Thus, both of these claims involve chimeric constructs where the variable and constant regions of the heavy or light chain are derived from different mammalian species, and, in the case of claim 2, the constant region of the heavy or light chain is specified to be human.

123. Claims 20, 27, 43 and 46 of Cabilly III also involve constructs where the constant regions of the heavy and light chains are human.

124. While the claims of Cabilly III require co-expression of a heavy and light chain in a single host cell, the claims of Cabilly I set forth a process in which a single heavy or a single light chain is expressed in a single host cell.

125. I have been informed that during the reexamination of Cabilly II, the Patent Office rejected the claims on obviousness-type double patenting grounds based on the claims of Cabilly I in view of various prior art references. Eventually, as I understand it, the Patent Office withdrew the rejections and, in an Office Action mailed February 16, 2007 (a copy of which has been provided to me), made the following statement on page 19: "The reference Cabilly 1 patented invention *differs* from the instant patent [Cabilly II] since it [Cabilly I] fails to claim the co-expression of light and heavy antibody chains in a single host cell" (emphasis in the original).

126. Like the claims of Cabilly II, the claims of Cabilly III reflect the concept of co-expression, but are of different scope than the claims of Cabilly II in that the Cabilly III claims all require that the heavy and light chain constructs have human constant regions.

127. I have been asked to assume that the Patent Office's characterization of the claims of Cabilly I as failing to involve co-expression is correct. This is consistent with my understanding of claim 1, which I believe one of ordinary skill in the art would share. The process claimed in Cabilly I involves making a chimeric heavy chain or a chimeric light chain in a host cell, *i.e.*, a single expression approach.

128. Thus, the distinction between the claims of Cabilly I and those of Cabilly III that I have been asked to address is the difference between expression of a single chimeric heavy or light chain in a host cell and co-expression of both the chimeric heavy and light chains in a single host cell, in view of Cohen & Boyer or Bujard alone or in further combination with Riggs & Itakura.

129. As I have discussed previously, I do not find any teaching in either Cohen & Boyer or Bujard to engineer a vector or a host cell to contain *both* a gene encoding a heavy chain *and* a gene encoding a light chain of an antibody. Adding Cohen & Boyer or Bujard to claim 2 of Cabilly I, which calls for making either a chimeric heavy chain *or* a chimeric light chain, therefore does not extend the concept of making a single antibody chain in a single host cell (single expression) to making both antibody chains in a single host cell (co-expression), as called for by the claims of Cabilly III. Consequently, I do not believe a person of ordinary skill in the art would find co-expression obvious from the combination of claim 2 of Cabilly I with Cohen & Boyer or Bujard. I also do not believe the combination of claim 2 of Cabilly I with Cohen & Boyer or Bujard would resolve the issues I've pointed out earlier regarding whether these particular polypeptides, *i.e.*, the heavy and light chains of an antibody, could be made in heterologous hosts such

as *E. coli*. without damage or degradation such that they could form a functional antibody.

130. Furthermore, as I have also previously discussed, adding Riggs & Itakura to the analysis only reinforces the one-protein-of-interest-per-cell approach that was prevalent at Cabilly's priority date.

131. As I have discussed throughout this report, I do find Cabilly *et al.*'s co-expression approach to be novel and non-obvious in view of the art relied on by Dr. Foote, given the state of the art in April 1983 (as apparently the Patent Office also concluded during the reexamination of Cabilly II). Therefore, it is my opinion that claims 20, 27, 43 and 46 of Cabilly III are not obvious over claim 2 of Cabilly I in combination with Cohen & Boyer or Bujard alone or further in view of Riggs & Itakura. These combinations do not, in my view, provide the motivation to switch from a one-protein-of-interest-per-cell approach nor a reasonable expectation that one could successfully produce a functional antibody from heavy and light chains produced in heterologous hosts.

Dated:

November 10, 2014

John Fiddes. Ph.D.

EXHIBIT A

John Fiddes, Ph.D.

28110 Story Hill Lane, Los Altos Hills, CA 94022 650.743.2266 jfiddes@sbcglobal.net

SUMMARY

- Accomplished biopharmaceutical executive with 30+ years experience in drug discovery and development.
- Experienced at moving research programs rapidly from discovery to clinical development.
- Focused on integration of science and business to generate commercial value from innovative research.

ACCOMPLISHMENTS

- Developed and implemented strategic business and R&D plans for early-stage companies.
- Built integrated research and development organization from scratch.
- Led groups of up to 50 R&D employees with full budget responsibility.
- Successfully presented strategic business and R&D plans to 50+ venture capital and mezzanine investors to support corporate financings.
- Moved research programs from the bench to the clinic—joint responsibility for Scios' first IND in wound healing and full responsibility for IntraBiotics' first antimicrobial IND, filed only 18 months after company start-up.
- Established and managed multiple corporate partnerships with pharmaceutical and biotechnology companies in the US, Europe and Japan—involved extensive interactions with business development and legal colleagues.
- Built portfolio value by identifying and in-licensing opportunities ranging from early-stage research technologies through clinical-stage programs.
- Developed broad areas of research and business focus including endocrinology, growth factors and angiogenesis, autoimmune diseases, antimicrobials and oncology.
- Established strong intellectual property positions through inventions and patent portfolio management.
- Identified antimicrobial product opportunities for non-profit organization.

CORPORATE EXPERIENCE

BIOPHARMACEUTICAL CONSULTANT *Los Altos Hills, California* **2005 – present**

- Provided support and direction for the HIV-focused non-profit, California Antiviral Foundation.
- Identified and developed antiinfectives strategies for the non-profit, Institute for OneWorld Health.
- Review investment and product opportunities in antimicrobials and protein therapeutics.
- Provide support for venture capital partnerships and biotechnology companies.

GENENCOR INTERNATIONAL INC. *Palo Alto, California* **2003 – 2005**
Vice President Research, Health Care

- Led 50-person research organization focused on oncology and inflammation.
- Moved lead oncology program from research to pre-IND development.

TAO BIOSCIENCES LLC *Alameda, California* **2002 – 2003**
Chief Executive Officer

- Developed business plan to re-focus discovery-stage, antiinfectives company.
- Presented plan to over 50 venture capital partnerships.
- Completed detailed scientific, business and IP due diligence with five VCs.

THE VERTICAL GROUP *Summit, New Jersey* **2001 – 2002**
Consultant

- Evaluated investment opportunities in tissue engineering.

INTRABIOTICS PHARMACEUTICALS INC. *Mountain View, California* **1994 – 2001**
Chief Technical Officer and Vice President, Preclinical Research 2000 - 2001
Vice President, Research and Development 1994 - 2000

- Worked with CEO to found company and secure initial VC financings.
- Built 50-person R&D organization.
- Led team that filed company's first IND for oral mucositis.
- Created follow-on anti-infectives discovery research program involving multiple corporate partnerships.

IMMULOGIC PHARMACEUTICAL CORPORATION Palo *Alto, California* **1991 – 1994**
Vice President, Discovery Research
- Led 40-person research organization focused on novel, antigen-based approaches to treat autoimmune diseases.

CALIFORNIA BIOTECHNOLOGY INC. (SCIOS INC.) *Mountain View, California* **1983 – 1991**
Deputy Director, Research 1988 - 1991
Vice President, Research 1986 - 1991
Senior Scientist 1983 - 1986
- Led team that cloned atrial natriuretic peptide, the precursor to the marketed product, Natrecor®.
- Championed bFGF program from "clone to clinic."
- Established company's worldwide proprietary position on bFGF and $VEGF_{121}$.
- Managed Kaken partnership that resulted in the Japanese marketing of bFGF (Fiblast®) for recalcitrant wounds.

ACADEMIC EXPERIENCE

COLD SPRING HARBOR LABORATORY *Cold Spring Harbor, New York* **1980 – 1983**
Senior Staff Investigator
Research focused on the human glycoprotein hormone genes.

EDUCATION

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO *San Francisco, California* **1977 – 1980**

Postdoctoral Research Fellow "Human growth hormone and human glycoprotein hormone genes"
Supported by Anna Fuller Fund Fellowship. Advisor: Dr. Howard Goodman

KINGS COLLEGE, CAMBRIDGE UNIVERSITY *Cambridge, England* **1973 – 1977**

Ph.D. "Sequencing of the bacteriophage ΦX174 and G4 genomes"
Research conducted at the MRC Laboratory of Molecular Biology. Advisor: Dr. Fred Sanger

UNIVERSITY OF EDINBURGH *Edinburgh, Scotland* **1969 – 1973**

B.Sc. Biological Sciences (Molecular Biology) with First Class Honors

CORPORATE BOARDS

ASILOMAR PHARMACEUTICALS INC. *Woodside, California* **2002 – 2006**

HELIX BIOMEDIX INC. *Bothell, Washington* **2003 – 2011**

VOLUNTEER ACTIVITIES

- Member of board of directors of the California Antiviral Foundation **2008 – 2013**
- Member of GlobalScot network supporting Scottish Development International **2003 – present**
- Consultant for the Institute for OneWorld Health **2008 – 2009**
- Mentor for Women Unlimited leadership program **2007**

PUBLICATIONS and ISSUED PATENTS

Author on over 60 peer-reviewed publications and review articles and 15 issued U.S., European, and Japanese patents

PUBLICATIONS

1. Fiddes JC (1976) Nucleotide sequence of the intercistronic region between genes G and F in bacteriophage ϕX174 DNA. *J. Mol. Biol*. 107:1-24

2. Sanger F, Air GM, Barrell BG, Brown NL, Coulson AR, Fiddes JC, Hutchison CA III, Slocombe PM and Smith M (1977) Nucleotide sequence of bacteriophage ϕX174 DNA. *Nature* 265:687-695

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ISSUED PATENTS

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EXHIBIT B

Materials Reviewed by John Fiddes, Ph.D.

1. U.S. Patent No. 4,816,567 (Cabilly, S., et al.)

2. U.S. Patent No. 6,331,415 (Cabilly, S., et al.)

3. U.S. Patent No. 7,923,221 (Cabilly, S., et al.)

4. October 13, 2014 Opening Expert Report of Jefferson Foote, Ph.D., *Bristol-Myers Squibb Company v. Genentech, Inc.*

5. October 13, 2014 Expert Report of Paolo Casali, M.D., *Bristol-Myers Squibb Company v. Genentech, Inc.*

6. October 13, 2014 Expert Report of Saul J. Silverstein, Ph.D., *Bristol-Myers Squibb Company v. Genentech, Inc.*

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10. October 13, 2014 Expert Report of Sir Gregory Winter, CBE, FRS, *Eli Lilly and Company v. Genentech, Inc.*

11. October 13, 2014 Expert Report of Daniel J. Capon, Ph.D., *Eli Lilly and Company v. Genentech, Inc.*

12. October 13, 2014 Expert Report of Richard A. Killworth, *Eli Lilly and Company v. Genentech, Inc.*

13. U.S. Patent No. 4,399,216 (Axel, R., et al.)

14. U.S. Patent No. 6,455,275 (Axel, R., et al.)

15. U.S. Patent No. 5,149,636 (Axel, R., et al.)

16. U.S. Patent No. 4,495,280 (Bujard, H., et al.)

17. U.S. Patent No. 4,237,224 (Cohen, S., et al.)

18. U.S. Patent No. 4,468,464 (Cohen, S., et al.)

19. U.S. Patent No. 4,740,470 (Cohen, S., et al.)

20. U.S. Patent No. 4,741,901 (Levinson, A., et al.)

21. U.S. Patent No. 4,642,334 (Moore, K., et al.)

22. U.S. Patent No. 5,840,545 (Moore, K., et al.)

23. U.S. Patent No. 4,517,294 (Bock, et al.)

24. U.S. Patent No. 4,530,901 (Weissmann)

25. U.S. Patent No. 4,563,424 (Riggs)

26. U.S. Patent No. 4,710,463 (Murray)

27. U.S. Patent No. 4,818,694 (Watson et al.)

28. U.S. Patent No. 4,840,896 (Reddy et al.)

29. U.S. Patent No. 5,639,639 (Reddy et al.)

30. Cabilly I Prosecution File History

31. Cabilly II Reexamination File History

32. International Application WO 82/03088 (Dallas, W.)

33. EPO 0073656 A3 (Levinson, A., et al.)

34. Plaintiffs BMS and Lilly's Claim Construction Order

35. Joint Claim Construction and Pre-Hearing Statement

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163. June 6, 2014 Letter from H. Renk to K. Davis re Election of Prior Art

164. June 2, 2014 Letter from R. McCormick to K. Davis re BMS-Medarex Final Election of Prior Art

165. January 27, 2012 Memorandum in support of Glaxo and Lonza's Motion for Summary Judgment of Invalidity of Claims 1, 3, 11, 12, 14, 19 and 33 for Failure to comply with Written Description (Motion No. 1)

166. January 27, 2012 Memorandum in support of Glaxo and Lonza's Motion for Summary Judgment of Invalidity of Claims 1, 3, 11, 12, 14, 15, 17, 19, and 33 for Failure to Comply with Written Description (Motion No. 2)

167. February 27, 2012 Genentech, Inc. and City of Hope's Opposition to Glaxo's and Lonza's Motions for Summary Judgment of Invalidity of Claims 1, 3, 11, 12, 14, 15, 17, 19 and 33 for Failure to comply with Written Description

168. March 12, 2012 Glaxo and Lonza's reply Brief in Support of their Motions Nos. 1 and 2 for Summary Judgment of Invalidity of Claims 1, 2, 11, 12, 14, 14, 17, 19 and 33 for Failure to Comply with 35 U.S.C. § 112

169. September 28, 2011 Expert Report of Jefferson Foote, Ph.D., *Glaxo Group Limited v. Genentech, Inc.*

170. September 28, 2011 Expert Report of James Larrick, M.D., Ph.D., *Glaxo Group Limited v. Genentech, Inc.*

171. September 23, 2011 Expert Report of Arne Skerra, Ph.D., *Glaxo Group Limited v. Genentech, Inc.*

172. October 26, 2011 Expert Report of Carlo M. Croce, M.D., *Glaxo Group Limited v. Genentech, Inc.*

173. October 26, 2011 Responsive Expert Report of James Larrick, M.D., Ph.D., *Glaxo Group Limited v. Genentech, Inc.*

174. November 16, 2011 Rebuttal Expert Report of James Larrick, M.D., Ph.D., *Glaxo Group Limited v. Genentech, Inc.*

175. November 16, 2011 Rebuttal Expert Report of Arne Skerra, Ph.D., *Glaxo Group Limited v. Genentech, Inc.*

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177. Reexamination Control No. 90/007,542 – November 23, 2005 Declaration of Dr. Timothy John Roy Harris Under 37 C.F.R. § 1.132

178. Reexamination Control No. 90/007,542 –November 23, 2005 Declaration of Dr. Douglas A. Rice Under 37 C.F.R. § 1.132

179. Reexamination Control No. 90/007,542 –November 22, 2005 Declaration of Dr. Arthur D. Riggs

180. Reexamination Control No. 90/007,542 –October 27, 2006 Declaration of Dr. Alan Colman Under 37 C.F.R. § 1.132

181. Reexamination Control No. 90/007,542 – October 26, 2006 Declaration of Dr. Timothy John Roy Harris Under 37 C.F.R. § 1.132

182. Reexamination Control No. 90/007,542 – October 26, 2006 Declaration of Dr. Douglas A. Rice Under 37 C.F.R. § 1.132

183. Reexamination Control No. 90/007,542 – May 15, 2007 Declaration of Sidney Altman Under 37 C.F.R. § 1.132

184. Reexamination Control No. 90/007,542 – May 20, 2007 Declaration of Michael Botchan Under 37 C.F.R. § 1.132

185. Reexamination Control No. 90/007,542 – May 18, 2007 Declaration of Steven Lanier McKnight Under 37 C.F.R. § 1.132

186. Reexamination Control No. 90/007,542 – May 17, 2007 Declaration of Matthew P. Scott Under 37 C.F.R. § 1.132

187. Reexamination Control No. 90/007,542 – June 3, 2008 Second Declaration of Dr. Steven L. McKnight Under 37 C.F.R. § 1.132

188. GenBank available at http://www.ncbi.nlm.nih.gov