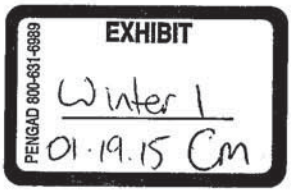
**UNITED STATES DISTRICT COURT**
**CENTRAL DISTRICT OF CALIFORNIA**

| | | |
|---|---|---|
| ELI LILLY AND COMPANY, and IMCLONE SYSTEMS LLC,<br><br>Plaintiffs,<br>v.<br><br>GENENTECH, INC. and CITY OF HOPE,<br><br>Defendants. | ) | Case No. 2:13-cv-07248-MRP-JEMx |

**EXPERT REPORT OF SIR GREGORY WINTER, CBE, FRS**
**REGARDING INVALIDITY OF U.S. PATENT NOS. 6,331,415 AND 7,923,221**



## TABLE OF CONTENTS

## I. Introduction

1. I have been retained by Eli Lilly and Company and ImClone Systems LLC (collectively, "Lilly"), to provide expert opinions and testimony concerning the invalidity of U.S. Patent Nos. 6,331,415 to Cabilly *et al.* ("the '415 Patent" or "Cabilly II") and 7,923,221 to Cabilly *et al.* ("the '221 Patent" or "Cabilly III") (together, "the Cabilly Patents").[1]

2. I understand that I am submitting this expert report pursuant to United States Federal Rule of Civil Procedure 26(a)(2). If I am called upon to testify at trial, I expect to testify about the matters and opinions set forth in this report.

3. I may also present a tutorial to the judge and/or jury concerning the terminology used in my report and the scientific principles underlying my analyses and opinions.

4. I understand that Genentech and City of Hope (collectively, "Genentech") may submit a rebuttal to my report through its own experts, and that additional discovery may take place in this case. With that in mind, I may need to supplement or amend my report and my expected testimony after I have reviewed these additional materials. I also expect to reply as needed to any positions, theories, or evidence advanced by Genentech or its experts in their rebuttals.

## II. Education and Professional Accomplishments

5. A copy of my current *curriculum vitae* is attached to my report as Exhibit A. Below I briefly summarize some of my relevant experience and accomplishments.

---

[1] I understand that another Cabilly Patent, U.S. Patent No. 4,816,567 ("Cabilly I") is now expired. Because I understand that all the Cabilly Patents share the same specification apart from their claims, I generally refer to Cabilly II and Cabilly III collectively as the "Cabilly Patents," and refer to the patents individually only where necessary. For convenience, all citations to column and line numbers refer to the Cabilly II specification.

6. I am currently the Master of Trinity College, University of Cambridge. I was previously the Deputy Director of the Laboratory of Molecular Biology, Cambridge, and of the Centre for Protein Engineering, Cambridge, institutions funded by the UK Medical Research Council. I have spent my career establishing and working in the field of therapeutic monoclonal antibodies.

7. In terms of my professional background, a brief chronology is as follows: I was awarded a B.A. degree in Natural Sciences at Trinity College, Cambridge University, in 1973. In 1976, I was awarded a Ph.D., also from Cambridge University.

8. I was a postdoctoral research fellow at Imperial College, London, from 1976 to 1977. I was a postdoctoral research fellow at the Laboratory of Molecular Biology ("LMB") of the U.K. Medical Research Council ("MRC"), Cambridge, from 1977 to 1980. I have been a member of the scientific staff at the LMB since 1981 and served as the Deputy Director from 2006 to 2011.

9. From 1990 to 2010, I was the Deputy Director of the Cambridge Centre for Protein Engineering. During part of that time (1994-2008), I was Joint Head of Division of Protein and Nucleic Acid Chemistry at the LMB. Throughout most of that time, I was also a Senior Research Fellow of Trinity College (1991-2012). In 2012, I became Master of Trinity College.

10. In 1986, I invented methods to humanize mouse monoclonal antibodies, commonly called CDR grafting. In the period 1989 to 1991, I invented methods for making fully human recombinant antibodies by antibody phage display technology using combinatorial gene repertoires.

11. During the course of my career I have received several awards, including the Novo Biotechnology Award, Denmark, 1986; the Emil von Behring Prize, Federal Republic of Germany, 1989; the Louis Jeantet Prize for Medicine, Switzerland, 1989; the Scheele Award of the Swedish Academy of Pharmaceutical Sciences, 1994; the King Faisal International Prize in Medicine, Saudi Arabia, 1995; the William B. Coley Award, Cancer Research Institute, USA, 1999; the Baly Medal of the Royal College of Physicians, 2005; the Biochemical Society Award, 2006; and the Royal Medal of the Royal Society in 2011. In 2013, I received the Canada Gairdner International Award for the engineering of humanized monoclonal antibodies and their widespread use in medical therapy, particularly for treatment of cancer and immune disorders.

12. In 1997, I received the honor of "Commander of the Order of the British Empire," and in 2004 the honor of "Knight Bachelor," each from Her Majesty the Queen for services to science.

13. I have also founded three biotechnology companies: Cambridge Antibody Technology (1989), Domantis (2000), and Bicycle Therapeutics (2009). Cambridge Antibody Technology and Domantis both pioneered the use of antibody repertoire technologies to develop fully human antibody therapeutics. Bicycle Therapeutics is focusing on the development of bicyclic peptides as small antibody mimics. In 2006, Cambridge Antibody Technology was acquired by AstraZeneca, and Domantis was acquired by GlaxoSmithKline.

14. As shown in Exhibit B, I have authored nearly 200 peer-reviewed papers. I have also presented on numerous occasions as an invited lecturer, and am an inventor on numerous patents issued in the United States and other countries.

## III. Prior Testimony

15. I have not testified as an expert at deposition or trial in the past four years.

## IV. Compensation

16. I am being compensated for my work in connection with this litigation at my customary consulting rate of $5,000 per day for work done in the UK, and at the rate of $10,000 per day for work that requires me to travel to the United States. My compensation is not dependent on the outcome of this litigation.

## V. Materials Considered

17. In reaching my opinions, I considered the materials identified in Exhibit C ("Materials Considered").

## VI. Person of Ordinary Skill in the Art

18. For purposes of this report, I define a person of ordinary skill in the relevant art ("POSA") to be an individual with a Ph.D. degree in molecular biology or a related discipline, such as biochemistry or immunology, and having at least 1-2 years of postdoctoral experience. The POSA would also have experience in protein chemistry, recombinant DNA technology, and the expression of recombinant proteins. The POSA would also have knowledge of the protein structure of antibodies and their genes. This opinion is based on the level of education and experience of persons working in the field of recombinant DNA technology as of April 1983 (the date I have been informed is the priority date of the Cabilly Patents).

## VII. Law of Written Description, Enablement And Double Patenting

19. Counsel has informed me of certain relevant legal principles that impact whether the claims of a patent are valid.

20. It has been explained to me that for a patent to be valid: (a) the specification must provide adequate written description of the invention (the "written description requirement");

and (b) the specification must explain how to make and use the invention, in such full, clear, concise, and exact terms to enable a POSA to carry out the invention (the "enablement requirement").

21. I understand the written description requirement is satisfied when the patent describes each and every limitation of a patent claim with reasonable clarity so that a POSA at the time of the invention would understand that the inventors were in possession of the full scope of the claimed invention as of the filing date of the patent. In other words, the specification must clearly allow a POSA to recognize that the inventors invented what is claimed.

22. Whether a patent complies with the written description requirement varies depending on the nature and scope of the claims, the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, and the predictability of the aspect at issue.

23. I understand that the enablement requirement is satisfied when a POSA at the time of the invention would be able to practice the full scope of the claimed invention without undue experimentation. I understand a permissible amount of experimentation to be an amount appropriate for the complexity of the field of the invention, and for the level of expertise and knowledge of persons skilled in that field. I also understand that enablement is tested as of the date the patent application was filed.

24. I have been informed that the following factors may be considered when determining whether undue experimentation would be necessary for a POSA to practice the claimed invention: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the

quantity of experimentation needed to make or use the invention based on the content of the disclosure.

25. I further understand that a patent does not need to expressly state information known to or obtainable by a POSA at the time of the invention, but that such supplementation cannot cure the patent's failure to provide information necessary to practice the full scope of the claimed invention, particularly in an emerging field.

26. Finally, it has been explained to me that the doctrine of double patenting prevents an inventor from obtaining more than one patent term on one invention. I understand that a patent claim is invalid for "obviousness-type double patenting" if it is not patentably distinct from the subject matter claimed in an earlier commonly owned patent. I am informed that a claim in a later patent is not patentably distinct from a claim in an earlier patent if the later claim is anticipated by, or obvious over, the earlier claim.

27. It has also been explained to me that there are two steps to an obviousness-type double patenting analysis. First, I understand that the earlier and later claims should be interpreted as they would be understood by a POSA to determine their scope, and that claims should be interpreted in light of the specification of which they are a part. Second, I understand that the differences between the coverage of the earlier and later claims should be determined in order to establish whether the later claim is patentably distinct from the earlier claim. I have adopted this analysis in forming my opinions.

28. It has further been explained to me that anticipation exists if the earlier claim describes every element of the later claim. And I am informed that an earlier generic claim (covering a limited set of options) anticipates a later claim to one or more of those options if a

POSA would "at once envisage," *i.e.*, would have before him or her, the limited set of options covered by the earlier claim.

## VIII. Summary of My Opinions

29. Based on my review of the materials identified in Exhibit C, together with my background and experience, it is my opinion that:

30. The claims of the Cabilly Patents are extremely broad. I understand the method claims cover the production of any recombinantly-produced immunoglobulin[2] of any type, whether assembled *in vitro* or *in vivo*, in any type of host cell. I further understand the product claims cover vectors comprising DNA encoding any immunoglobulin of any type, or any host cell comprising such a vector. However, I do not believe the Cabilly Patents describe the full scope of the claims. By contrast with the claims, the disclosure of the Cabilly specification is narrow; the only experimental data in the specification relates to the expression of IgG heavy and light chains in *E. coli* in an insoluble form and the attempted assembly of those two chains *in vitro* using denaturing chemicals and sulfhydryl reagents.

31. The Cabilly Patents do not provide sufficient written description to demonstrate with reasonable clarity to a POSA in April 1983 that the inventors were in possession of the extremely broad scope of vectors, host cells, and methods for making immunoglobulins that the claims cover. Nor would a POSA in April 1983 have been taught how to make the broad scope of vectors and host cells, or practice the full scope of the claimed methods for making immunoglobulins, without undue experimentation. This is especially true because the field of

[2] For convenience, in this report I will use the word "immunoglobulin" to mean assembled immunoglobulins and fragments thereof, and assembled antibodies and fragments thereof, unless there is a reason to use more specific terminology.

heterologous protein expression (the expression of a protein in cells that do not normally express the protein) was an emerging and unpredictable field in April 1983, and the Cabilly Patents provide little or no disclosure. In particular, there are no working or predictive examples regarding the expression and assembly *in vivo* of immunoglobulins in mammalian cells.

32. For the purposes of this report, I focus my opinions on the issue of expression and assembly *in vivo* in mammalian cells. I am informed that another expert will opine on the issues of expression and assembly *in vivo* in bacteria.[3] In nature, immunoglobulins are produced in mammalian lymphoid cells (*i.e.*, cells produced by the immune system) called B cells. As of April 1983, however, there were several issues that would have been important when considering the possibility (or impossibility) of expression and assembly of recombinant immunoglobulins in mammalian cells, including the roles of chaperone proteins, promoters or other regulatory sequences, and signal sequences. Most of these issues are hardly discussed in the Cabilly Patents. Given the limited understanding and unpredictability of the field, and the absence of detailed guidance or a working example in the Cabilly Patents, a POSA in April 1983 would not have reasonably concluded that the inventors were in possession of vectors, host cells, or methods for producing immunoglobulins, assembled *in vivo*, in non-lymphoid mammalian cells. Additionally, a POSA would not have been taught how to make them or practice those methods without undue experimentation.

---

[3] I note that functional immunoglobulin and/or immunoglobulin fragment assembly and secretion were not published until 1988 in *E. coli* and yeast, and until 1989 in plants. (Skerra, A. & Plückthun, A., *Assembly of a functional immunoglobulin Fv fragment in Escherichia coli*, 240 SCIENCE 1038 (1988); Better, M., *et al.*, *Escherichia coli secretion of an active chimeric antibody fragment*, 240 SCIENCE 1041 (1988); Horwitz, A.H., *et al.*, *Secretion of functional antibody and Fab fragment from yeast cells*, 85 PROC. NAT'L. ACAD. SCI. USA 8678 (1988); Hiatt, A., *et al.*, *Production of antibodies in transgenic plants*, 342 NATURE 76 (1989).)

33. Furthermore, while the Cabilly Patents encompass several immunoglobulin types and immunoglobulin fragments, including "mammalian antibodies," "composite immunoglobulins," "hybrid antibodies," "chimeric antibodies," "univalent antibodies," and "Fab protein," most of these are described only in functional terms, with no structural information, and little or no guidance is provided regarding how to make these types of immunoglobulins and immunoglobulin fragments. A POSA in April 1983 would thus not have believed that the Cabilly inventors were in possession of these different immunoglobulin types and immunoglobulin fragments, and would not have been taught how to make them without undue experimentation. In particular, although encompassed by the claims, the Cabilly Patents do not describe and did not provide a specific and useful teaching to a POSA in April 1983 on how to make humanized and fully human antibodies, both of which were only made possible by inventions made after the Cabilly Patents were filed. My own group was responsible for the invention of humanized antibodies, and (in combination with the group of Richard Lerner) was also responsible for one of the two major methods for making fully human antibodies, namely, "phage display/antibody repertoire technology."

34. Finally, though the claims of the Cabilly Patents also encompass IgA and IgM immunoglobulins, the patents ignore that IgA and IgM immunoglobulins were known by April 1983 to be assembled as higher-order multimeric structures that contain a third polypeptide chain, the "J chain," in addition to the heavy and light chains. However, nothing in the Cabilly Patents would have either convinced a POSA in April 1983 that the inventors were in possession of vectors, host cells, or methods of making assembled IgA or IgM immunoglobulins, or taught a POSA how to make such immunoglobulins without undue experimentation.

35. It is also my opinion that the asserted claims of the later Cabilly II and III patents are not patentably distinct from claims 1, 2, 6, and 7 of the earlier Cabilly I patent.

36. First, it is my opinion that Cabilly II process claim 33 and Cabilly III method claims 20, 27, and 43 are not patentably distinct from method claims 1 and 2 of Cabilly I. Cabilly I method claim 1 covers a method for making a chimeric immunoglobulin that includes all three of the transformation options set forth in the patent: (i) transforming separate host cells with separate vectors each containing either a heavy or light chain DNA sequence, (ii) transforming a single host cell with separate vectors each containing either a heavy or light chain DNA sequence, and (iii) transforming a single host cell with a single vector containing both heavy and light chain DNA sequences. (Col. 12, lines 24-30.) A POSA would at once envisage this limited number of options from the claim language, when interpreted in light of the specification. Cabilly II process claim 33 and Cabilly III method claims 20, 27, and 43 cover a method for making a chimeric immunoglobulin (Cabilly II process claim 33) or a chimeric antibody (Cabilly III method claims 20, 27, and 43) using one or two of these same three transformation options. Therefore, the later claims are anticipated by the earlier claims, and, thus, are not patentably distinct from the earlier claims.

37. Second, it is my opinion that Cabilly II vector claim 15 is not patentably distinct from Cabilly I vector claim 6. Because Cabilly I vector claim 6 covers vectors that can be used for all three of the transformation options disclosed in the Cabilly Patents (listed above), a POSA would at once envisage this limited number of options from the claim language, when interpreted in light of the specification. Cabilly II vector claim 15 covers a vector that can be used for the third transformation option, namely, transforming a single host cell with a single vector

containing both heavy and light chain DNA sequences. Therefore, the later claim is anticipated by the earlier claim, and thus is not patentably distinct from the earlier claim.

38. Third, it is further my opinion that Cabilly II host cell claim 17 and Cabilly III host cell claim 46 are not patentably distinct from Cabilly I host cell claim 7. Because Cabilly I host cell claim 7 covers a host cell transformed according to all three of the transformation options disclosed in the Cabilly Patents, a POSA would at once envisage this limited number of options from the claim language, when interpreted in light of the specification. Cabilly II host cell claim 17 and Cabilly III host cell claim 46 cover a host cell transformed according to the third of the three transformation options. Therefore, the later claims are anticipated by the earlier claim and thus, are not patentably distinct from the earlier claim.

## IX. The Claims at Issue

39. I understand that claims 15, 17, and 33 of Cabilly II are at issue in this case. Those claims 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.

40. I understand that claims 20, 27, 43, and 46 of Cabilly III are at issue in this case.

Those claims read as follows (including independent claims as necessary for clarity):

> 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.

41. I have been informed that the terms "antibody" and "immunoglobulin" have not been construed by the Court. (Claim Construction Order ("CC Ord."), D.I. 158, at 2 n.1.) Therefore, my understanding of those terms for the purpose of rendering my opinions here is based on the definitions presented in the Cabilly Patents at col. 6, lines 3-11. That is, "antibody" means a tetrameric assembly, comprising light and heavy polypeptide chains, which has specific immunoreactive activity (*i.e.*, specifically binds a particular antigen), or multimeric aggregates thereof. (Col. 6, lines 3-7.) "Immunoglobulin" means a tetrameric assembly, comprising light and heavy polypeptide chains, whether or not specific immunoreactive activity is a property, or multimeric aggregates thereof. (Col. 6, lines 7-11.) "Antibodies" are thus a subset of "immunoglobulins."

42. Claim 33 of Cabilly II claims "[a] process for producing an immunoglobulin molecule or an immunologically functional immunoglobulin fragment" and thus requires that practicing the claimed process results in the formation of an assembled immunoglobulin or fragment thereof. I have been informed that during prosecution, Genentech stated that the Cabilly II claims, including claim 33, require assembly. (CC Ord. at 15-16.)

43. Claims 20 and 43 of Cabilly III similarly claim a method that "results in the production of an antibody" and thus require that practicing the claimed methods results in the formation of an assembled antibody. Claim 27 of Cabilly III includes a recovery step, which I

understand the Court has held covers both recovery of an antibody assembled *in vitro* from separate chains and recovery of an antibody assembled *in vivo*. (CC Ord. at 17-18.)

44. An assembled antibody is shown in Figure 1 of the Cabilly Patents, which is reproduced below.

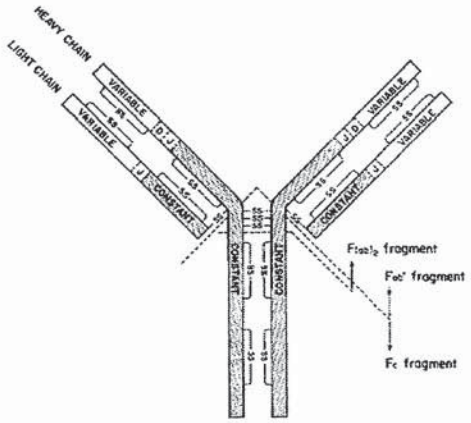



**Fig. 1: Structure of an Immunoglobulin Tetramer**

The assembled antibody is a tetramer (or multimer of tetramers) that consists of four polypeptide chains—two heavy chains and two light chains—held together by disulphide bonds (labeled as "—SS—" in the figure) both within (intrachain) and between (interchain) polypeptide chains. Assembled immunoglobulins have the same basic structure.

45. As noted above, the Court found that claim 27 of Cabilly III covers both assembly *in vitro* (using chemical processes), and *in vivo* (using the host cell's own protein folding and assembly machinery). (CC Ord. at 17-18.) Method claims 33 of Cabilly II and 20 and 43 of Cabilly III likewise say nothing about how and where the heavy and light chains are assembled and therefore are also broad enough to cover immunoglobulin or antibodies, respectively, assembled *in vitro* and *in vivo*. I am informed that in a prior case, Genentech specifically acknowledged that Cabilly II "claim 33 is broad enough to encompass assembly of an

immunoglobulin both inside the host cell and outside the host cell." (Claim Construction Order, *Centocor Inc., v. Genentech, Inc., et al.*, 08-cv-03573 (C.D. Cal., 2009), D.I. 93 at 17.)

46. The Cabilly Patents note that there are different types of heavy chain, γ (gamma), μ (mu), α (alpha), δ (delta), and ε (epsilon), as well as two types of light chain, kappa and lambda. (Col. 3, lines 27-32.) The type of heavy chain determines the immunoglobulin/antibody class. (Col. 3, lines 27-31.) The terms "immunoglobulin" and "antibody" as used in the Cabilly Patents are not limited to a specific type of heavy or light chain but instead broadly cover all five of the major immunoglobulin/antibody classes, IgG, IgM, IgA, IgD, and IgE. (Col. 3, lines 60-65.) As of April 1983, it was known that IgM and IgA are pentamers and dimers of the basic tetrameric structure, respectively, and the Cabilly Patents expressly state, for example, that "immunoglobulins" and "antibodies" include these aggregates of tetramers. (Col. 6, lines 3-9.)

47. In the context of the Cabilly Patents, the broad terms "immunoglobulin" and "antibody" also cover several different immunoglobulin or antibody types, including "mammalian antibodies" (col. 6, lines 12-18; col. 11, line 19-col. 12, line 56), "composite immunoglobulins" (col. 6, lines 30-34; col. 14, lines 40-63), "hybrid antibodies" (col. 6, lines 19-29; col. 14, line 64-col. 15, line 9), "chimeric antibodies" (col. 6, lines 35-56; col. 15, lines 10-33), and "univalent antibodies" (col. 7, lines 25-34; col. 15, line 49-col. 16, line 2).

48. While the term "antibody" requires specific immunoreactive activity (col. 6, lines 3-7), the term "immunoglobulin" does not require specific binding to a particular known antigen (col. 6, lines 7-9). However, the Cabilly Patents contain no restriction on the types of antigens that the "antibodies" bind and thus, the term "antibodies" covers antibodies that bind to any antigen.

49. Claim 33 of Cabilly II additionally requires "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." Claim 15 of Cabilly II similarly requires "[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," and claim 17 requires a host cell transformed with the vector of claim 15. Because "immunoglobulin" is not limited to a particular type or species source, the DNA sequences encoding immunoglobulins covered by the claims are similarly unlimited.

50. Claims 27 and 45 of Cabilly III also require DNA encoding an antibody heavy and light chain (or their fragments). Because the claimed antibodies are not limited to a particular type, species source, or antigen, the DNA sequences encoding antibodies covered by the claims are similarly unlimited.

51. Claims 17 and 33 of Cabilly II also recite a "host cell" and claims 20, 27, 38 and 46 of Cabilly III recite a "recombinant host cell." I understand that the Court has construed "host cell" in Cabilly II 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." (CC Ord. at 9.) I further understand that the parties have agreed that "recombinant host cell" in Cabilly III 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." (CC Ord. at 4.) However, neither "host cell" nor "recombinant host cell" is limited to a particular type of cell and thus the terms cover any host cell. The Cabilly Patents expressly include prokaryotic cells,

such as bacteria, and eukaryotic cells, such as yeast and "cells derived from multicellular organisms," *e.g.*, mammalian cells. (Col. 8, line 40-col. 10, line 29.)

52. In sum, as written and as interpreted by the Court and Genentech, a POSA would understand that the Cabilly claims variously cover any immunoglobulin or immunoglobulin fragment, or any antibody or antibody fragment—regardless of type, species source, or target antigen—assembled *in vivo* or *in vitro*, in any type of cell.

53. Finally, I understand that the parties' agreed constructions of "vector" in Cabilly II and "replicable expression vector" in Cabilly III require "a DNA construct comprising DNA foreign to the DNA host cell, which DNA construct is capable of effecting the expression of foreign DNA." (CC Ord. at 5.)

## X. Producing Immunoglobulins Assembled *In Vivo* in Mammalian Cells Was Unpredictable Given the Immature State of the Art in April 1983

54. At the outset, it may be useful to describe my own interest in expressing immunoglobulins in the period from 1983 to 1985. In April 1983, I had experience in protein chemistry, and most aspects of recombinant DNA technology, including cloning and sequencing (*see, e.g.*, Winter, G. & Fields, S., *Nucleotide sequence of human influenza A/PR/8/34 segment 2*, 10 NUCLEIC ACIDS RES 2135 (1982); Fields, S. & Winter, G., *Nucleotide sequences of influenza virus segments 1 and 3 reveal mosaic structure of a small viral RNA segment*, 28 CELL 303 (1982)), site-directed mutagenesis (*see, e.g.*, Winter, G., *et al.*, *Redesigning enzyme structure by site-directed mutagenesis: tyrosyl tRNA synthetase and ATP binding*, 299 NATURE 756 (1982)), and expression and purification of soluble and active recombinant enzymes from bacteria (*see, e.g.,* Wilkinson, A.J., *et al.*, *Site-directed mutagenesis as a probe of enzyme structure and catalysis: tyrosyl tRNA synthetase cysteine-35 to glycine-35 mutation,* 22 BIOCHEM. 3581 (1983); Waye, M.M., *et al.*, *Deletion mutagenesis using an 'M13 splint': the N-terminal structural*

*domain of tyrosyl-tRNA synthetase (B. stearothermophilus) catalyses the formation of tyrosyl adenylate*, 2 EMBO J 1827 (1983)). At that time, I was focused on using recombinant DNA technology to make single amino acid changes in enzymes in order to identify the key amino acid residues in their active sites (*see, e.g.*, references cited above and Barker, D.G. & Winter, G., *Conserved cysteine and histidine residues in the structure of the tyrosyl and methionyl-tRNA synthetases*, 145 FEBS LETT 191 (1982); Carter, P.J., *et al.*, *The use of double mutants to detect structural changes in the active site of the tyrosyl-tRNA synthetase (Bacillus stearothermophilus)*, 38 CELL 835 (1984)). At that time, I knew about the structure of the antibody molecule and its genes; my laboratory was adjacent to that of three antibody experts, Cesar Milstein, Michael Neuberger, and Terence Rabbitts.

55. Cesar Milstein was the first person to make monoclonal antibodies, for which he received a Nobel Prize; Terence Rabbitts was studying the genetic structure of antibodies; and Michael Neuberger was studying the regulatory elements required for expression of antibodies, later using this knowledge to create several engineered antibodies. I followed the work of the Milstein, Rabbitts, and Neuberger groups as presented in departmental seminars, as well as the work in the field of recombinant heterologous protein expression in the published literature. I therefore believe that in key respects my experience and knowledge in 1983 was similar or superior to that of the POSA described above.

56. In early 1983, when I was working on the engineering of enzyme active sites, Cesar Milstein, the Head of Division, encouraged me to undertake a similar analysis of functional sites on antibodies (this later led to our identification of the binding sites for complement C1q (Duncan, A.R. & Winter, G., *The binding site for C1q on IgG*, 332 NATURE 738 (1988)) and a high affinity Fc receptor (Duncan, A.R., *et al.*, *Localization of the binding site*

*for the human high-affinity Fc receptor on IgG*, 322 NATURE 563 (1988))). In order to conduct this analysis, it was first necessary to clone and express recombinant antibodies in a folded and functional form. In April 1983, there was a single paper describing the expression of an antibody light chain fusion protein in bacteria (Amster, O., *et al.*, *Synthesis of part of a mouse immunoglobulin light chain in a bacterial clone*, 8 NUCLEIC ACIDS RESEARCH 2055 (1980)), but there were four papers describing the expression, or at least the attempted expression, of recombinant antibody light chains in mammalian cells using "genomic" constructs (constructs comprising genomic DNA including introns) and endogenous or viral promoters: Rice, D. & Baltimore, D., *Regulated expression of an immunoglobulin κ gene introduced into a mouse lymphoid cell line*, 79 PROC. NAT'L ACAD. SCI. USA 7862 (1982); Falkner, F.G. & Zachau, H.G., *Expression of mouse immunoglobulin genes in monkey cells*, 298 NATURE 286 (1982); Ochi, A., *et al.*, *Transfer of a cloned immunoglobulin light-chain gene to mutant hybridoma cells restores specific antibody production*, 302 NATURE 340 (1983); Oi, V., *et al.*, *Immunoglobulin gene expression in transformed lymphoid cells*, 80 PROC. NAT'L ACAD. SCI. USA 825 (1983). However, the reasons for success or failure in the expression or secretion of the light chain in different cell types were not clear.

57. In three of the papers, Rice & Baltimore 1982, Ochi *et al.* 1983, and Oi *et al.* 1983, the authors were able to demonstrate the secretion and assembly of a recombinant light chain with the endogenous heavy chain in a hybridoma. However, there were no publications describing the expression of recombinant antibody heavy chains in mammalian cells.

58. In the only example describing the expression of light chains in non-lymphoid cells, Falkner & Zachau 1982, it was not clear (due to the experimental design) whether the light chain had been secreted. Furthermore, it was not clear whether the expression and assembly of

antibody heavy and light chains could be correctly regulated in non-lymphoid cells in the absence of heavy chain binding protein BiP. (Wabl, M. & Steinberg, C., *A theory of allelic and isotypic exclusion for immunoglobulin genes*, 79 PROC. NAT'L. ACAD. SCI. USA 6976 (1982); *see also* Haas, I.G. & Wabl, M., *Immunoglobulin heavy chain binding protein*, 306 NATURE 387 (1983) (published after the Cabilly filing date but repeating the suggestion of BiP's importance in the regulation of immunoglobulin chain synthesis).)

59. In April 1983, it was therefore not evident to me, or a POSA, how to express recombinant antibodies in mammalian cells. In particular, it was not clear whether non-lymphoid cells would be suitable hosts for expression and secretion of both heavy and light chains. Lymphoid cells seemed more promising, but it was not clear whether to use secreting or non-secreting lymphoid host cells. Hybridomas that secreted endogenous antibodies would have led to complex mixtures of endogenous and recombinant chains, and it was not clear whether a non-secreting myeloma would have allowed the secretion of recombinant antibodies. Nor was it clear whether to use genomic constructs with endogenous promoters, or cDNA constructs (in which introns are spliced out), as used by the Cabilly inventors.

60. A further consideration was yield. I anticipated a range of studies would be necessary to characterize any expressed protein and to determine whether, in fact, immunoglobulin expression was successful. To do so, I believed we would need up to milligram quantities of purified material from each mutant (at a later date we had to make more than 20 different mutants of a mouse antibody in order to identify the C1q binding site (Duncan, A.R. & Winter, G., *The binding site for C1q on IgG*, 332 NATURE 738 (1988))).

61. I was sufficiently uncertain in the spring of 1983 about how to express recombinant antibodies, and in sufficient yield, that I postponed my proposed project to engineer

the functional sites of antibodies. The lack of a proven expression system was the major issue, and it would not be simple to just "try" a number of different expression systems. Instead, it would first have been necessary to procure a cell line producing a suitable antibody (at that time, there were very few cell lines producing well characterized monoclonal antibodies), the genes for heavy and light chains would then have to be cloned, and then tailored as necessary to insert into different expression vectors. This would be a major undertaking without any certainty of success.

62. Later in 1983, several authors published work that identified a heavy chain enhancer within the immunoglobulin gene (Gillies, S.D., *et al.*, *A tissue-specific transcription enhancer element is located in the major intron of a rearranged immunoglobulin heavy chain gene*, 33 CELL 717 (1983); Neuberger, M.S., *Expression and regulation of immunoglobulin heavy chain gene transfected into lymphoid cells*, 2 EMBO J. 1373 (1983); Banerji, J., *et al.*, *A lymphocyte-specific cellular enhancer is located downstream of the joining region in immunoglobulin heavy chain genes*, 33 CELL 729 (1983)); this was the first tissue specific mammalian enhancer to be discovered. At about the same time, another group showed that recombinant antibody heavy chains and recombinant light chains could be expressed, assembled and secreted from a non-secreting myeloma cell line (Ochi, A., *et al.*, *Functional immunoglobulin M production after transfection of cloned immunoglobulin heavy and light chain genes into lymphoid cells*, 80 PROC. NAT'L ACAD. SCI. USA 6351 (1983)). All of this work used vectors containing genomic constructs with endogenous immunoglobulin promoters.

63. Thus, by the end of 1983, the vector and host cell requirements for antibody expression in lymphoid cells had become much clearer than earlier in the year. However, it was some time before the same could be said for antibody expression in non-lymphoid cells.

(Weidle, U., *et al.*, *Reconstitution of functionally active antibody directed against creatine kinase from separately expressed heavy and light chains in non-lymphoid cells*, 51 GENE 21 (1987).)

64. By early 1984, my work on engineering enzymes had led me to the notion that antibodies might be used as universal frameworks for designing and building catalytic sites. In the course of inspecting the architecture of antibodies for this purpose, I realized that it might be possible to transplant binding sites from one antibody to another by transplanting the antigen-binding loops. I realized that this approach might provide a powerful means of turning rodent antibodies into near human antibodies (*see* ¶¶ 96-97 for further description of the concept). I therefore returned with some urgency to the issue of antibody expression. I noted the publications of Boss (Boss, M.A., *et al.*, *Assembly of functional antibodies from immunoglobulin heavy and light chains synthesized in E. coli*, 12 NUCLEIC ACIDS RESEARCH 3791 (1984)) and Cabilly (Cabilly, S., *et al.*, *Generation of antibody activity from immunoglobulin polypeptide chains produced in Escherichia coli*, 81 PROC. NAT'L ACAD. SCI. USA 3273 (1984)) on the expression of antibodies in bacteria. But in both cases, poor yields of functional antibody were obtained by *in vitro* reconstitution and no antibody was assembled *in vivo*. In view of these failed attempts, I turned to the only method that had been validated by early 1984, namely, expression in lymphoid cells using genomic DNA constructs.

65. Michael Neuberger offered the use of his DNA vectors for expression of genomic antibody heavy chain sequences, to be used in the first instance in association with the endogenous light chain of a mouse myeloma. He was in the process of making other antibody constructs, including a F(ab')2 fusion with an enzyme (Neuberger, M.S., *et al.*, *Recombinant antibodies possessing novel effector functions*, 312 NATURE 604 (1984)) and a chimeric antibody (Neuberger, M.S., *et al.*, *A hapten-specific chimeric IgE antibody with human physiological*

*effector function*, 314 NATURE 268 (1985)). As we were unsure of the location of all the necessary regulatory signals, I engineered the vectors so as to allow a substitution of the mouse variable region gene with the corresponding synthetic humanized sequence (Jones P.T., *et al.*, *Replacing the complementarity-determining regions in a human antibody with those from a mouse*, 321 NATURE 522 (1986)), and minimized all other changes because I did not know (indeed it was not publicly known) what regulatory sequences upstream, downstream or within the immunoglobulin gene were required for expression in the lymphoid cells. I was concerned that additional changes would destroy the ability of the vector to express immunoglobulin genes. This conservative approach, more than one year later than the Cabilly filing, illustrates the uncertain state of the art at the time.

66. Given the state of the art in April 1983, it would have been unpredictable to a POSA whether one could express and assemble *in vivo* a heterologous immunoglobulin in non-lymphoid mammalian cells. As discussed below, key factors in mammalian protein expression and assembly remained poorly understood, including the roles of mammalian chaperone proteins, the maintenance of appropriate relative levels of heavy and light chain polypeptides, as well as the necessary regulatory elements. There was uncertainty and unpredictability as to whether non-lymphoid cells contained the correct chaperone proteins to assist in immunoglobulin assembly, and as to whether the promoters or other regulatory signals required for immunoglobulin expression in lymphoid cells would be active in non-lymphoid cell types. Consistent with my opinion, I understand that Genentech's expert Dr. Rice has stated:

> [T]he processes governing immunoglobulin assembly and secretion in B-lymphocytes were not understood in April of 1983. Instead, it was known from studies involving cultures of B-lymphocyte cells, such as hybridomas or myeloma lines, that production and secretion of intact immunoglobulin tetramers were subject to many unknown and uncharacterized variables.

(Rice Decl. II, ¶ 14.)

**A. Chaperones**

67. It was known in April 1983 that immunoglobulin assembly relies on "chaperone proteins," which are proteins that assist in the folding and assembly of other proteins. One chaperone protein, the immunoglobulin binding protein BiP, was known in 1983, but its role in immunoglobulin assembly was not well-understood. (Wabl, M. & Steinberg, C., *A theory of allelic and isotypic exclusion for immunoglobulin genes*, 79 PROC. NAT'L. ACAD. SCI. USA 6976 (1982).) BiP had been found in a murine pre-B cell line and in some myelomas, but it was not known whether BiP or a similar protein was expressed in other mammalian cell types or whether the expression and assembly of antibody heavy and light chains could be correctly regulated in non-lymphoid cells in the absence of heavy chain binding protein BiP. (*See* Wabl, M. & Steinberg, C., *A theory of allelic and isotypic exclusion for immunoglobulin genes*, 79 PROC. NAT'L. ACAD. SCI. USA 6976 (1982).) A cDNA encoding BiP was not cloned until 1988, when it was cloned from a mouse pre-B cell line, and thus a recombinant form of BiP was not available in April 1983. (Haas, I.G. & Meo, T., *cDNA cloning of the immunoglobulin heavy chain binding protein,* 85 PROC. NAT'L. ACAD. SCI. USA 2250 (1988).) Furthermore, it was also not known in April 1983 whether murine BiP would work with a non-murine immunoglobulin, and thus, whether one could assemble a mammalian immunoglobulin *in vivo* in a lymphoid cell from another species.

68. My opinion is also consistent with that of Dr. Rice, who has stated:

> [A] person of ordinary skill in early April of 1983 would have assumed that the expression, production, assembly and secretion of immunoglobulins were dependent on the unique transcriptional machinery and other cellular agents found in the B-lymphocytes that produce immunoglobulins.

(Rice Decl. II, ¶ 15.) Dr. Rice has further stated that:

> A person of ordinary skill also would have assumed that other types of differentiated cells do not possess these unique attributes and capabilities, because other types of differentiated cells do not produce immunoglobulins.

(*Id.*)

**B. Correct Proportions of Heavy and Light Chain Polypeptides**

69. In mature B cells, where both the heavy chain and light chain are produced, the light chain is produced in excess to avoid the effects of heavy chain toxicity. In mammalian cells, "heavy chain toxicity" refers to the decreased viability of lymphoid cells (such as pre-B cells) that produce a significant excess of heavy chain versus light chain. (*See, e.g.*, Köhler, G., *Immunoglobulin chain loss in hybridoma lines*, 77 PROC. NAT'L ACAD. SCI. USA 2197 (1980); Wilde, C. D. & Milstein, C., *Analysis of immunoglobulin chain secretion using hybrid myelomas*,10 EUR. J. IMMUNOL. 462 (1980).) Wabl & Steinberg reported in 1982 that BiP bound to free heavy chain polypeptides in pre-B cells (which do not express a light chain), and hypothesized that BiP might be involved in neutralizing heavy chain toxicity. (Wabl, M. & Steinberg, C., *A theory of allelic and isotypic exclusion for immunoglobulin genes*, 79 PROC. NAT'L. ACAD. SCI. USA 6976 (1982).)

70. As mentioned above, it was not known in April 1983 whether non-lymphoid cell types expressed BiP or a similar protein. As such, a POSA would have believed that over expression of a recombinant immunoglobulin heavy chain could lead to heavy chain toxicity in a non-lymphoid host cell.

71. I understand that Genentech's experts have also previously recognized the importance of the balance between levels of the heavy and light chains. For example, Dr. Colman noted that it was known that the unbalanced expression of the two immunoglobulin

genes in a lymphoid cell could affect the production of the immunoglobulin polypeptides by that cell, as well as the subsequent folding, assembly and secretion of the immunoglobulin tetramer, among other events. (*See* Colman Decl., ¶ 31.) And Dr. Harris stated that:

> [A] person of ordinary skill in the art in early April of 1983 would have expected that successful production of an immunoglobulin tetramer would depend at least in part, on "correct" levels of expression of the immunoglobulin light and heavy chain genes.

(Harris Decl. II, ¶ 85.)

### C. Regulatory Elements

72. Regulatory elements were another source of unpredictability with respect to expression of immunoglobulins in mammalian non-lymphoid cell types.

73. Promoters are DNA sequences that define where transcription of a gene is initiated. RNA polymerase and proteins called transcription factors bind to the promoter to initiate transcription of DNA into mRNA. Promoters are usually located directly upstream of their associated gene. Enhancers are regulatory elements that increase expression from promoters. Enhancers can act on multiple promoters at the same time, and can act at a distance, whether located upstream or downstream of the promoter they are acting on. Enhancers are sometimes located a great distance away from the promoter(s) they influence.

74. As noted above, it was not until after April 1983 that the immunoglobulin heavy chain and light chain enhancers were identified. (*See, e.g.*, Gillies, S.D., *et al.*, *A tissue-specific transcription enhancer element is located in the major intron of a rearranged immunoglobulin heavy chain gene*, 33 CELL 717 (1983); Banerji, J., *et al.*, *A lymphocyte-specific cellular enhancer is located downstream of the joining region in immunoglobulin heavy chain genes*, 33 CELL 729 (1983); Neuberger, M.S., *Expression and regulation of immunoglobulin heavy chain gene transfected into lymphoid cells*, 2 EMBO J. 1373 (1983).)

75. As of April 1983, however, it had been hypothesized that the endogenous immunoglobulin regulatory sequences were specific to lymphoid cells and required for lymphoid cell gene expression. For example, Falkner & Zachau 1982 reported no significant expression of light chain genes under the control of their own promoter. (Falkner, F.G. & Zachau, H.G., *Expression of mouse immunoglobulin genes in monkey cells*, 298 NATURE 286 (1982).) They suggested that immunoglobulin expression "requires DNA sequences further upstream and/or downstream than those present in [their] plasmids" or that "in immunoglobulin gene expression, some as yet undefined factors provided in the tissue-specific differentiation events may have a role." (*Id.*) Similarly, Ochi *et al.* 1983, reported that "differences in the cellular environments might underlie the different requirements for [light]-chain gene expression." (Ochi, A., *et al.*, *Transfer of a cloned immunoglobulin light-chain gene to mutant hybridoma cells restores specific antibody production*, 302 NATURE 340 (1983).) And Oi *et al.* 1983, reported that light chains were produced in mouse myeloma and hybridoma cell lines but were not produced in rat myeloma or mouse thymoma cells. (Oi, V., *et al.*, *Immunoglobulin gene expression in transformed lymphoid cells*, 80 PROC. NAT'L ACAD. SCI. USA 825 (1983).) They hypothesized that the "lack of light chain expression in the transformed thymoma may reflect tissue-specific gene regulation." (*Id.*) Accordingly, a POSA in April 1983 would not have expected that non-lymphoid mammalian cells could express and assemble immunoglobulins *in vivo*.

76. Even after the filing date of the Cabilly Patents, Ochi *et al.* 1983, reported that "[b]ecause immunoglobulin production is a specialized function of cells of the B-lymphocyte lineage, it is expected that the conditions for proper Ig gene expression will be provided only in appropriate immunocompetent cells." (Ochi, A., *et al.*, *Functional immunoglobulin M production after transfection of cloned immunoglobulin heavy and light chain genes into*

*lymphoid cells*, 80 PROC. NAT'L ACAD. SCI. USA 6351 (1983).) As heavy and light chain promoters became better understood, those promoters were indeed shown to exhibit lymphoid cell specificity. (*See, e.g.*, Foster, J., *et al.*, *An immunoglobulin promoter displays cell-type specificity independently of the enhancer*, 315 NATURE 423 (1985); Picard, D. & Schaffner, W., *Cell-type preference of immunoglobulin kappa and lambda gene promoters*, 4 EMBO J. 2831 (1985).) And it was later reported that an "immunoglobulin locus enhancer element" was required for transcription of heterologous gene in mouse myeloma cells. (Neuberger, M.S., *Expression and regulation of immunoglobulin heavy chain gene transfected into lymphoid cells*, 2 EMBO J. 1373 (1983).)

77. I understand that in other contexts, Genentech's experts have testified that additional research was required to understand the regulatory elements needed to express and assemble immunoglobulin heavy and light chains into an immunoglobulin *in vivo*:

> [Rice and Baltimore] reports that it was unclear what enabled the lymphoid cell to express the introduced gene, and that expression may have been due to the presence of uncharacterized regulatory elements in the light chain gene . . . Instead, they demonstrate that expression of immunoglobulin genes in lymphoid cells was not well understood, was regulated by unknown and uncharacterized factors and processes, and that additional research was needed to identify and understand what actually controlled expression in lymphoid cells.

(McKnight Decl. I, ¶ 83 *citing* Rice, D. & Baltimore, D., *Regulated expression of an immunoglobulin κ gene introduced into a mouse lymphoid cell line*, 79 PROC. NAT'L ACAD. SCI. USA 7862 (1982).)

**D. Signal Sequences**

78. A signal sequence (also called a "signal peptide" or a "pre-sequence") is a relatively short, specialized amino acid sequence found at the N-terminus of secreted proteins.

Immunoglobulin heavy chain and light chain polypeptides both naturally have signal sequences that are required for immunoglobulin assembly *in vivo* in B cells.

79. Generally speaking, a polypeptide bearing a signal sequence is translated on ribosomes residing at the outer membrane of the rough endoplasmic reticulum ("RER") in mammalian cells, and is directed into the lumen (inside compartment) of the RER, where the signal sequence is removed by an enzyme called a "signal peptidase" to produce a "mature" polypeptide. The lumen of the RER is an oxidizing environment, in contrast to the reducing environment of the cytoplasm. In a mammalian cell, only in the oxidizing environment of the RER can immunoglobulin chains properly fold, form disulphide bonds, and assemble into immunoglobulins that are then secreted from the cell lines.

* * *

80. Based on my education and experience, and for the reasons set forth above, it is my opinion that it would have been unpredictable to a POSA in April 1983 whether one could express and assemble *in vivo* a recombinant immunoglobulin in non-lymphoid mammalian cells.

## XI. The Cabilly Patents Do Not Describe or Enable Vectors, Host Cells, or Methods for Producing Immunoglobulins Assembled *In Vivo* in Mammalian Cells

81. No working or even hypothetical example of expression and *in vivo* assembly of an immunoglobulin in any mammalian cell is disclosed in the Cabilly Patents. The Cabilly Patents set forth only one "working" example, and that example concerns the expression in *E. coli*, which is a bacterium and not a mammalian cell line, and attempted ***in vitro*** reconstitution of heavy and light chains of an anti-CEA antibody. (Col. 23, line 1- col. 25, line 62.)

82. The uncertainties, discussed above, associated with producing assembled recombinant immunoglobulins in non-lymphoid mammalian cells are neither addressed nor

contemplated in the Cabilly Patents. Thus, the inventors provide no disclosure that would allow a POSA to reasonably conclude that the inventors were in possession of vectors, host cells, or methods of producing immunoglobulins *in vivo* in the full range of mammalian cell lines.

83. As to mammalian cells, the Cabilly Patents disclose only that "in addition to microorganisms cultures of cells derived from multicellular organisms may also be used as hosts," and provide a list of "useful host cell lines." (Col. 9, lines 56-66.) Those mammalian cell types, namely, VERO, HeLa, CHO, W138, BHK, COS-7 and MDCK cells, are all non-lymphoid cell types. (Col. 9, lines 56-66.) However, it was not known in April 1983 whether non-lymphoid cell types expressed BiP (or a similar protein). Thus, a POSA in April 1983 would not have expected that non-lymphoid cells, including those listed in the Cabilly Patents, would be able to express and assemble immunoglobulins *in vivo*. Indeed, the role of BiP or any other chaperone is not mentioned anywhere in the Cabilly specification.

84. As discussed above, a POSA would have believed that over expression of a recombinant immunoglobulin heavy chain could lead to heavy chain toxicity, particularly in the absence of BiP, which Wabl & Steinberg hypothesized was involved in neutralizing heavy chain toxicity. (Wabl, M. & Steinberg, C., *A theory of allelic and isotypic exclusion for immunoglobulin genes*, 79 PROC. NAT'L. ACAD. SCI. USA 6976 (1982).) However, the Cabilly Patents do not address the control of levels of expression of the immunoglobulin heavy and light chains in mammalian cells. Instead, the Cabilly Patent claims require "independent" expression of the heavy and light chains, without providing any guidance regarding stoichiometry. Furthermore, because neither BiP nor any other chaperone is mentioned in the Cabilly specification, a POSA would not have been taught a means to ameliorate the possibility of heavy chain toxicity in mammalian non-lymphoid host cells.

85. The Cabilly Patents state that:

> It is also possible, and often desirable, to utilize promoter or control sequences normally associated with the desired gene sequence, provided such control sequences are compatible with the host cell systems.

(Col. 10, lines 15-18.) But they give no guidance that would tell a POSA which control sequences would be compatible with any particular host cell system, and as shown by the papers discussed above, the work of determining whether a particular promoter was compatible with a particular host cell type was substantial and unpredictable. In addition, as of 1983, it was not known whether there were additional regulatory sequences located upstream, downstream or even within the immunoglobulin genes themselves, that were necessary for expression and assembly of immunoglobulins or whether such regulatory signals were compatible with non-lymphoid cells or cells from another mammalian species. In fact, in April 1983, the endogenous regulatory sequences that the Cabilly Patents say are "desirable" to use were believed (and later shown) to exhibit lymphoid cell specificity and thus, would not have been functional in the mammalian non-lymphoid cells listed in the Cabilly Patents. (*See* ¶¶ 75-76, 81-83 above.)

86. The Cabilly Patents also do not discuss the role of signal sequences, including how they might be utilized in conjunction with the vectors, host cells, or methods that the patent claims encompass. In Figure 3 of the patents, an anti-CEA light chain sequence is described by its nucleotide and amino acid sequences, but the depicted light chain lacks a complete signal sequence. Only nine of the twenty-four amino acids of the light chain signal sequence are shown. The remaining fifteen amino acids were not published until more than a year later, in June 1984. (Cabilly, S., *et al.*, *Generation of antibody activity from immunoglobulin polypeptide chains produced in Escherichia coli*, 81 PROC. NAT'L ACAD. SCI. USA 3273 (June 1984).) The

truncated sequence reported in the Cabilly Patents would not be expected to function to secrete the light chain.

87. Notably, the cell lines used to make the monoclonal antibody products could not exist without integration and selection, because plasmids that exist only in extrachromosomal ("episomal") form are quickly lost from host cell cultures, and are not useful for expression over a period of more than a few days. Nothing in the Cabilly Patents mandates that a vector must be integrated into the chromosome, or that a selectable marker must be used. At most, the patent specification mentions that an expression vector ***may be*** integrated, without explaining how such integration would take place in the context of a mammalian cell, and mentions selection only generally:

> It is implied, although not always explicitly stated, that these expression vectors must be replicable in the host organisms either as episomes ***or as an integral part of the chromosomal DNA.***
>
> * * *
>
> ***A useful, but not a necessary, element of an effective expression vector is a marker encoding sequence***—i.e. a sequence encoding a protein which results in a phenotypic property (e.g. tetracycline resistance) of the cells containing the protein which permits those cells to be readily identified.
>
> * * *
>
> An origin of replication may be provided either by construction of the vector to include an exogenous origin, such as may be derived from SV40 or other viral (e.g. Polyoma, Adeno, VSV, BPV, etc.) source, or may be provided by the host cell chromosomal replication mechanism. ***If the vector is integrated into the host cell chromosome, the latter is often sufficient.***

(Col. 8, lines 6-9, 11-15; col. 10, line 19-25 (emphasis supplied).)

88. Finally, the Cabilly Patents also do not address how to obtain a sufficient yield of assembled immunoglobulin in a mammalian non-lymphoid cell such that a POSA would be able to determine that he or she had made the desired product. (*See* ¶¶ 60-61, 64 above.)

89. In sum, given the immature state of the art in April 1983 with respect to both regulatory elements and immunoglobulin assembly, including the role of mammalian chaperone proteins, the resulting lack of predictability regarding recombinant immunoglobulin expression and assembly in non-lymphoid cells, coupled with the Cabilly Patents' general lack of disclosure, and the complete absence of working or predictive examples of expression and assembly of immunoglobulin chains *in vivo* in non-lymphoid mammalian cells, a POSA would not have reasonably concluded that the Cabilly inventors were in possession of the claimed vectors, host cells, or methods for producing a recombinant immunoglobulin assembled *in vivo* in non-lymphoid cells in April 1983. Furthermore, the Cabilly Patents would not have taught a POSA how to make such vectors and host cells, or practice such claimed methods without undue experimentation.

## XII. The Cabilly Patents Do Not Describe or Enable Vectors, Host Cells, or Methods for Producing the Full Scope of Immunoglobulins or Fragments Thereof

90. The Cabilly Patents claims cover vectors, host cells and methods for making several immunoglobulin types and immunoglobulin fragments, including "mammalian antibodies" (col. 6, lines 12-18; col. 11, line 19-col. 12, line 56), "composite immunoglobulins" (col. 6, lines 30-34; col. 14, lines 40-63), "hybrid antibodies" (col. 6, lines 19-29; col. 14, line 64-col. 15, line 9), "chimeric antibodies" (col. 6, lines 35-56; col. 15, lines 10-48), "univalent antibodies" (col. 7, lines 25-34; col. 15, line 49-col. 16, line 2), and "Fab protein" (col. 7, line 53-col. 8, line 2; col. 16, lines 3-10) but most are described only in functional terms, with no

structural information, and little or no guidance regarding how to make these types of antibodies is provided.

91. In its sole "working" example, the Cabilly Patents purport to describe a mouse anti-CEA IgG antibody. The Cabilly Patents show the sequences (*i.e.*, structures) of one gamma heavy chain (Fig. 4) and one kappa light chain with a partial signal sequence (Fig. 3). But no other antibody from any other class (*e.g.*, IgA, or IgM, which have alpha and mu heavy chains, respectively) or isolated from any other species except a mouse is described in the Cabilly specification, except in generic terms. The Cabilly Patents further discuss one chimeric mouse-human anti-CEA antibody, one altered antibody, and one anti-CEA Fab fragment but only in hypothetical terms and no specific structural information is provided. No other chimeric antibody, altered antibody, or Fab fragment are described. The Cabilly Patents describe no antibody species with improved "antigen binding characteristics," and do not provide any information regarding what changes would be required to make one. Likewise, there is no description of a composite immunoglobulin, hybrid antibody, or univalent antibody.

92. As discussed, given the immature state of the art with respect to recombinant immunoglobulins, coupled with the Cabilly Patents' lack of disclosure of any antibody sequence other than a mouse anti-CEA, and given the complete absence of working examples, a POSA in April 1983 would not have reasonably concluded that the Cabilly inventors were in possession of the full scope of vectors, host cells or methods for producing the claimed immunoglobulin types and fragments. For similar reasons, a POSA would not have been enabled to make such vectors and host cells, or practice the claimed methods without undue experimentation.

93. In fact, the first successful report of the creation of a chimeric antibody in which the heavy and light chains were recombinantly expressed and assembled in the same cell was

made after April 1983 by other scientists. (Morrison, S., *et al.*, *Chimeric human antibody molecules: Mouse antigen-binding domains with human constant region domains*, 81 PROC. NAT'L. ACAD. SCI. USA 6851 (1984).)

94. I also note that the patent specification states that composite immunoglobulins are assembled from heavy chains and light chains prepared in separate cultures and reassembled "as desired." (Col. 14, lines 45-50.) Similarly, the patent specification states that hybrid antibodies are assembled from "pairs of heavy chains and light chains" prepared in four separate cultures, with "subsequent mixing of the four separately prepared peptides." (Col. 14, line 65-col. 15, line 5.) Though the scope of the method claims is not so-limited, these statements make plain that the inventors did not contemplate *in vivo* assembly of composite immunoglobulins and hybrid antibodies, because *in vivo* assembly requires that both chains be expressed in the same cell. The patent specification further states that chimeric antibodies are assembled according to section D.2 of the specification. (Col. 15, lines 11-33.) Section D.2 of the specification is limited to *in vitro* recombination (assembly) techniques. (Col. 12, line 57-col. 13, line 52.) Thus, the Cabilly Patents contemplate only *in vitro* assembly of chimeric antibodies.

95. In particular, the Cabilly Patents do not describe and did not teach a POSA in April 1983 how to make humanized antibodies (which would be encompassed by "altered antibodies") and fully human antibodies (which would be encompassed by "mammalian immunoglobulins"), both of which only became possible by inventions made after the Cabilly Patents were filed. My own group was responsible for the invention of humanized antibodies, and (in combination with the group of Richard Lerner) for one of the two major methods of making fully human antibodies, namely, "phage display/antibody repertoire technology" (discussed further below).

96. In concept, humanized antibodies are human antibodies in which the six antigen-binding loops of the variable domain are replaced by the six antigen-binding loops (complementarity determining regions or CDRs) of a rodent monoclonal antibody of desired specificity. The humanized antibodies may bind to the antigen with similar affinity as the original rodent antibodies, and are as much as 95% human in origin. This contrasts with chimeric antibodies, such as the exemplary chimeric antibody in the Cabilly Patents, which comprise the entire variable regions of a rodent antibody fused to the constant regions of a human antibody. Such chimeric antibodies are only about 65% human.

97. In some cases, the binding affinity of the humanized antibodies may be less than that of the original rodent antibody. In such cases, it may be necessary to substitute one or more amino acid residues of the human V-region framework with residues from the corresponding position of the rodent antibody, so that the rodent CDRs pack against the (human) framework in a manner similar to the original rodent antibody.

98. Although the Cabilly Patents generally contemplate "altered" antibodies, at no place do the Cabilly Patents disclose that the inventors were in possession of humanized antibodies, nor do they provide a specific and useful teaching sufficient to enable a POSA to make one without undue experimentation.

## XIII. The Cabilly Patents Do Not Describe or Enable Vectors, Host Cells, or Methods for Producing Fully Human Immunoglobulins

99. In April 1983, monoclonal antibodies had been recognized as potentially useful agents for treating disease. Because antibodies made in non-human organisms (*e.g.*, mice) were known to provoke a significant immune response in humans, fully human monoclonal antibodies were considered to be the Holy Grail of the field.

100. The full scope of "mammalian antibodies" encompasses antibodies from any mammal, including humans. Furthermore, as noted, the Cabilly Patents contain no restriction on the types of antigens that the "antibodies" bind and thus, the term "antibodies" covers antibodies that bind to any antigen, including human antigens.

101. To make human recombinant antibodies, however, one needs to make light chain and heavy chain expression vectors, which, in turn, require a source of mRNA encoding at least the variable regions of the heavy and light chains of actual human antibodies. That requirement exists because the variable regions confer antigen binding specificity in the context of an assembled antibody.

102. The Cabilly Patents do not describe the sequence of any fully human antibodies. While they mention human-human hybridomas and human-mouse hybridomas in the "Background of the Invention" section (*see* col. 2, lines 11-17), the Cabilly Patents do not describe or provide a specific and useful teaching sufficient to enable the production of fully human antibodies with specific immunoreactive activity (*i.e.*, specific binding to a particular antigen). As discussed further below, in April 1983, there were a number of problems associated with obtaining human DNA sequences encoding antibodies that specifically bound a particular antigen.

103. First, for obvious ethical reasons, one could not in April 1983, and cannot today, simply immunize a human being with an antigen of interest to isolate antibody-producing B cells to make a hybridoma and clone heavy and light chain cDNAs. Even where people had been challenged with an antigen accidentally, as in the case of infections with pathogens, there was simply no practical way to gain access to their B cells.

104. Second, it was near impossible in April 1983, without the benefit of later-developed techniques like phage display and transgenic mice, to create human antibodies against human self-antigens, and absolutely certain that not all self-antigens would evoke an antibody response in a human. That is because immune tolerance mechanisms, which are a key feature of human immunity, allow the immune system to distinguish self from non-self and inhibit the body from mounting immune responses against itself. For example, it would have been very difficult in April 1983 to make a human anti-CEA antibody by immortalisation of human B-cells (whether by generating a hybridoma or by using a virus such as Epstein Barr Virus (EBV)), because there are very few B-cells directed against self-antigens (like CEA) due to these immune tolerance mechanisms. However, self-antigens are often of key importance in diseases like rheumatoid arthritis (RA) and various cancers, and almost all currently FDA-approved therapeutic antibodies (chimeric, humanized and fully human) are directed to human self-antigens,[4] and all the currently FDA-approved fully human therapeutic antibodies were made either by phage display/antibody repertoire technology or from transgenic mice.

105. Third, even if one did have access to human antibody-producing B cells, there would be no guarantee of success in making a human-human hybridoma. That is because one needs a suitable human "fusion partner" to make a hybridoma, and fusion partners with appropriate traits (*e.g.*, the absence of endogenous antibodies and genomic stability) were not easily obtained. Although a few human-human hybridomas had been produced by early 1983, many laboratories had been unsuccessful using such hybridomas, and questions remained as to their practical value. (Olsson, L., *et al.*, *Antibody producing human-human hybridomas, 1.*

[4] The only therapeutic anti-infective approved for use is Synagis®, which is directed against respiratory syncytial virus ("RSV").

*Technical aspects*, 61 J. IMMUNOL. METH. 17 (1983).) Additionally, the antibody yield from such hybridomas was significantly lower than when mouse lymphocytes were used as fusion partners. Further, human-human hybridomas were known to have more chromosomal instability and to be slower-growing than mouse hybridomas. (*Id.*)

106. Problems existed with human-mouse hybridomas as well. Before April 1983, human-mouse hybridomas had been shown to preferentially segregate certain human chromosomes, with some chromosomes preferentially retained while others were preferentially lost as the hybridoma cells divided. (Croce, C.M., *et al.*, *Production of human hybridomas secreting antibodies to measles virus*, 288 NATURE 488 (1980), citing Croce, C.M., *Loss of mouse chromosomes in somatic cell hybrids between HT-1080 human fibrosarcoma cells and mouse peritoneal macrophages*, 72 PROC. NAT'L ACAD. SCI. USA 3248 (1976).) This resulted in some immunoglobulin chain loci being lost. (*Id.; see also* Teng, N.N.H., *et al.*, *Construction and testing of mouse-human heteromyelomas for human monoclonal antibody production*, 80 PROC. NAT'L. ACAD. SCI. USA 7308 (1983).)

107. The Cabilly Patents provide no help regarding how to obtain human DNA sequences encoding antibodies that specifically bound to a particular antigen, especially human antigens, without great (and possibly insurmountable) difficulty. Consequently, given the state of the art in April 1983, coupled with the Cabilly Patents' general lack of disclosure, a POSA would not have reasonably concluded that the Cabilly inventors were in possession of vectors, host cells, or a method for producing fully human antibodies. Nor would a POSA have been taught how to make such vectors and host cells, or practice such a method without undue experimentation.

### A. Human Antibodies Are Produced by Phage Display/Antibody Repertoire Technology or Transgenic Mouse Technology

108. Today there exist several commercial fully human monoclonal antibody products, including Humira® (AbbVie) (which was the first fully-human antibody product marketed), Stelara® (Janssen Biotech), and Yervoy® (Bristol-Myers Squibb). None of these fully human antibodies are made by any technique described in the Cabilly Patents, though I understand the patent claims are broad enough to cover them. (I have been informed, for example, that BMS is involved in a companion litigation involving Yervoy®.)

109. Human antibodies were developed in a series of experiments using concepts, technology and inventions that were completely unknown at the time of filing the Cabilly Patents. In essence our work (and that of the competing group of Richard Lerner) involved the generation of large repertoires of human antibody fragments, and the selection of those with desired binding activities. Humira®, the first human antibody to be approved for therapy, was derived by this approach.

110. The first problem in making fully human antibodies was the generation of large repertoires of human antibody genes. This was solved by PCR[5] amplification of rearranged heavy (VH) and light chain (VL) variable region genes from populations of lymphocytes. (Orlandi, R., *et al.*, *Cloning immunoglobulin variable domains for expression by the polymerase chain reaction*, 86 Proc. Nat'l Acad. Sci. USA 3833 (1989); Marks, J.D., *et al.*, *Oligonucleotide primers for polymerase chain reaction amplification of human immunoglobulin variable genes and design of family-specific oligonucleotide probes*, 21 EUR J IMMUNOL 985 (1991); Ward, E.S.,

[5] PCR did not appear in the literature until 1985, and was a technique of such far-reaching significance that its inventor, Dr. Kary Mullis, won the Nobel Prize in Chemistry in 1993. (*See* Saiki, R.K., *et al.*, *Enzymatic amplification of beta-globin genomic sequences and restriction site analysis for diagnosis of sickle cell anemia*, 230 SCIENCE 1350 (1985).)

*et al.*, *Binding activities of a repertoire of single immunoglobulin variable domains secreted from Escherichia coli*, 341 NATURE 544 (1989).) The individual VH and VL gene libraries were then combined into much larger combinatorial library (VH x VL) gene libraries (Huse, W.D., *et al.*, *Generation of a large combinatorial library of the immunoglobulin repertoire in phage lambda*, 246 SCIENCE 1275 (1989)) potentially encoding antibody fragments with associated heavy and light chain variable domains (Clackson, T., *et al.*, *Making antibody fragments using phage display libraries*, 352 NATURE 624 (1991); Marks, J.D., *et al.*, *By-passing immunization. human antibodies from V-gene libraries displayed on phage*, 222 J MOL BIOL 581 (1991)). These libraries were potentially huge and highly diverse, with in excess of a million million ($10^{12}$) different antibodies.

111. The second problem in making fully human antibodies was to select those rare antibodies with binding activities to a desired antigen. This was solved by use of phage display technology. Bacteriophage, or "phage" for short, are viruses that infect bacteria. Phage have outer coat proteins that are encoded by phage DNA. DNA encoding other polypeptides can be inserted into genes that encode phage coat proteins, and those polypeptides will thus be "displayed" on the surface of the phage. The phage constitutes a replicable genetic package, in which the phenotype (the ability of the displayed peptide to bind to a target) is linked to the genotype (the DNA encoding the displayed peptide). Phage that bind to a desired target may therefore be captured on a solid phase to which the target is attached (Smith, G.P., *Filamentous fusion phage: novel expression vectors that display cloned antigens on the virion surface*, 228 SCIENCE 1315 (1985)), and the gene encoding the displayed polypeptide isolated or sequenced. In 1990, it was shown that antibody fragments could be displayed on phage. (McCafferty, J., *et*

*al.*, *Phage antibodies: filamentous phage displaying antibody variable domains*, 348 NATURE 552 (1990).)

112. Most conveniently the VH x VL combinatorial gene libraries were linked together as single chain Fv fragments (Bird, R., *et al.*, *Single-chain antigen-binding proteins*, 242 SCIENCE 423 (1988)), fused at their N-termini to a signal sequence (to allow secretion from the bacterial host) and at their C-termini to the coat protein of a filamentous bacteriophage (to allow display and selection). By this means, a library of bacteriophage was created in which each member encoded and displayed a different antibody fragment, and from which "binders" could be selected by capture on solid phase antigen. From such phage antibody libraries it was possible to isolate antibody fragments with the desired binding activities. Antibody fragments, which had been derived entirely from the VH and VL genes of human lymphocytes (Marks, J.D., *et al.*, *By-passing immunization. human antibodies from V-gene libraries displayed on phage*, 222 J MOL BIOL 581 (1991)), could be rebuilt into fully human antibodies by recombinant methods (Jespers, L.S., *et al.*, *Guiding the selection of human antibodies from phage display repertoires to a single epitope of an antigen*, 12 NATURE BIOTECHNOLOGY 899 (1994)).

113. In April 1983, such concepts had not been described nor had the technologies required for implementing them (PCR, phage display, phage antibody display, combinatorial antibody libraries, and single chain Fv fragments) been invented.

114. The other major method for making fully human antibodies came from the use of mice into whose genome has been inserted the complete gene sequences from human origins necessary for expression of human antibodies. Moreover, the naturally-occurring heavy chain and Ig kappa light chain genes in such mice must be silenced. Such transgenic mice when exposed to a desired human antigen respond, as they are now programmed to do, by making

antibodies that are fully human.[6] Such transgenic mice were first described in 1994, more than ten years after the Cabilly Patents were filed. (Green, L.L., *et al.*, *Antigen-specific human monoclonal antibodies from mice engineered with human Ig heavy and light chain YACs*, 7 NATURE GENETICS 13 (1994); Lonberg, N., *et al.*, *Antigen-specific human antibodies from mice comprising four distinct genetic modifications*, 368 NATURE 856 (1994).) Since 1994, even more V gene segments have been expressed in transgenic mice, and the collection of recoverable antibodies continues to expand. (*See* Lonberg 2005.) Once a transgenic mouse expressing a human antibody has been made, B cells that express human antibodies can be isolated and cloned to make monoclonal antibodies. Again, these methods involve concepts that had not been described in April 1983, as well as technologies that had not yet been invented.

115. In sum, the Cabilly Patents present no viable method for making a fully human antibody, despite the fact that such antibodies are encompassed by the scope of the Cabilly Patents' claims; combinatorial human antibody libraries displayed on phage did not exist until 1991, nor were suitable transgenic mice available until 1994. In April 1983, a POSA would not have believed that the Cabilly inventors had invented fully human recombinant antibodies, and the Cabilly specification certainly does not provide a specific and useful teaching to a POSA on how to make them.

---

[6] Both these important techniques were reviewed in the same issue of NATURE BIOTECHNOLOGY in 2005: Hoogenboom, H.R., *Selecting and screening recombinant antibody libraries*, 23 NATURE BIOTECHNOL. 1105 (2005); Lonberg, N., *Human antibodies from transgenic animals*, 23 NATURE BIOTECHNOL. 1117 (2005).

## XIV. The Cabilly Patents Do Not Describe or Enable Vectors, Host Cells, or Methods for Producing IgA or IgM Immunoglobulins

116. As discussed above, the scope of the claims of the Cabilly Patents encompasses all five main classes of immunoglobulins: IgG, IgA, IgM, IgD, and IgE. (Col. 3, lines 60-63.)

117. Although IgA and IgM immunoglobulins fall within the scope of the method claims of the Cabilly Patents, in April 1983, a POSA would have understood that the Genentech inventors were not in possession of vectors, host cells or methods of producing these immunoglobulins, and thus, their production was not enabled. As described below, the complexities of IgA and IgM immunoglobulins require unique structural elements not present in the immunoglobulins discussed in the Cabilly Patents, in particular, the addition of a third immunoglobulin chain, the J chain.

118. All immunoglobulins are constructed from the same basic tetrameric unit consisting of two "heavy" and two "light" polypeptide chains held together by disulphide bonds. For example, IgG antibodies are composed of a single tetramer, as shown schematically here:

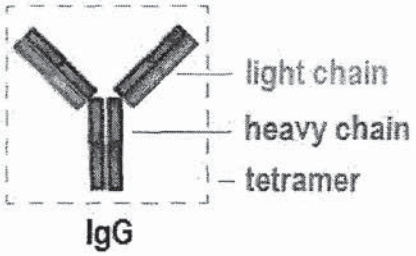



**Figure 3: IgG Immunoglobulins Consist of a Single Tetramer, Comprised of Two Heavy Chains and Two Light Chains**

119. IgA and IgM antibodies are much more complex, and exist as multimers of tetramers—that is, each antibody is comprised of multiple conjoined tetramers joined by a J chain, as shown here:

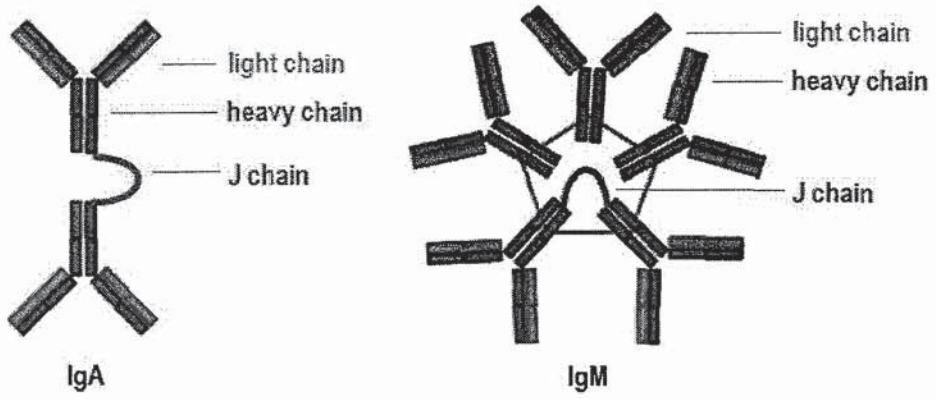



**Figure 4: IgA and IgM Immunoglobulins Consist of Multiple Tetramers Linked Together by a J Chain**

120. IgA immunoglobulins primarily exist as dimers of tetramers, and IgM immunoglobulins exist as pentamers of tetramers. As seen in Figure 4, the individual tetramers in both IgA and IgM immunoglobulins are linked together by a polypeptide chain known as the "J chain." The J chain is a 15 kilodalton polypeptide chain encoded by a separate gene from those that encode the heavy and light chains, and the J chain assists in the multimerization of both IgA and IgM immunoglobulins. No polypeptide chain similar to the J chain exists in single tetramer immunoglobulins such as IgG antibodies.

121. A POSA in April 1983 would have understood that the structural addition of a J chain adds complexity to the creation of recombinant IgA and IgM immunoglobulins. For example, gene isolation, expression plasmid construction, host cell transformation, and IgM/IgA immunoglobulin assembly are all compounded by the necessity of expressing a polypeptide J chain in addition to the heavy and light chains required for single tetramer immunoglobulins. The Cabilly Patents do not discuss J chains at all, let alone teach anything about how to isolate or express one and produce an multimeric immunoglobulin.

122. The Cabilly inventors did not purport to have recombinantly produced either IgA or IgM antibodies as of April 1983. Additionally, the Cabilly Patents are devoid of any disclosures or examples indicating that the production of IgA or IgM immunoglobulins was possible in April 1983 by practicing the claimed methods.

123. Given the immature state of the art in April 1983 with respect to both regulatory elements and immunoglobulin assembly, the resulting lack of predictability regarding recombinant immunoglobulin expression and assembly, coupled with the Cabilly Patents' general lack of disclosure, and the complete absence of working or predictive examples of expression and assembly of IgM and IgA immunoglobulins, a POSA would not have reasonably concluded that the Cabilly inventors were in possession of the claimed vectors, host cells, or methods for producing recombinant IgM and IgA immunoglobulins; nor would a POSA have been taught how to make such an immunoglobulin (or vector and host cell) based on the Cabilly Patents without undue experimentation.

## XV. The Asserted Cabilly II and III Claims Are Invalid for Double Patenting

124. All three Cabilly Patents state that the alleged invention relates to the use of recombinant DNA technology to make immunoglobulins or antibodies, including "chimeric" antibodies. A "chimeric" antibody is one whose heavy and/or light chain polypeptides contain amino acid sequences derived from different species (*e.g.*, human and mouse).

125. The Cabilly Patents set forth three "options" for transforming one or more host cells with one or more vectors containing the two DNA sequences encoding the heavy and light chains: (i) separate host cells are transformed with separate vectors, *i.e.*, one host cell is transformed with a heavy chain expression vector, and one is transformed with a light chain expression vector; (ii) one host cell is transformed with two vectors, a heavy chain expression

vector and a separate light chain expression vector, and (iii) one host cell is transformed with one vector containing the DNA encoding both the heavy and light chains. In the case where heavy and light chains are expressed in a single host cell transformed according to option (ii) or (iii), the heavy and light chains are said to be "coexpressed" in the same host cell.

126. I am informed that Genentech has asserted against Lilly's chimeric Erbitux® product only Cabilly II claims 15, 17, and 33, and Cabilly III claims 20, 27, 43, and 46. I am informed that Lilly contends that the subject matter of each of these asserted claims is not patentably distinct from the subject matter claimed in claims 1, 2, 6, or 7 of Cabilly I, and that, therefore, the asserted claims are invalid for "obviousness-type double patenting." Counsel for Lilly has asked me to examine and provide my opinion on this issue.

127. For the reasons discussed below, it is my opinion that the asserted claims of the later Cabilly II and III patents are not patentably distinct from claims 1, 2, 6 and 7 of the earlier Cabilly I patent.

**A. Cabilly I Claims 1 and 2 Cover Three Transformation Options**

128. Independent claim 1 of Cabilly I recites a method for making "a chimeric immunoglobulin heavy or light chain having specificity for a particular known antigen," the constant and variable regions of which are homologous to antibody constant and variable regions of different mammalian species. Claim 2 of Cabilly I is a dependent claim, depending from claim 1. Claim 2 states that the constant region is human. Thus, Claim 2 of Cabilly I covers chimeric heavy and light chains with a human constant region and a non-human variable region.

129. The recited method steps of Cabilly I claims 1and 2 are: (a) preparing "a DNA sequence encoding a chimeric immunoglobulin heavy or light chain," (b) inserting "the sequence" into "a replicable expression vector" having a promoter compatible with "a host cell,"

(c) transforming "the host cell" with the vector, (d) culturing the host cell, and (e) recovering the "chimeric heavy or light chain" from the cell culture.

130. I understand that the claims of Cabilly I should be interpreted in light of the specification of which they are a part. That specification discloses that the invention, in significant part, is directed to recombinant DNA processes for making antibodies and non-specific immunoglobulins formed of assembled heavy and light chains. (Col. 1, lines 14-16, col. 3, lines 16-22, 53-54.) The disclosed recombinant DNA processes include inserting the appropriate DNA sequences encoding the heavy and light chains into one or two vectors, and transforming one or two host cells with such vectors. In particular, the Cabilly specification expressly contemplates only three transformation options: (i) transforming separate host cells with separate vectors each containing a DNA sequence, (ii) transforming a single host cell with separate vectors, and (iii) transforming a single host cell with a single vector containing both DNA sequences. (Col. 12, lines 23-30.) In my opinion, a POSA would consider all three transformation options to be part of the same invention. Indeed, the Cabilly Patents state that "***regardless*** of which of the three foregoing [transformation] options is chosen, the cells are grown under conditions appropriate to the production of the desired protein" and "[t]he protein thus produced is then recovered from the cell culture by methods known in the art." (Col. 12, lines 31-38 (emphasis supplied).)

131. In light of the teaching in the Cabilly Patents, it is my opinion that a POSA would understand Cabilly I claims 1and 2 to cover a method for the production of immunoglobulins and antibodies comprising heavy and light chains by a process that includes a transformation step that may be any one of the three disclosed options. For this reason, a POSA would understand

that the claim language "heavy or light chain" is inclusive, *i.e.*, as encompassing the production of the heavy chain, or the light chain, or both the heavy and light chains.

132. Accordingly, it is my opinion that a POSA would understand that Cabilly I claims 1 and 2 cover preparing (and inserting) DNA sequences encoding both the heavy and light chains, and, therefore, that the claim is not limited to the use of only one "replicable expression vector." Instead, a POSA would at once envisage that the Cabilly I claim 1 step of "transforming" covers all three of the disclosed transformation options. Any of these options would allow either separate recovery of the expressed chains (and formation of a chimeric immunoglobulin by *in vitro* assembly) or recovery of the expressed chains in the form of an immunoglobulin (or antibody) assembled *in vivo*.

**B. Cabilly II Claim 33 Is Not Patentably Distinct from Cabilly I Claim 1**

133. Cabilly II claim 33 is a "process" claim. It sets forth a process for making, in part, "an immunoglobulin molecule" that contains "at least the variable domains of the immunoglobulin heavy and light chains." The heavy and light chains are otherwise not defined, and thus are not otherwise limited. Therefore, a POSA would understand that Cabilly II claim 33 covers the production of heavy and light chains that are chimeric.

134. The only expressly recited method step of Cabilly II claim 33 is "independently expressing" the two DNA sequences encoding the heavy and light chains "in [a] single host cell," which, of course, a POSA would understand had previously been transformed with the heavy and light chain sequences. Thus, although a POSA would understand that Cabilly II claim 33 claims coexpressing the heavy and light chains in a single transformed host cell, the number of vectors used for the transformation is not specified. Thus, a POSA would understand that the claim covers the same second and third transformation options disclosed in the Cabilly Patents (either the use of two vectors each with a separate immunoglobulin chain, or the use of only a

single vector with both immunoglobulin chains, to transform a single host cell) and encompassed by Cabilly I claim 1 (and claim 2).

135. The process of claim 33 of Cabilly II results in the formation of "an immunoglobulin molecule." According to Genentech, the claim requires assembly of the heavy and light chains to form an immunoglobulin molecule. (CC Ord. at 15-16.) But the claim says nothing about how or where the heavy and light chains are recovered and assembled into an immunoglobulin molecule; therefore, the claim covers recovering both separate chains for subsequent *in vitro* assembly or *in vivo* assembled chains in the form of an immunoglobulin molecule.

136. As set forth above, like Cabilly II claim 33, a POSA would understand that the preparing/inserting/transforming steps of Cabilly I claim 1 cover the production of a single host cell transformed with the heavy and light chain sequences by the second and third transformation options disclosed in the Cabilly Patents. The culturing step of Cabilly I claim 1 produces the protein encoded by the foreign DNA contained in the transformed host cell. Thus, a POSA would understand that Cabilly I claim 1 includes "independently expressing" the immunoglobulin DNA sequences in a single host cell transformed with the heavy and light chain sequences, as claimed in Cabilly II claim 33. Finally, a POSA would understand that the recovery step of Cabilly I claim 1 includes both recovery of separate chains (and formation of a chimeric antibody by *in vitro* assembly) and recovery of *in vivo* assembled chains in the form of an antibody. In other words, a POSA would understand that Cabilly I claim 1 claims a process that results in the formation of an immunoglobulin molecule as in Cabilly II claim 33. For the same reasons, a POSA would understand that Cabilly I claim 2 claims a process that results in

the formation of an immunoglobulin molecule having a human heavy or light chain constant region and that Cabilly II claim 33 covers processes for producing such immunoglobulins.

137. Because subject matter claimed in Cabilly I claims 1 and 2 (which cover a method for making chimeric immunoglobulins using any of the three disclosed transformation options and independently expressing the heavy and light chains in a single host cell) is the same as subject matter claimed in Cabilly II claim 33 (which covers the same method using either the second or third of the disclosed transformation options), it is my opinion that the later Cabilly II claim 33 is not patentably distinct from the earlier claim because it is anticipated by the earlier claim.

### C. Cabilly III Claims 20, 27, and 43 Are Not Patentably Distinct from Cabilly I Claim 2

138. Cabilly III claims 20, 27, and 43 are "method" claims. Cabilly III claim 20 sets forth a method that produces a chimeric antibody, one whose heavy and light chains both comprise a "human constant region sequence" and "a variable region sequence comprising non human mammalian variable region sequences." Cabilly III claims 27 and 43 set forth methods that produce an antibody (in which the heavy and light chains comprise "a variable region sequence and a human constant region sequence") that can be chimeric (when the "variable region sequence" is non-human).

139. The methods of Cabilly III claims 20 and 43 require "coexpressing" the chimeric heavy and light chains in "a recombinant host cell," which, of course, a POSA would understand had previously been transformed with the heavy and light chain sequences. Because the way in which the "recombinant host cell" is made is not specified, a POSA would understand that the claims cover the second and third transformation options disclosed in the Cabilly Patents (use of two vectors or only a single vector to transform a single host cell).

140. Cabilly III claim 27 recites a method of making heavy and light chains in "a recombinant host cell" comprising a vector encoding the heavy and light chains. A POSA thus would understand that this claim covers coexpressing the heavy and light chains in a single recombinant host cell. But because only one vector is used, a POSA would understand that the claim covers only the third transformation option disclosed in the Cabilly Patents, namely transformation with a single vector containing DNA sequences for both the heavy and light chains.

141. The methods of claims 20 and 43 of Cabilly III result in "an antibody." But the claims say nothing about how or where the heavy and light chains are recovered and assembled into an antibody, and, therefore, these claims cover both recovery of separate chains for subsequent *in vitro* assembly and recovery of *in vivo* assembled chains in the form of an antibody. (CC Ord. at 17-18.)

142. As set forth above, like Cabilly III claims 20, 27 and 43, a POSA would understand that the preparing/inserting/transforming steps of Cabilly I claim 2 cover the production of a recombinant host cell prepared by transformation options (ii) or (iii) disclosed in the Cabilly Patents. The culturing step of Cabilly I claim 2 produces the protein encoded by the foreign DNA contained in the recombinant host cell. Thus, a POSA would understand that Cabilly I claim 2 includes a method of "making" or "coexpressing" the heavy and light chains in "a recombinant host cell," as claimed in Cabilly III claims 20, 27, and 43. Finally, a POSA would understand that the recovery step of Cabilly I claim 2 includes both recovery of separate chains (and formation of a chimeric antibody by *in vitro* assembly) and recovery of *in vivo* assembled chains in the form of an antibody. In other words, Cabilly I claim 2 claims a process

that results in the formation of a chimeric antibody as in Cabilly III claims 20 and 43, and it discloses the recovery step of Cabilly III claim 27.

143. Because subject matter claimed in Cabilly I claim 2 (which covers a method for making chimeric antibodies using any of the three disclosed transformation options, making or coexpressing the heavy and light chains in a recombinant host cell, and the separate recovery of the chains for assembly *in vitro* or as assembled *in vivo*), is the same as the subject matter claimed in Cabilly III claim 20, 27, and 43 (which cover the same method using the second or third of the disclosed transformation options), it is my opinion that the later claims are not patentably distinct from the earlier claim. The later Cabilly III claims 20, 27, and 43 are anticipated by the earlier claim.

### D. Cabilly I Claim 6 Covers Three Transformation Options

144. Independent claim 5 of Cabilly I claims a "replicable expression vector" comprising "DNA encoding a chimeric immunoglobulin heavy or light chain having specificity for a particular known antigen," the constant and variable regions of which are homologous to antibody constant and variable regions of different mammalian species. Claim 6 of Cabilly I is a dependent claim, depending from claim 5. Claim 6 states that the first mammalian species is human. Thus, the heavy and light chains of claim 6 are both chimeric; each may have a human constant region and a variable region that is "homologous" to the corresponding regions of an antibody of a "second, different mammalian species."

145. As discussed above (¶¶ 128-132), it is my opinion that, in light of the teaching in the specification, a POSA would understand Cabilly I claim 6 to cover vectors that can be used for the production of immunoglobulins and antibodies comprising heavy and light chains. For this reason, a POSA would understand that the claim language "heavy or light chain" in Cabilly I

claim 6 covers a vector containing DNA sequences encoding, in addition to either the heavy or light chains alone, both the heavy and light chains.

146. Accordingly, it is my opinion that a POSA would understand that Cabilly I claim 6 is not limited to a "replicable expression vector" comprising only one chimeric immunoglobulin heavy or light chain DNA sequence. Instead, in my opinion, a POSA would at once envisage that the claim covers vectors that can be used for all three of the disclosed transformation options.

### E. Cabilly II Claim 15 Is Not Patentably Distinct From Cabilly I Claim 6

147. Cabilly II claim 15 claims a "vector" comprising two DNA sequences encoding "at least [the] variable domain[s] of immunoglobulin heavy and light chains" without any further limitation. Thus, this claim covers vectors containing DNA sequences that encode chimeric heavy and light chains. A POSA would understand that Cabilly II claim 15 covers vectors that can be used for the third transformation option disclosed in the Cabilly Patents.

148. As set forth above, like Cabilly II claim 15, a POSA would understand that the vector of Cabilly I claim 6 includes a vector comprising two DNA sequences encoding chimeric heavy and light chains. Because the subject matter claimed in Cabilly I claim 6 (which covers one or two vectors that can be used for all three of the disclosed transformation options) is the same as subject matter claimed in Cabilly II claim 15 (which covers vectors that can be used for the third transformation option), it is my opinion that the later claim is not patentably distinct from the earlier claim. The later Cabilly II claim 15 is anticipated by the earlier claim.

### F. Cabilly I Claim 7 Covers Three Transformation Options

149. Claim 7 of Cabilly I claims a "[r]ecombinant host cell[]" transformed with the vector of claim 5, *i.e.*, a "replicable expression vector" comprising "DNA encoding a chimeric immunoglobulin heavy or light chain having specificity for a particular known antigen."

150. As discussed above (¶¶ 128-132), it is my opinion that, in light of the teaching in the specification, a POSA would understand Cabilly I claim 7 to cover host cells that can be used for the production of immunoglobulins and antibodies comprising heavy and light chains. For this reason, a POSA would understand that the claim language "heavy or light chain" in Cabilly I claim 7 covers vectors containing DNA sequences encoding, in addition to either the heavy or light chains alone, both the heavy and light chains. Accordingly, it is my opinion that a POSA would understand that Cabilly I claim 7 is not limited to a "[r]ecombinant host cell[]" transformed with the vector comprising only one immunoglobulin DNA sequence, and that the claim is not limited to the use of only one "replicable expression vector." Instead, in my opinion, a POSA would at once envisage that the claim covers a "[r]ecombinant host cell[]" transformed according to all of the three transformation options disclosed in the Cabilly Patents.

### G. Cabilly II Claim 17 Is Not Patentably Distinct From Cabilly I Claim 7

151. Cabilly II claim 17 claims a "host cell[]" transformed with the vector of claim 15, *i.e.*, a "vector" comprising two DNA sequences that include chimeric heavy and light chains.

152. As set forth above, like Cabilly II claim 17, a POSA would understand that Cabilly I claim 7 covers host cells transformed with a vector comprising two DNA sequences encoding chimeric heavy and light chains. Because the subject matter claimed in Cabilly I claim 7 (which covers host cells transformed according to any of the three disclosed transformation options) is the same as subject matter in Cabilly II claim 17 (which covers host cells transformed according to the third disclosed transformation option), it is my opinion that the later claim is not patentably distinct from the earlier claim. The later Cabilly II claim 17 is anticipated by the earlier claim.

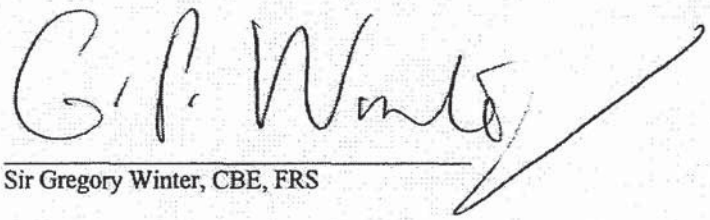
### H. Cabilly III Claim 46 Is Not Patentably Distinct From Cabilly I Claim 7

153. Cabilly III claim 46 claims "[a] recombinant host cell comprising the vector of claim 45," *i.e.*, a "replicable expression vector" comprising DNA encoding an antibody heavy and light chain having specificity for a desired antigen and a human constant region sequence.

154. As set forth above, like Cabilly III claim 46, a POSA would understand that Cabilly I claim 7 covers host cells transformed with a vector comprising two DNA sequences encoding chimeric heavy and light chains. Because the subject matter claimed in Cabilly I claim 7 (which covers host cells transformed according to any of the three disclosed transformation options) is the same as subject matter claimed in Cabilly III claim 46 (which covers host cells transformed according to the third disclosed transformation option), it is my opinion that the later claim is not patentably distinct from the earlier claim. The later Cabilly III claim 46 is anticipated by the earlier claim.

## XVI. Conclusion

155. For the reasons set forth above, it is my opinion that the Cabilly Patents did not provide sufficient written description to demonstrate with reasonable clarity to a POSA in April 1983 that the inventors were in possession of the extremely broad scope of vectors, host cells, and methods that the patent claims encompass. Nor, for the reasons explained above, do the Cabilly Patents enable a POSA in April 1983 to make or use the extremely broad range of vectors, host cells, and methods that are claimed without undue experimentation. In addition, the asserted claims of Cabilly II and III are not patentably distinct from the claims of Cabilly I.



Sir Gregory Winter, CBE, FRS

Date: October 13, 2014

# Exhibit A

Expert Report of Sir Gregory Winter, CBE, FRS

# CURRICULUM VITAE: Sir Gregory WINTER CBE, FRS

*Master, Trinity College, Cambridge*

**Work / Home**
Master's Lodge
Trinity College
Trinity Street
Cambridge CB2 1TQ

Tel: +44 (0) 1223 330864 (direct)
Tel: +44 (0) 1223 338595 (secretary)
Mob: +44 (0) 7919 340856
Fax: +44 (0) 1223 338500 (secretary)

E-mail masters.secretary@trin.cam.ac.uk

Born: 14 April 1951, four children ages 18 – 30 years.

## CAREER TO DATE

| | |
|---|---|
| 1970-73: | Scholar, Trinity College, Cambridge. |
| 1973: | BA Natural Sciences |
| 1973-76: | PhD student at MRC Laboratory of Molecular Biology (LMB). |
| 1976: | MA and PhD, Cambridge. |
| 1976-80: | Junior Research Fellow, Trinity College, Cambridge. |
| 1976-77: | Postdoctoral research fellow at Imperial College, London. |
| 1977-80: | Postdoctoral research fellow at LMB, Cambridge. |
| 1981- : | Member of scientific staff at LMB, Cambridge. |
| 1990-2010: | Deputy Director of Cambridge Centre for Protein Engineering. |
| 1991-2011: | Senior Research Fellow of Trinity College. |
| 1994-2008: | Joint Head of Division of Protein and Nucleic Acid Chemistry at LMB. |
| 2006-2011: | Deputy Director of the LMB. |
| 2007-2008: | Acting Director of the LMB |
| 2012-: | Master, Trinity College, Cambridge |

## PRIZES & DISTINCTIONS

| | |
|---|---|
| 1984: | Perutz Prize, MRC Laboratory of Molecular Biology. |
| 1986: | Colworth medal of the Biochemical Society (UK). |
| 1986: | Novo Biotechnology Award (Denmark), shared with AR Fersht. |
| 1988: | Member of EMBO. |
| 1989: | Prix Louis Jeantet de Medecine (Switzerland), shared with RJ Poljak & W. Schaffner. |
| 1989: | Pfizer Academic Award (UK). |
| 1990: | Emil von Behring Preis (Germany). |
| 1990: | Milano Prize (Italy). |
| 1990: | Fellow of the Royal Society (UK). |
| 1994: | Scheele Award of the Swedish Academy of Pharmaceutical Sciences. |
| 1995: | Biochemical Analysis prize German Society for Clinical Chemistry. |
| 1995: | King Faisal International Prize in Medicine (Saudi Arabia), shared with TW Mak & MM Davies |
| 1997: | Commander of the Order of the British Empire (CBE). |
| 1999: | William B. Coley Award of the Cancer Research Institute (USA), shared with RA Lerner. |
| 2001: | Docteur Honoris Causa, Nantes University (France). |
| 2002: | Jacob Heskel Gabbay Award in Biotechnology & Medicine, Brandeis (USA), shared with WH Rastetter & DJ Slamon. |
| 2002: | Honorary Doctorate of Natural Sciences, ETH Zurich (Switzerland). |

| | |
|---|---|
| 2002: | Jean-Pierre Lecocq Award, L'Académie des Sciences (France), shared with MS Neuberger. |
| 2002: | Foreign Fellow of the Australian Academy of Technological Sciences & Engineering (FTSE). |
| 2003: | Honorary Fellow of the Royal College of Physicians (Hon. FRCP) |
| 2004: | National Biotechnology Ventures Award (USA). |
| 2004: | Knight Bachelor. |
| 2005: | Baly Medal, the Royal College of Physicians (UK). |
| 2006: | Biochemical Society Award (UK). |
| 2006: | Fellow of the Academy of Medical Sciences (FMedSci) (UK) |
| 2007: | Honorary Member of the Biochemical Society (UK) |
| 2007: | Foreign Member of Swedish Academy of Engineering Sciences |
| 2008: | BioIndustry Association Award (UK) |
| 2009: | Honorary Fellow of Royal Society of Medicine |
| 2011: | Royal Medal, the Royal Society (UK) |
| 2011: | Honorary member of British Biophysical Society. |
| 2012: | Prince of Asturias Award for Scientific and Technical Research, shared with R. A. Lerner |
| 2013: | Millennium Prize of the Medical Research Council (UK) |
| 2013: | Canada Gairdner International Award, shared. |
| 2013: | Honorary Fellow, the Royal Society of Chemistry (UK) |

**OTHER EXPERIENCE**

| | |
|---|---|
| 1979 - 1992: | Co-Organizer of Practical Courses on DNA Sequencing, Site-Directed Mutagenesis, and Phage Antibody Display run by FEBS and EMBO. |
| 1986 -: | Inventor on multiple patents (granted and applied for) in the field of Antibody Engineering including Humanizing, Antibody Repertoires and Phage Display. |
| 1987 -: | Scientific consultancies with companies have included PA Technology, Scotgen, Amersham, Celltech, Unilever, Behringwerke, Peptech, Cambridge Antibody Technology, Domantis, Pfizer, Takeda, Heptares; and currently Bicycle Therapeutics, F-star, ProteinLogic, Covagen, Biosceptre and Selexis. |
| 1989 - 1996: | Co-Founder, Research Coordinator and non-Executive Director of Cambridge Antibody Technology (UK). |
| 2001 - 2006: | Co-Founder and non-Executive Director of Domantis (originally Diversys) (UK) |
| 2001 -2003: | Non-Executive Director Peptech (Australia). |
| 2009 -: | Trustee of Cambridge Trusts and Kennedy Trust for Rheumatology Research, trustee (ex officio) of Newton Trust (Cambridge) and member of Governing body of Westminster School London |
| 2009 -: | Co-Founder, and non-Executive Director of Bicycle Therapeutics (UK). |

# Exhibit B

Expert Report of Sir Gregory Winter, CBE, FRS

**PUBLICATIONS**


1. Walker I.D., Winter G. & Worthington D.J. (1976). Structural Investigations of Peptides and Proteins. I: Primary Structure and Chemical Modification. *In: Amino-acids Peptides and Proteins*, The Chemical Society, London. Specialist Periodical Reports Vol. 8, 29-151.
2. Winter G., Hartley B.S., McLachlan A.D., Lee M. & Muench K.H. (1977). Sequence homologies between the tryptophanyl tRNA synthetases of *Bacillus stearothermophilus* and *Escherichia coli*. *FEBS Lett* **82**, (2) 348-350.
3. Winter G. & Hartley B.S. (1977). The amino acid sequence of tryptophanyl tRNA synthetase from *Bacillus stearothermophilus*. *FEBS Lett* **80**, (2) 340-342.
4. Winter G. & Brownlee G.G. (1978). 3' end labelling of RNA with $^{32}P$ suitable for rapid gel sequencing. *Nucleic Acids Res* **5**, (9) 3129-3139.
5. Winter G. & Dell A. (1978). Chemical Modification. *In: Amino-acids Peptides and Proteins*, The Chemical Society, London. Specialist Periodical Reports Vol 9, 114-196.
6. Atkinson A., Banks G.T., Bruton C.J., Comer M.J., Jakes R., Kamalagharan A., Whittaker A.R. & Winter G. (1979). Large-scale isolation of enzymes from *Bacillus stearothermophilus*. *J Applied Biochem* **1**, 247-258.
7. Winter G., Koch G.L.E., Dell A. & Hartley B.S. (1979). The tryptophanyl- and tyrosyl-tRNA synthetases from *Bacillus stearothermophilus*. *In Transfer RNA: Structure, Properties and Recognition*, eds. P.R. Schimmer, D. Soll & J.N. Abelson (Cold Spring Harbor).
8. Winter G. & Fields S. (1980). Cloning of influenza cDNA into M13: the sequence of the RNA segment encoding the A/PR/8/34 matrix protein. *Nucleic Acids Res* **8**, (9) 1965-1974.
9. Fields S. & Winter G. (1981). Influenza virus A/PR/8/34 genes: sequencing by a shotgun approach. *Genetic Variation among Influenza Viruses* (6), 55-64.
10. Brownlee G.G., Winter G. & Fields S. (1981). The haemagglutinin gene of influenza A/PR/8/34. *Genetic Variation among Influenza Viruses* (6), 65-75.
11. Fields S. & Winter G. (1981). Nucleotide-sequence heterogeneity and sequence rearrangements in influenza virus cDNA. *Gene* **15**, (2-3) 207-214.
12. Fields S., Winter G. & Brownlee G.G. (1981). Structure of the neuraminidase gene in human influenza virus A/PR/8/34. *Nature* **290**, (5803) 213-217.
13. Winter G., Fields S. & Ratti G. (1981). The structure of two subgenomic RNAs from human influenza virus A/PR/8/34. *Nucleic Acids Res* **9**, (24) 6907-6915.
14. Winter G. & Fields S. (1981). The structure of the gene encoding the nucleoprotein of human influenza virus A/PR/8/34. *Virology* **114**, (2) 423-428.
15. Winter G., Fields S., Gait M.J. & Brownlee G.G. (1981). Nucleotide sequence of the haemagglutinin gene of the human influenza virus H1 subtype. *Nature* **292**, (5818) 72-75.
16. Winter G., Fields S., Gait M.J. & Brownlee G.G. (1981). The use of synthetic oligodeoxynucleotide primers in cloning and sequencing segment 8 of influenza virus (A/PR/8/34). *Nucleic Acids Res* **9**, (2) 237-245.
17. Barker D.G., Bruton C.J. & Winter G. (1982). The tyrosyl-tRNA synthetase from *Escherichia coli:* complete nucleotide sequence of the structural gene. *FEBS Lett* **150**, (2) 419-423.
18. Barker D.G. & Winter G. (1982). Conserved cysteine and histidine residues in the structure of the tyrosyl and methionyl-tRNA synthetases. *FEBS Lett* **145**, (2) 191-193.
19. Fields S. & Winter G. (1982). Nucleotide sequences of influenza virus segments 1 and 3 reveal mosaic structure of a small viral RNA segment. *Cell* **28**, (2) 303-313.
20. Winter G., Fersht A.R., Wilkinson A.J., Zoller M. & Smith M. (1982). Redesigning enzyme structure by site-directed mutagenesis: tyrosyl tRNA synthetase and ATP binding. *Nature* **299**, (5885) 756-758.
21. Winter G. & Fields S. (1982). Nucleotide sequence of human influenza A/PR/8/34 segment 2. *Nucleic Acids Res* **10**, (6) 2135-2143.

22. Jennings P.A., Finch J.T., Winter G. & Robertson J.S. (1983). Does the higher order structure of the influenza virus ribonucleoprotein guide sequence rearrangements in influenza viral RNA? *Cell* **34**, (2) 619-627.

23. Waye M.M., Winter G., Wilkinson A.J. & Fersht A.R. (1983). Deletion mutagenesis using an 'M13 splint': the N-terminal structural domain of tyrosyl-tRNA synthetase *(B. stearothermophilus)* catalyses the formation of tyrosyl adenylate. *EMBO J* **2**, (10) 1827-1829.

24. Wilkinson A.J., Fersht A.R., Blow D.M. & Winter G. (1983). Site-directed mutagenesis as a probe of enzyme structure and catalysis: tyrosyl-tRNA synthetase cysteine-35 to glycine-35 mutation. *Biochemistry* **22**, (15) 3581-3586.

25. Winter G., Koch G.L., Hartley B.S. & Barker D.G. (1983). The amino acid sequence of the tyrosyl-tRNA synthetase from *Bacillus stearothermophilus*. *Eur J Biochem* **132**, (2) 383-387.

26. Carter P.J., Winter G., Wilkinson A.J. & Fersht A.R. (1984). The use of double mutants to detect structural changes in the active site of the tyrosyl-tRNA synthetase *(Bacillus stearothermophilus)*. *Cell* **38**, (3) 835-840.

27. Fersht A.R. & Winter G. (1984). Studying enzyme-substrate interactions by site-directed mutagenesis. *Pontificiae Acad Sci Scripta Varia* **55**, 123-132.

28. Fersht A.R., Shi J-P., Wilkinson A.J., Blow D.M., Carter P., Waye M.M. & Winter G. (1984). Analysis of enzyme structure and activity by protein engineering. *Angew Chemie* **23**, 467-473.

29. Wilkinson A.J., Fersht A.R., Blow D.M., Carter P. & Winter G. (1984). A large increase in enzyme-substrate affinity by protein engineering. *Nature* **307**, 187-188.

30. Winter G., Carter P., Waye M.M., Blow D.M., Wilkinson A.J., Shi J-P. & Fersht A.R. (1984). Genetic dissection of tyrosyl-tRNA synthetase. *Biochem Soc Trans* **12**, (2) 224-225.

31. Winter G. & Fersht A.R. (1984). Engineering enzymes. *Trends in Biotechnology* **2**, 115-119.

32. Bedouelle H., Carter P., Waye M.M., Winter G., Lowe D.M., Wilkinson A.J. & Fersht A.R. (1985). Engineering of tyrosyl tRNA synthetase. *Biochimie* **67**, (7-8) 737-743.

33. Carter P., Bedouelle H. & Waye M.M. & Winter G. (1985). Oligonucleotide site-directed mutagenesis in M13. An experimental manual. *Based on a practical course held at EMBL Heidelberg in Sep 1984.*

34. Carter P., Bedouelle H. & Winter G. (1985). Improved oligonucleotide site-directed mutagenesis using M13 vectors. *Nucleic Acids Res* **13**, (12) 4431-4443.

35. Fersht A.R., Wilkinson A.J., Carter P. & Winter G. (1985). Fine structure-activity analysis of mutations at position 51 of tyrosyl-tRNA synthetase. *Biochemistry* **24**, (21) 5858-5861.

36. Fersht A.R., Shi J-P., Knill-Jones J.W., Lowe D.M., Wilkinson A.J., Blow D.M., Brick P., Carter P., Waye M.M. & Winter G. (1985). Hydrogen bonding and biological specificity analysed by protein engineering. *Nature* **314**, (6008) 235-238.

37. Fersht A.R. & Winter G. (1985). Redesigning enzymes by site-directed mutagenesis. *Ciba Found Symp* **111**, 204-218.

38. Jones D.H., McMillan A.J., Fersht A.R. & Winter G. (1985). Reversible dissociation of dimeric tyrosyl-tRNA synthetase by mutagenesis at the subunit interface. *Biochemistry* **24**, (21) 5852-5857.

39. Leatherbarrow R.J., Fersht A.R. & Winter G. (1985). Transition-state stabilization in the mechanism of tyrosyl-tRNA synthetase revealed by protein engineering. *Proc Natl Acad Sci USA* **82**, (23) 7840-7844.

40. Lowe D.M., Fersht A.R., Wilkinson A.J., Carter P. & Winter G. (1985). Probing histidine-substrate interactions in tyrosyl-tRNA synthetase using asparagine and glutamine replacements. *Biochemistry* **24**, (19) 5106-5109.

41. Waye M.M., Verhoeyen M.E., Jones P.T. & Winter G. (1985). *Eco*K selection vectors for shotgun cloning into M13 and deletion mutagenesis. *Nucleic Acids Res* **13**, (23) 8561-8571.

42. Bedouelle H. & Winter G. (1986). A model of synthetase/tRNA interaction as deduced by protein engineering. *Nature* **320**, (6060) 371-373.

43. Bedouelle H., Carter P. & Winter G. (1986). Protein engineering of tyrosyl-tRNA synthetase: the charging of tRNA. *Philos Trans R Soc Lond A* **317**, 433-441.

44. Carter P., Bedouelle H. & Winter G. (1986). Construction of heterodimer tyrosyl-tRNA synthetase shows tRNATyr interacts with both subunits. *Proc Natl Acad Sci USA* **83**, (5) 1189-1192.

45. Jones P.T., Dear P.H., Foote J., Neuberger M.S. & Winter G. (1986). Replacing the complementarity-determining regions in a human antibody with those from a mouse. *Nature* **321**, (6069) 522-525.

46. Todd J.A., Roberts A.N., Johnstone K., Piggot P.J., Winter G. & Ellar D.J. (1986). Reduced heat resistance of mutant spores after cloning and mutagenesis of the *Bacillus subtilis* gene encoding penicillin-binding protein 5. *J Bacteriol* **167**, (1) 257-264.

47. Waye M.M. & Winter G. (1986). A transcription terminator in the 5' non-coding region of the tyrosyl tRNA synthetase gene from *Bacillus stearothermophilus*. *Eur J Biochem* **158**, (3) 505-510.

48. Winter G. (1986). Manual sequence strategy - a personal view. *In: Practical Protein Chemistry - A Handbook*, ed. A. Darbre (John Wiley & Sons Ltd, UK) 345-366.

49. Winter G. (1986). Manual sequencing by the Dansyl-Edman Reaction. *In: Practical Protein Chemistry - A Handbook*, ed. A. Darbre (John Wiley & Sons Ltd, UK) 367-374.

50. Lowe D.M., Winter G. & Fersht A.R. (1987). Structure-activity relationships in engineered proteins: characterization of disruptive deletions in the alpha-ammonium group binding site of tyrosyl-tRNA synthetase. *Biochemistry* **26**, (19) 6038-6043.

51. Duncan A.R. & Winter G. (1988). The binding site for C1q on IgG. *Nature* **332**, (6166) 738-740.

52. Duncan A.R., Woof J.M., Partridge L.J., Burton D.R. & Winter G. (1988). Localization of the binding site for the human high-affinity Fc receptor on IgG. *Nature* **332**, (6164) 563-564.

53. Fersht A.R., Knill-Jones J.W., Bedouelle H. & Winter G. (1988). Reconstruction by site-directed mutagenesis of the transition state for the activation of tyrosine by the tyrosyl-tRNA synthetase: a mobile loop envelopes the transition state in an induced-fit mechanism. *Biochemistry* **27**, (5) 1581-1587.

54. Hale G., Dyer M.J., Clark M.R., Phillips J.M., Marcus R., Riechmann L., Winter G. & Waldmann H. (1988). Remission induction in non-Hodgkin lymphoma with reshaped human monoclonal antibody CAMPATH-1H. *Lancet* **2**, (8625) 1394-1399.

55. Riechmann L., Foote J. & Winter G. (1988). Expression of an antibody Fv fragment in myeloma cells. *J Mol Biol* **203**, (3) 825-828.

56. Riechmann L., Clark M., Waldmann H. & Winter G. (1988). Reshaping human antibodies for therapy. *Nature* **332**, (6162) 323-327.

57. Verhoeyen M., Milstein C. & Winter G. (1988). Reshaping human antibodies: grafting an anti-lysozyme activity. *Science* **239**, (4847) 1534-1536.

58. Bruggemann M., Winter G., Waldmann H. & Neuberger M.S. (1989). The immunogenicity of chimeric antibodies. *J Exp Med* **170**, (6) 2153-2157.

59. Clackson T. & Winter G. (1989). 'Sticky feet'-directed mutagenesis and its application to swapping antibody domains. *Nucleic Acids Res* **17**, (24) 10163-10170.

60. Gussow D., Ward E.S., Griffiths A.D., Jones P.T. & Winter G. (1989). Generating binding activities from *Escherichia coli* by expression of a repertoire of immunoglobulin variable domains. *In: Cold Spring Harb Symp Quant Biol* **54**, Pt 1 265-272.

61. Mariuzza R.A. & Winter G. (1989). Secretion of a homodimeric V alpha C kappa T-cell receptor-immunoglobulin chimeric protein. *J Biol Chem* **264**, (13) 7310-7316.

62. Orlandi R., Gussow D.H., Jones P.T. & Winter G. (1989). Cloning immunoglobulin variable domains for expression by the polymerase chain reaction. *Proc Natl Acad Sci USA* **86**, (10) 3833-3837.

63. Ward E.S., Gussow D., Griffiths A.D., Jones P.T. & Winter G. (1989). Binding activities of a repertoire of single immunoglobulin variable domains secreted from *Escherichia coli*. *Nature* **341**, (6242) 544-546.

64. Wawrzynczak E.J., Parnell G.D., Cumber A.J., Jones P.T. & Winter G. (1989). Blood clearance in the mouse of an aglycosyl recombinant monoclonal antibody. *Biochem Soc Trans* **17**, (6) 1061-1062.

65. Winter G. (1989). Antibody engineering. *In: Philos Trans R Soc Lond B Biol Sci* **324**, (1224) 537-547.

66. Winter G. (1989). The engineering of enzymes and antibodies. Texte de la Conférence présentée par Monsieur Greg Winter à l'occasion de la remise du Prix Louis Jeantet de Médecine le 21 Avril 1989 à Genève.

67. Boulot G., Eisele J-L., Bentley G.A., Bhat T.N., Ward E.S., Winter G. & Poljak R.J. (1990). Crystallization and preliminary X-ray diffraction study of the bacterially expressed Fv from the monoclonal anti-lysozyme antibody D1.3 and of its complex with the antigen, lysozyme. *J Mol Biol* **213**, (4) 617-619.

68. McCafferty J., Griffiths A.D., Winter G. & Chiswell D.J. (1990). Phage antibodies: filamentous phage displaying antibody variable domains. *Nature* **348**, (6301) 552-554.

69. Winter G. (1990). Gene technologies for antibody engineering. *Behring Inst Mitt* **87**, 10-20.

70. Clackson T., Hoogenboom H.R., Griffiths A.D. & Winter G. (1991). Making antibody fragments using phage display libraries. *Nature* **352**, (6336) 624-628.

71. Hoogenboom H.R., Griffiths A.D., Johnson K.S., Chiswell D.J., Hudson P. & Winter G. (1991). Multi-subunit proteins on the surface of filamentous phage: methodologies for displaying antibody (Fab) heavy and light chains. *Nucleic Acids Res* **19**, (15) 4133-4137

72. Lund J., Winter G., Jones P.T., Pound J.D., Tanaka T., Walker M.R., Artymiuk P.J., Arata Y., Burton D.R., Jefferies R. & Woof J.M. (1991). Human Fc gamma RI and Fc gamma RII interact with distinct but overlapping sites on human IgG. *J Immunol* **147**, (8) 2657-2662.

73. Marks J.D., Hoogenboom H.R., Bonnert T.P., McCafferty J., Griffiths A.D. & Winter G. (1991). By-passing immunization. Human antibodies from V-gene libraries displayed on phage. *J Mol Biol* **222**, (3) 581-597.

74. Marks J.D., Tristem M., Karpas A. & Winter G. (1991). Oligonucleotide primers for polymerase chain reaction amplification of human immunoglobulin variable genes and design of family-specific oligonucleotide probes. *Eur J Immunol* **21**, (4) 985-991.

75. Skerra A., Dreher M.L. & Winter G. (1991). Filter screening of antibody Fab fragments secreted from individual bacterial colonies: specific detection of antigen binding with a two-membrane system. *Anal Biochem* **196**, (1) 151-155.

76. Winter G. & Milstein C. (1991). Man-made antibodies. *Nature* **349**, (6307) 293-299.

77. Bye J.M., Carter C., Cui Y., Gorick B.D., Songsivilai S., Winter G., Hughes-Jones N.C. & Marks J.D. (1992). Germline variable region gene segment derivation of human monoclonal anti-Rh(D) antibodies. Evidence for affinity maturation by somatic hypermutation and repertoire shift. *J Clin Invest* **90**, (6) 2481-2490.

78. Chothia C., Lesk A.M., Gherardi E., Tomlinson I.M., Walter G., Marks J.D., Llewelyn M.B. & Winter G. (1992). Structural repertoire of the human $V_H$ segments. *J Mol Biol* **227**, (3) 799-817.

79. Cumber A.J., Ward E.S., Winter G., Parnell G.D. & Wawrzynczak E.J. (1992). Comparative stabilities *in vitro* and *in vivo* of a recombinant mouse antibody FvCys fragment and a bisFvCys conjugate. *J Immunol* **149**, (1) 120-126.

80. Embleton M.J., Gorochov G., Jones P.T. & Winter G. (1992). In-cell PCR from mRNA: amplifying and linking the rearranged immunoglobulin heavy and light chain V-genes within single cells. *Nucleic Acids Res* **20**, (15) 3831-3837

81. Fersht A.R. & Winter G. (1992). Protein engineering. *Trends Biochem Sci* **17**, (8) 292-295.

82. Foote J. & Winter G. (1992). Antibody framework residues affecting the conformation of the hypervariable loops. *J Mol Biol* **224**, (2) 487-499.

83. Hawkins R.E., Russell S.J. & Winter G. (1992). Selection of phage antibodies by binding affinity. Mimicking affinity maturation. *J Mol Biol* **226**, (3) 889-896.

84. Hawkins R.E. & Winter G. (1992). Cell selection strategies for making antibodies from variable gene libraries: trapping the memory pool. *Eur J Immunol* **22**, (3) 867-870.

85. Hoogenboom H.R., Marks J.D., Griffiths A.D. & Winter G. (1992). Building antibodies from their genes. *Immunol Rev* **130**, 41-68.

86. Hoogenboom H.R. & Winter G. (1992). By-passing immunisation. Human antibodies from synthetic repertoires of germline $V_H$ gene segments rearranged *in vitro*. *J Mol Biol* **227**, (2) 381-388.

87. Lund J., Pound J.D., Jones P.T., Duncan A.R., Bentley T., Goodall M., Levine B.A., Jefferies R. & Winter G. (1992). Multiple binding sites on the $C_H2$ domain of IgG for mouse Fc gamma RII. *Mol Immunol* **29**, (1) 53-59.

88. Marks J.D., Hoogenboom H.R., Griffiths A.D. & Winter G. (1992). Molecular evolution of proteins on filamentous phage. Mimicking the strategy of the immune system. *J Biol Chem* **267**, (23) 16007-16010.

89. Marks J.D., Griffiths A.D., Malmqvist M., Clackson T.P., Bye J.M. & Winter G. (1992). By-passing immunization: building high affinity human antibodies by chain shuffling. *Biotechnology (NY)* **10**, (7) 779-783.

90. Marks J.D. & Winter G. (1992). An artificial immune system for making antibodies. *Behring Inst Mitt* **91**, 6-12.

91. Orlandi R., Gussow D.H., Jones P.T. & Winter G. (1992). Cloning immunoglobulin variable domains for expression by the polymerase chain reaction. 1989. *Biotechnology* **24**, 527-531.

92. Tomlinson I.M., Walter G., Marks J.D., Llewelyn M.B. & Winter G. (1992). The repertoire of human germline $V_H$ sequences reveals about fifty groups of $V_H$ segments with different hypervariable loops. *J Mol Biol* **227**, (3) 776-798.

93. Wawrzynczak E.J., Denham S., Parnell G.D., Cumber A.J., Jones P.T. & Winter G. (1992). Recombinant mouse monoclonal antibodies with single amino acid substitutions affecting Clq and high affinity Fc receptor binding have identical serum half-lives in the BALB/c mouse. *Mol Immunol* **29**, (2) 221-227.

94. Wawrzynczak E.J., Cumber A.J., Parnell G.D., Jones P.T. & Winter G. (1992). Blood clearance in the rat of a recombinant mouse monoclonal antibody lacking the *N*-linked oligosaccharide side chains for the $C_H2$ domains. *Mol Immunol* **29**, (2) 213-220.

95. Griffiths A.D., Malmqvist M., Marks J.D., Bye J.M., Embleton M.J., McCafferty J., Baier M., Holliger P., Gorick B.D., Hughes-Jones N.C., Hoogenboom H.R. & Winter G. (1993). Human anti-self antibodies with high specificity from phage display libraries. *EMBO J* **12**, 725-734.

96. Hawkins R.E., Russell S.J., Baier M. & Winter G. (1993). The contribution of contact and non-contact residues of antibody in the affinity of binding to antigen. The interaction of mutant D1.3 antibodies with lysozyme. *J Mol Biol* **234**, (4) 958-964.

97. Hawkins R.E., Winter G., Hamblin T.J., Stevenson F.K. & Russell S.J. (1993). A genetic approach to idiotypic vaccination. *J Immunother* **14**, (4) 273-278.

98. Holliger P. & Winter G. (1993). Engineering bispecific antibodies. *Curr Opin Biotechnol* **4**, (4) 446-449.

99. Holliger P., Prospero T.D. & Winter G. (1993). "Diabodies": small bivalent and bispecific antibody fragments. *Proc Natl Acad Sci USA* **90**, (14) 6444-6448.

100. Hoogenboom H.R., Marks J.D., Griffiths A.D. & Winter G. (1993). Building antibodies from their genes. *Rev Fr Transfus Hemobiol* **36**, (1) 19-47. Review.

101. Marks J.D., Ouwehand W.H., Bye J.M., Finnern R., Gorick B.D., Voak D., Thorpe S.J., Hughes-Jones N.C. & Winter G. (1993). Human antibody fragments specific for human blood group antigens from a phage display library. *Biotechnology (NY)* **11**, (10) 1145-1149.

102. Russell S.J., Hawkins R.E. & Winter G. (1993). Retroviral vectors displaying functional antibody fragments. *Nucleic Acids Res* **21**, (5) 1081-1085.

103. Walter G., Tomlinson I.M., Cook G.P., Winter G., Rabbitts T.H. & Dear P.H. (1993). HAPPY mapping of a YAC reveals alternative haplotypes in the human immunoglobulin VH locus. *Nucleic Acids Res* **21**, (19) 4524-4529.

104. Waterhouse P., Griffiths A.D., Johnson K.S. & Winter G. (1993). Combinatorial infection and *in vivo* recombination: a strategy for making large phage antibody repertoires. *Nucleic Acids Res* **21**, (9) 2265-2266.

105. Williams S.C. & Winter G. (1993). Cloning and sequencing of human immunoglobulin V lambda gene segments. *Eur J Immunol* **23**, (7) 1456-1461.

106. Winter G. & Harris W.J. (1993). Humanized antibodies. *Immunol Today* **14**, (6) 243-246.

107. Winter G. & Harris W.J. (1993). Humanized antibodies. *Trends Pharmacol Sci* **14**, (5) 139-143.

108. Winter G. (1993). Immunological techniques. Editorial overview. *Curr Opin Immunol* **5**, (2) 253-255.

109. Winter G. & Ward S. (1993). Antibody Engineering. *Clinical Aspects of Immunology* **5**, 817-828.

110. Chester K.A., Begent R.H., Robson L., Keep P., Pedley R.B., Boden J.A., Boxer G., Green A., Winter G., Cochet O. & Hawkins R.E. (1994). Phage libraries for generation of clinically useful antibodies. *Lancet* **343**, (8895) 455-456.

111. Cook G.P., Tomlinson I.M., Walter G., Riethman H., Carter N.P., Buluwela L., Winter G. & Rabbitts T.H. (1994). A map of the human immunoglobulin $V_H$ locus completed by analysis of the telomeric region of chromosome 14q. *Nat Genet* **7**, (2) 162-168.

112. Cox J.P., Tomlinson I.M. & Winter G. (1994). A directory of human germ-line V kappa segments reveals a strong bias in their usage. *Eur J Immunol* **24**, (4) 827-836.

113. Doorbar J. & Winter G. (1994). Isolation of a peptide antagonist to the thrombin receptor using phage display. *J Mol Biol* **244**, (4) 361-369.

114. Figini M., Marks J.D., Winter G. & Griffiths A.D. (1994). *In vitro* assembly of repertoires of antibody chains on the surface of phage by renaturation. *J Mol Biol* **239**, (1) 68-78.

115. Griffiths A.D., Williams S.C., Hartley O., Tomlinson I.M., Waterhouse P., Crosby W.L., Kontermann R.E., Jones P.T., Low N.M., Allison T.J., Prospero T.D., Hoogenboom H.R., Nissim A., Cox J.P., Harrison J.L., Zaccolo M., Gherardi E. & Winter G. (1994). Isolation of high affinity antibodies directly from large synthetic repertoires. *EMBO J* **13**, (14) 3245-3260.

116. Hawkins R.E., Zhu D., Ovecka M., Winter G., Hamblin T.J., Long A. & Stevenson F.K. (1994). Idiotypic vaccination against human B-cell lymphoma. Rescue of variable region gene sequences from biopsy material for assembly as single-chain Fv personal vaccines. *Blood* **83**, (11) 3279-3288.

117. Jespers L.S., Roberts A., Mahler S.M., Winter G. & Hoogenboom H.R. (1994). Guiding the selection of human antibodies from phage display repertoires to a single epitope of an antigen. *Biotechnology (NY)* **12**, (9) 899-903.

118. Nissim A., Hoogenboom H.R., Tomlinson I.M., Flynn G., Midgley C., Lane D. & Winter G. (1994). Antibody fragments from a 'single pot' phage display library as immunochemical reagents. *EMBO J* **13**, (3) 692-698.

119. Perisic O., Webb P.A., Holliger P., Winter G. & Williams R.L. (1994). Crystal structure of a diabody, a bivalent antibody fragment. *Structure* **2**, (12) 1217-1226.

120. Soumillion P., Jespers L.S., Bouchet M., Marchand-Brynaert J., Winter G. & Fastrez J. (1994). Selection of beta-lactamase on filamentous bacteriophage by catalytic activity. *J Mol Biol* **237**, (4) 415-422.

121. Tomlinson I.M., Cook G.P., Walter G., Carter N.P., Elaswarapu R., Smith S., Walter G., Buluwela L., Rabbitts T.H. & Winter G. (1994). Human immunoglobulin $V_H$ and D segments on chromosomes 15q11.2 and 16p11.2. *Hum Mol Genet* **3**, (6) 853-860.

122. Winter G., Griffiths A.D., Hawkins R.E. & Hoogenboom H.R. (1994). Making antibodies by phage display technology. *Annu Rev Immunol* **12**, 433-455.

123. Chester K.A., Begent R.H., Robson L., Keep P., Pedley R.B., Boden J.A., Boxer G., Green A., Michael P., Winter G., Cochet O. & Hawkins R.E. (1995). Filamentous phage antibodies: the power of selection for clinical use. *In: New Antibody Technology & the Emergence of Useful Cancer Therapy,* 15-17.

124. Frippiat J-P., Williams S.C., Tomlinson I.M., Cook G.P., Cherif D., Le Paslier D., Collins J.E., Dunham I., Winter G. & Lefranc M-P. (1995). Organization of the human immunoglobulin lambda light-chain locus on chromosome 22q11.2. *Hum Mol Genet* **4**, (6) 983-991.

125. Hodits R.A., Nimpf J., Pfistermueller D.M., Hiesberger T., Schneider W.J., Vaughan T.J., Johnson K.S., Haumer M., Kuechler E., Winter G. & Blass D. (1995). An antibody fragment from a phage display library competes for ligand binding to the low density lipoprotein receptor family and inhibits rhinovirus infection. *J Biol Chem* **270**, (41) 24078-24085.

126. Neri D., de Lalla C., Petrul H., Neri P. & Winter G. (1995). Calmodulin as a versatile tag for antibody fragments. *Biotechnology (NY)* **13**, (4) 373-377.

127. Neri D., Momo M., Prospero T.D. & Winter G. (1995). High-affinity antigen binding by chelating recombinant antibodies (CRAbs). *J Mol Biol* **246**, (3) 367-373.

128. Nissim A., Griffiths A.D., Tomlinson I.M., Williams S.C., Walter G., Cook G.P., Hartley O., Waterhouse P., Jones P.T., Low N.M., Cox J.P., Hoogenboom H.R., Harrison J.L., Prospero T.D. & Winter G. (1995). Mimicking the immune system using phage antibody technology. *Tumour Targeting* **1**, 13-16.

129. Tomlinson I.M., Cook G.P., Walter G., Carter N.P., Riethman H., Buluwela L., Rabbitts T.H. & Winter G. (1995). A complete map of the human immunoglobulin VH locus. *Ann NY Acad Sci* **764**, 43-46. Review.

130. Walter G., Tomlinson I.M., Dear P.H., Sonnhammer E.L., Cook G.P. & Winter G. (1995). Comparison of the human germline and rearranged VH repertoire reveals complementarity between germline variability and somatic mutation. *Ann NY Acad Sci* **764**, 180-182.

131. Bruggeman Y.E., Boogert A., van Hoek A., Jones P.T., Winter G., Schots A. & Hilhorst R. (1996). Phage antibodies against an unstable hapten: oxygen sensitive reduced flavin. *FEBS Lett* **388**, (2-3) 242-244.

132. Carnemolla B., Neri D., Castellani P., Leprini A., Neri G., Pini A., Winter G. & Zardi L. (1996). Phage antibodies with pan-species recognition of the oncofoetal angiogenesis marker fibronectin ED-B domain. *Int J Cancer* **68**, (3) 397-405.

133. Fisch I., Kontermann R.E., Finnern R., Hartley O., Soler-Gonzalez A.S., Griffiths A.D. & Winter G. (1996). A strategy of exon shuffling for making large peptide repertoires displayed on filamentous bacteriophage. *Proc Natl Acad Sci USA* **93**, (15) 7761-7766.

134. Harrison J.L., Williams S.C., Winter G. & Nissim A. (1996). Screening of phage antibody libraries. *In: Methods Enzymol, "Combinatorial Chemistry". Ed J.N. Abelson.* **267**, 83-109.

135. Holliger P., Brissinck J., Williams R.L., Thielemans K. & Winter G. (1996). Specific killing of lymphoma cells by cytotoxic T-cells mediated by a bispecific diabody. *Protein Eng* **9**, (3) 299-305.

136. Low N.M., Holliger P. & Winter G. (1996). Mimicking somatic hypermutation: affinity maturation of antibodies displayed on bacteriophage using a bacterial mutator strain. *J Mol Biol* **260**, (3) 359-368.

137. Neri D., Petrul H., Winter G., Light Y., Marais R., Britton K.E. & Creighton A.M. (1996). Radioactive labeling of recombinant antibody fragments by phosphorylation using human casein kinase II and [gamma-$^{32}$P]-ATP. *Nat Biotechnol* **14**, (4) 485-490.

138. Neri D., Prospero T.D., Petrul H., Winter G., Browne M. & Vanderpant L. (1996). Multipurpose high sensitivity luminescence analyzer (LUANA): use in gel electrophoresis. *Biotechniques* **20**, (4) 708-713.

139. Tomlinson I.M., Walter G., Jones P.T., Dear P.H., Sonnhammer E.L. & Winter G. (1996). The imprint of somatic hypermutation on the repertoire of human germline V genes. *J Mol Biol* **256**, (5) 813-817.

140. Ueda H., Tsumoto K., Kubota K., Suzuki E., Nagamune T., Nishimura H., Schueler P.A., Winter G., Kumagai I. & Mahoney W.C. (1996). Open sandwich ELISA: a novel immunoassay based on the interchain interaction of antibody variable region. *Nat Biotechnol* **14**, (13) 1714-1718.

141. Williams S.C., Frippiat J-P., Tomlinson I.M., Ignatovich O., Lefranc M.P. & Winter G. (1996). Sequence and evolution of the human germline V lambda repertoire. *J Mol Biol* **264**, (2) 220-232.

142. Corbett S.J., Tomlinson I.M., Sonnhammer E.L., Buck D. & Winter G. (1997). Sequence of the human immunoglobulin diversity (D) segment locus: a systematic analysis provides no evidence for the use of DIR segments, inverted D segments, "minor" D segments or D-D recombination. *J Mol Biol* **270**, (4) 587-597.

143. Doorbar J., Foo C., Coleman N., Medcalf L., Hartley O., Prospero T.D., Napthine S., Sterling J., Winter G. & Griffin H. (1997). Characterization of events during the late stages of HPV16 infection in vivo using high-affinity synthetic Fabs to E4. *Virology* **238**, (1) 40-52.

144. FitzGerald K., Holliger P. & Winter G. (1997). Improved tumour targeting by disulphide stablized diabodies expressed in *Pichia pastoris*. *Protein Eng* **10**, (10) 1221-1225.

145. Frippiat J-P., Dard P., Marsh S., Winter G. & Lefranc M-P. (1997). Immunoglobulin lambda light chain orphons on human chromosome 8q11.2. *Eur J Immunol* **27**, (5) 1260-1265.

146. Hawkins R.E., Russell S.J., Marcus R., Ashworth L.J., Brissnik J., Zhang J., Winter G., Bleehen N.M., Shaw M.M., Williamson L., Ouwehand W., Stevenson F., Hamblin T., Oscier D., Zhu D., King C., Kumar S., Thompsett A. & Stevenson G.T. (1997). A pilot study of idiotype vaccination for follicular B-cell lymphoma using a genetic approach. CRC NO: 92/33. Protocol NO: PH1/027. *Hum Gene Ther* **8**, (10) 1287-1299.

147. Holliger P. & Winter G. (1997). Diabodies: small bispecific antibody fragments. *Cancer Immunol Immunother* **45**, (3-4) 128-130.

148. Holliger P., Wing M., Pound J.D., Bohlen H. & Winter G. (1997). Retargeting serum immunoglobulin with bispecific diabodies. *Nat Biotechnol* **15**, (7) 632-636.

149. Ignatovich O., Tomlinson I.M., Jones P.T. & Winter G. (1997). The creation of diversity in the human immunoglobulin V lambda repertoire. *J Mol Biol* **268**, (1) 69-77.

150. Kontermann R.E., Wing M.G. & Winter G. (1997). Complement recruitment using bispecific diabodies. *Nat Biotechnol* **15**, (7) 629-631.

151. Kontermann R.E., Martineau P., Cummings C.E., Karpas A., Allen D., Derbyshire E. & Winter G. (1997). Enzyme immunoassays using bispecific diabodies. *Immunotechnology* **3**, (2) 137-144.

152. Neri D., Carnemolla B., Nissim A., Leprini A., Querze G., Balza E., Pini A., Tarli L., Halin C., Neri P., Zardi L. & Winter G. (1997). Targeting by affinity-matured recombinant antibody fragments of an angiogenesis associated fibronectin isoform. *Nat Biotechnol* **15**, (12) 1271-1275.

153. Zaccolo M., Griffiths A.D., Prospero T.D., Winter G. & Gherardi E. (1997). Dimerization of Fab fragments enables ready screening of phage antibodies that affect hepatocyte growth factor/scatter factor activity on target cells. *Eur J Immunol* **27**, (3) 618-623.

154. Figini M., Obici L., Mezzanzanica D., Griffiths A.D., Colnaghi M.I., Winter G. & Canevari S. (1998). Panning phage antibody libraries on cells: isolation of human Fab fragments against ovarian carcinoma using guided selection. *Cancer Res* **58**, (5) 991-996.

155. Hartmann G., Prospero T.D., Brinkmann V., Ozcelik C., Winter G., Hepple J., Batley S., Bladt F., Sachs M., Birchmeier C., Birchmeier W., Gherardi E. & Ozcelik O. (1998). Engineered mutants of HGF/SF with reduced binding to heparan sulphate proteoglycans, decreased clearance and enhanced activity *in vivo*. *Curr Biol* **8**, (3) 125-134.

156. Krebs B., Griffin H., Winter G. & Rose-John S. (1998). Recombinant human single chain Fv antibodies recognizing human interleukin-6: specific targeting of cytokine-secreting cells. *J Biol Chem* **273**, (5) 2858-2865.

157. Kristensen P. & Winter G. (1998). Proteolytic selection for protein folding using filamentous bacteriophages. *Fold Des* **3**, (5) 321-328.

158. Martineau P., Jones P.T. & Winter G. (1998). Expression of an antibody fragment at high levels in the bacterial cytoplasm. *J Mol Biol* **280**, (1) 117-127.

159. Smith G.P., Patel S.U., Windass J.D., Thornton J.M., Winter G. & Griffiths A.D. (1998). Small binding proteins selected from a combinatorial repertoire of knottins displayed on phage. *J Mol Biol* **277**, (2) 317-332.

160. Winter G. (1998). Making antibody and peptide ligands by repertoire selection technologies. *J Mol Recognit* **11**, (1-6) 126-127.

161. Winter G. (1998). Synthetic human antibodies and a strategy for protein engineering. *FEBS Lett* **430**, (1-2) 92-94.

162. Carnemolla B., Castellani P., Ponassi M., Borsi L., Urbini S., Nicolo G., Dorcaratto A., Viale G., Winter G., Neri D. & Zardi L. (1999). Identification of a glioblastoma-associated tenascin-C isoform by a high affinity recombinant antibody. *Am J Pathol* **154**, (5) 1345-1352.

163. Chatellier J., Hartley O., Griffiths A.D., Fersht A.R., Winter G. & Riechmann L. (1999). Interdomain interactions within the gene 3 protein of filamentous phage. *FEBS Lett* **463**, (3) 371-374.

164. de Wildt R.M., van Venrooij W.J., Winter G., Hoet R.M. & Tomlinson I.M. (1999). Somatic insertions and deletions shape the human antibody repertoire. *J Mol Biol* **294**, (3) 701-710.

165. de Wildt R.M., Hoet R.M., van Venrooij W.J., Tomlinson I.M. & Winter G. (1999). Analysis of heavy and light chain pairings indicates that receptor editing shapes the human antibody repertoire. *J Mol Biol* **285**, (3) 895-901.

166. Demartis S., Huber A., Viti F., Lozzi L., Giovannoni L., Neri P., Winter G. & Neri D. (1999). A strategy for the isolation of catalytic activities from repertoires of enzymes displayed on phage. *J Mol Biol* **286**, (2) 617-633.

167. Holliger P., Manzke O., Span M., Hawkins R., Fleischmann B., Qinghua L., Wolf J., Diehl V., Cochet O., Winter G. & Bohlen H. (1999). Carcinoembryonic antigen (CEA)-specific T-cell activation in colon carcinoma induced by anti-CD3 x anti-CEA bispecific diabodies and B7 x anti-CEA bispecific fusion proteins. *Cancer Res* **59**, (12) 2909-2916.

168. Ignatovich O., Tomlinson I.M., Popov A.V., Bruggemann M. & Winter G. (1999). Dominance of intrinsic genetic factors in shaping the human immunoglobulin V lambda repertoire. *J Mol Biol* **294**, (2) 457-465.

169. Jestin J-L., Kristensen P. & Winter G. (1999). A method for the selection of catalytic activity using phage display and proximity coupling. *Angew Chem Int Ed* **38**, 1124-1127.

170. Kirkham P.M., Neri D. & Winter G. (1999). Towards the design of an antibody that recognises a given protein epitope. *J Mol Biol* **285**, (3) 909-915.

171. de Wildt R.M., Tomlinson I.M., van Venrooij W.J., Winter G. & Hoet R.M. (2000). Comparable heavy and light chain pairings in normal and systemic lupus erythematosus IgG(+) B cells. *Eur J Immunol* **30**, (1) 254-261.

172. Riechmann L. & Winter G. (2000). Novel folded protein domains generated by combinatorial shuffling of polypeptide segments. *Proc Natl Acad Sci USA* **97**, (18) 10068-10073.

173. Ueda H., Kawahara M., Aburatani T., Tsumoto K., Todokoro K., Suzuki E., Nishimura H., Schueler P.A., Winter G., Mahoney W.C., Kumagai I. & Nagamune T. (2000). Cell-growth control by monomeric antigen: the cell surface expression of lysozyme-specific Ig V-domains fused to truncated Epo receptor. *J Immunol Methods* **241**, (1-2) 159-170.

174. Jestin J-L., Volioti G. & Winter G. (2001). Improving the display of proteins on filamentous phage. *Res Microbiol* **152**, (2) 187-191.

175. Vaisbourd M., Ignatovich O., Dremucheva A., Karpas A. & Winter G. (2001). Molecular characterization of human monoclonal antibodies derived from fusions of tonsil lymphocytes with a human myeloma cell line. *Hybrid Hybridomics* **20**, (5-6) 287-297.

176. Wang P.L., Sait F. & Winter G. (2001). The 'wildtype' conformation of p53: epitope mapping using hybrid proteins. *Oncogene* **20**, (18) 2318-2324.

177. Goletz S., Christensen P.A., Kristensen P., Blohm D., Tomlinson I.M., Winter G. & Karsten U. (2002). Selection of large diversities of anti-idiotypic antibody fragments by phage display. *J Mol Biol* **315**, (5) 1087-1097.

178. Sanz L., Kristensen P., Blanco B., Facteau S., Russell S.J., Winter G. & Alvarez-Vallina L. (2002). Single-chain antibody-based gene therapy: inhibition or tumor growth by *in situ* production of phage-derived human antibody fragments blocking functionally active sites of cell-associated matrices. *Gene Ther* 9, (15) 1049-1053.

179. Christ D. & Winter G. (2003). Identification of functional similarities between proteins using directed evolution. *Proc. Natl. Acad. Sci.* 100, (23) 13202-13206.

180. Fischer N., Riechmann L. & Winter G. (2004). A native-like artificial protein from antisense DNA. *Protein Eng Des Sel.* 1:13-20.

181. Jespers L., Schon, O, James, L.C., Veprintsev D., Winter G (2004). Crystal structure of HEL4, a soluble, refoldable human VH single domain with germ-line scaffold. *J Mol Biol* 337, 893-903.

182. Jespers L., Famm K., Schon, O. & Winter G. (2004). Aggregation resistant proteins selected by thermal cycling. *Nature Biotech.,* 22, 1161-1165.

183. Abelian A., Burling K., Easterbrook P. & Winter G (2004). Hyperimmuno-globulinemia and rate of HIV type 1 infection progression. *AIDS Res Hum Retroviruses.* (2004) 1:127-8.

184. Ueda H., Kristensen P. & Winter G. (2004). Stabilization of antibody VH-domains by proteolytic selection. *J Mol Catalysis B: Enzymatic,* **28**, 173-179.

185. de Bono S., Riechmann L., Girard E., Williams R.L. & Winter G. (2005). A segment of cold shock protein directs the folding of a combinatorial protein. *PNAS*, **102**, 1396-1401.

186. Jespers L., Bonnert T.P. & Winter G. (2005). Selection of optical biosensors from chemisynthetic antibody libraries. *Protein Eng., Design & Selection* **17**, 709-713.

187. Wang P.L., Lo B.K.C. & Winter G. (2005). Generating molecular diversity by homologous recombination in *Escherichia coli. Protein Eng., Design & Selection* **18**, 397-404.

188. Griffin H., Elston R., Jackson D., Ansell K., Coleman M., Winter G. & Doorbar J. (2006). Inhibition of papillomavirus protein function in cervical cancer cells by intrabody targeting, *J Mol Biol*, **355**, 360-378.

189. Christ, D. & Winter, G. (2006). Identification of protein domains by shotgun proteolysis. *J Mol Biol.* **358,** 364-371.

190. Paus, D. & Winter, G. (2006). Mapping epitopes and antigenicity by site-directed masking. *PNAS*, **103**, 9172-9177.

191. Famm, K. & Winter, G. (2006). Engineering aggregation-resistant proteins by directed evolution. *Protein Eng., Design & Selection*, **19**, 479-481.

192. Christ, D., Famm, K. & Winter, G. (2006). Tapping diversity lost in transformations – *in vitro* amplification of ligation reactions. *Nucleic Acids Res*, 34: Art. No. e108 Sep 2006.

193. Riechmann, L. & Winter, G (2006). Early protein evolution: building domains from ligand-binding polypeptide segments. *J Mol. Biol.* **363**, 460-468.

194. James, L., Jones, P.C., McCoy, A., Tennent, G., Pepys, M.B., Famm, K. & Winter, G. (2007). β-edge interactions in a pentadecameric human antibody $V_K$ domain. *J. Mol. Biol.* **367**: 603-608.

195. Christ, D., Famm, K. & Winter, G. (2007). Repertoires of aggregation-resistant human antibody domains. *Protein Eng., Design and Selection*, **20**: 413-416.

196. Famm, K., Hansen, L., Christ, D. & Winter, G. (2008). Thermodynamically stable aggregation-resistant antibody domains through directed evolution. *J. Mol. Biol.* **376**: 926-931

197. Heinis, C., Rutherford, T., Freund, S. & Winter, G. (2009). Phage encoded combinatorial chemical libraries based on bicyclic peptides. *Nature Chemical Biology*, **5** 502-507.

198. Angelini, A., Cendron, L., Chen, S., Touati, J., Winter, G., Zanotti, G. & Heinis, C. (2012). Bicyclic peptide inhibitor reveals large contact interface with a protease target. ACS Chem. Biol. 7, 817-821

199. Baeriswyl, V., Rapley, H., Pollaro, L., Stace, C., Teufel, D., Walker, E., Chen, S., Winter, G. & Heinis, C. (2012). Bicyclic peptides with optimized ring size inhibit human plasma kallikrein and its orthologues while sparing parologous proteases. ChemMedChem 7, 1173-1176.

# Exhibit C

## Expert Report of Sir Gregory Winter, CBE, FRS

**EXPERT REPORT OF SIR GREGORY WINTER, CBE, FRS**
**REGARDING INVALIDITY OF U.S. PATENT NOS. 6,331,415 AND 7,923,221**
**(13-cv-07248)**
**Exhibit C Materials Considered**

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

2. U.S. Patent No. 7,923,221

3. U.S. Patent No. 4,816,567

4. Skerra, A. & Plückthun, A., *Assembly of a functional immunoglobulin Fv fragment in Escherichia coli*, 240 SCIENCE 1038 (1988)

5. Better, M, *et al.*, *Escherichia coli secretion of an active chimeric antibody fragment*, 240 SCIENCE 1041 (1988)

6. Horwitz, A.H., *et al.*, *Secretion of functional antibody and Fab fragment from yeast cells*, 85 PROC. NAT'L. ACAD. SCI. USA 8678 (1988)

7. Hiatt, A., *et al.*, *Production of antibodies in transgenic plants*, 342 NATURE 76 (1989)

8. Claim Construction Order dated April 18, 2014

9. Claim Construction Order, *Centocor Inc., v. Genentech, Inc., et al.*, 08-cv-03573 (C.D. Cal., 2009), D.I. 93

10. Winter, G. & Fields, S., *Nucleotide sequence of human influenza A/PR/8/34 segment 2*, 10 NUCLEIC ACIDS RES 2135 (1982)

11. Fields, S. & Winter, G., *Nucleotide sequences of influenza virus segments 1 and 3 reveal mosaic structure of a small viral RNA segment*, 28 CELL 303 (1982)

12. Winter, G., *et al.*, *Redesigning enzyme structure by site-directed mutagenesis: tyrosyl tRNA synthetase and ATP binding*, 299 NATURE 756 (1982)

13. Wilkinson, *et al.*, *Site-directed mutagenesis as a probe of enzyme structure and catalysis: tyrosyl tRNA synthetase cysteine-35 to glycine-35 mutation*, 22 BIOCHEMISTRY 3581 (1983)

14. Waye, M.M., *et al.*, *Deletion mutagenesis using an 'M13 splint': the N-terminal structural domain of tyrosyl-tRNA synthetase (B. stearothermophilus) catalyses the formation of tyrosyl adenylate*, 2 EMBO J 1827 (1983)

15. Barker, D.G. & Winter, G., *Conserved cysteine and histidine residues in the structure of the tyrosyl and methionyl-tRNA synthetases*, 145 FEBS LETT 191 (1982)

16. Carter, P.J., *et al.*, *The use of double mutants to detect structural changes in the active site of the tyrosyl-tRNA synthetase (Bacillus stearothermophilus)*, 38 CELL 835 (1984)

17. Duncan, A.R. & Winter, G., *The binding site for C1q on IgG*, 332 NATURE 738 (1988)

18. Duncan, A.R., *et al.*, *Localization of the binding site for the human high-affinity Fc receptor on IgG*, 332 NATURE 563 (1988))

19. Amster, O., *et al.*, *Synthesis of part of a mouse immunoglobulin light chain in a bacterial clone*, 8 NUCLEIC ACIDS RESEARCH 2055 (1980)

20. Rice, D. & Baltimore, D., *Regulated expression of an immunoglobulin κ gene introduced into a mouse lymphoid cell line*, 79 PROC. NAT'L ACAD. SCI. USA 7862 (1982)

21. Falkner, F.G. & Zachau, H.G., *Expression of mouse immunoglobulin genes in monkey cells*, 298 NATURE 286 (1982)

22. Ochi, A., *et al.*, *Transfer of a cloned immunoglobulin light-chain gene to mutant hybridoma cells restores specific antibody production*, 302 NATURE 340 (1983)

23. Oi, V., *et al.*, *Immunoglobulin gene expression in transformed lymphoid cells*, 80 PROC. NAT'L ACAD. SCI. USA 825 (1983)

24. Wabl, M. & Steinberg, C., *A theory of allelic and isotypic exclusion for immunoglobulin genes*, 79 PROC. NAT'L. ACAD. SCI. USA 6976 (1982)

25. Haas, I.G. & Wabl, M., *Immunoglobulin heavy chain binding protein*, 306 NATURE 387 (1983)

26. Gillies, S.D. *et al.*, *A tissue-specific transcription enhancer element is located in the major intron of a rearranged immunoglobulin heavy chain gene*, 33 CELL 717 (1983)

27. Neuberger, M.S., *Expression and regulation of immunoglobulin heavy chain gene transfected into lymphoid cells*, 2 EMBO J. 1373 (1983)

28. Banerji, J., *et al.*, *A lymphocyte-specific cellular enhancer is located downstream of the joining region in immunoglobulin heavy chain genes*, 33 CELL 729 (1983)

29. Ochi, A., *et al.*, *Functional immunoglobulin M production after transfection of cloned immunoglobulin heavy and light chain genes into lymphoid cells*, 80 PROC. NAT'L ACAD. SCI. USA 6351 (1983)

30. Weidle, U., *et al.*, *Reconstitution of functionally active antibody directed against creatine kinase from separately expressed heavy and light chains in non-lymphoid cells*, 51 GENE 21 (1987)

31. Boss, M.A., *et al.*, *Assembly of functional antibodies from immunoglobulin heavy and light chains synthesized in E. coli*, 12 NUCLEIC ACIDS RESEARCH 3791 (1984)

32. Cabilly, S., *et al.*, *Generation of antibody activity from immunoglobulin polypeptide chains produced in Escherichia coli*, 81 PROC. NAT'L ACAD. SCI. USA 3273 (1984)

33. Neuberger, M.S., *et al.*, *Recombinant antibodies possessing novel effector functions*, 312 NATURE 604 (1984)

34. Neuberger, M.S., *et al.*, *A hapten-specific chimeric IgE antibody with human physiological effector function*, 314 NATURE 268 (1985)

35. Jones, P.T., *et al.*, *Replacing the complementarity-determining regions in a human antibody with those from a mouse*, 321 Nature 522 (1986)

36. Declaration of Douglas A. Rice dated Oct. 26, 2006

37. Haas, I.G. & Meo, T., *cDNA cloning of the immunoglobulin heavy chain binding protein*, 85 PROC. NAT'L. ACAD. SCI. USA 2250 (1988)

38. Köhler, G., *Immunoglobulin chain loss in hybridoma lines*, 77 PROC. NAT'L ACAD. SCI. USA 2197 (1980)

39. Wilde, C. D. & Milstein, C., *Analysis of immunoglobulin chain secretion using hybrid myelomas*,10 EUR. J. IMMUNOL. 462 (1980)

40. Declaration of Alan Colman dated Oct. 27, 2006

41. Declaration of Timothy John Roy Harris dated Oct. 26, 2006

42. Foster, J., *et al.*, *An immunoglobulin promoter displays cell-type specificity independently of the enhancer*, 315 NATURE 423 (1985)

43. Picard, D. & Schaffner, W., *Cell-type preference of immunoglobulin kappa and lambda gene promoters*, 4 EMBO J. 2831 (1985)

44. Declaration of Steven L. McKnight dated May 18, 2007

45. Morrison, S, *et al.*, *Chimeric human antibody molecules: Mouse antigen-binding domains with human constant region domains*, 81 PROC. NAT'L. ACAD. SCI. USA 6851 (1984)

46. Olsson, L., *et al.*, *Antibody producing human-human hybridomas, 1. Technical aspects*, 61 J. IMMUNOL. METH. 17 (1983)

47. Croce, C.M. *et al.*, *Production of human hybridomas secreting antibodies to measles virus*, 288 NATURE 488 (1980)

48. Croce, C.M., *Loss of mouse chromosomes in somatic cell hybrids between HT-1080 human fibrosarcoma cells and mouse peritoneal macrophages*, 72 PROC. NAT'L ACAD. SCI. USA 3248 (1976)

49. Teng, N.N.H., *et al.*, *Construction and testing of mouse-human heteromyelomas for human monoclonal antibody production*, 80 PROC. NAT'L. ACAD. SCI. USA 7308 (1983)

50. Saiki, R.K. *et al.*, *Enzymatic amplification of beta-globin genomic sequences and restriction site analysis for diagnosis of sickle cell anemia*, 230 SCIENCE 1350 (1985)

51. Orlandi, R., *et al.*, *Cloning immunoglobulin variable domains for expression by the polymerase chain reaction*, 86 Proc. Nat'l Acad. Sci. USA 3833 (1989)

52. Marks, J.D., *et al.*, *Oligonucleotide primers for polymerase chain reaction amplification of human immunoglobulin variable genes and design of family-specific oligonucleotide probes*, 21 EUR J IMMUNOL 985 (1991)

53. Ward, E.S., *et al.*, *Binding activities of a repertoire of single immunoglobulin variable domains secreted from Escherichia coli*, 341 NATURE 544 (1989)

54. Huse, W.D., *et al.*, *Generation of a large combinatorial library of the immunoglobulin repertoire in phage lambda*, 246 SCIENCE 1275 (1989)

55. Clackson, T., *et al.*, *Making antibody fragments using phage display libraries*, 352 NATURE 624 (1991)

56. Marks, J.D., *et al.*, *By-passing immunization. human antibodies from V-gene libraries displayed on phage*, 222 J MOL BIOL 581 (1991)

57. Smith, G.P., *Filamentous fusion phage: novel expression vectors that display cloned antigens on the virion surface*, 228 SCIENCE 1315 (1985)

58. McCafferty, J. *et al.*, *Phage antibodies: filamentous phage displaying antibody variable domains*, 348 NATURE 552 (1990)

59. Bird, R. *et al.*, *Single-chain antigen-binding proteins*, 242 SCIENCE 423 (1988)

60. Jespers, L.S., *et al.*, *Guiding the selection of human antibodies from phage display repertoires to a single epitope of an antigen*, 12 NATURE BIOTECHNOLOGY 899 (1994)

61. Green, L.L., *et al.*, *Antigen-specific human monoclonal antibodies from mice engineered with human Ig heavy and light chain YACs*, 7 NATURE GENETICS 13 (1994)

62. Lonberg, N., *et al.*, *Antigen-specific human antibodies from mice comprising four distinct genetic modifications*, 368 NATURE 856 (1994)

63. Hoogenboom, H.R., *Selecting and screening recombinant antibody libraries*, 23 NATURE BIOTECHNOL. 1105 (2005)

64. Lonberg, N., *Human antibodies from transgenic animals*, 23 NATURE BIOTECHNOL. 1117 (2005)