Patent
Attorney's Docket No. 22338-10230

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Control Nos.:	**90/007,542** **90/007,859**		Group Art Unit:	3991
Confirmation Nos.:	7585 ('542) 6447 ('859)		Examiner:	B.M. Celsa
Filed:	13 May 2005 23 December 2005	('542) ('859)		
Patent Owner:	Genentech, Inc. and City of Hope			

For: Merged Reexaminations of U.S. Patent No. 6,331,415 (Cabilly *et al.*)

DECLARATION OF DR. TIMOTHY JOHN ROY HARRIS UNDER 37 C.F.R. § 1.132

I, Timothy Harris, do hereby declare and state

1. I am a citizen of the United Kingdom, and reside in San Diego, California.

2. I am the same Timothy John Roy Harris who provided a Declaration in Reexamination No. 90/007,542 on November 25, 2005 ("First Declaration").

3. As I indicated in my First Declaration, I have been retained by Genentech and City of Hope to provide my views on certain issues that have been raised in the reexamination of U.S. Patent No. 6,331,415 ("the '415 patent"). I also note that I have been, and am being, compensated for my time at a rate of $500 per hour.

4. My credentials and experience are essentially as I indicated in paragraphs 1 to 3 of my First Declaration. I also note that the company of which I was Chief Executive Officer, Novasite Pharmaceuticals, recently ceased operations.

5. For the reasons set forth in my First Declaration, I believe, based on my educational training and work experience, I am able to report views that would be representative of a person of ordinary skill in the art in early April of 1983 (*i.e.*, just prior to April 8, 1983). I believe a person of ordinary skill in the field of the '415 patent claims would have a doctorate in molecular biology or a similar scientific discipline, along with about two years of post-doctoral experience.

6. In addition to all of the patents and printed publications I previously reviewed in preparing my First Declaration, I reviewed the following publications:

   - Deacon et al., Biochemical Society Transactions, 4:818-20 (1976) ("Deacon");

- Valle et al., Nature, 291:338-340 (1981) ("Valle 1981");
- Valle et al., Nature, 30:71-74 (1982) ("Valle 1982");
- Dallas, WO 82/03088 ("Dallas");
- Ochi et al., Nature, 302:340-342 (1983) ("Ochi"); and
- Oi et al., Proc. Nat'l. Acad. Sci., 80:825-829 (1983) ("Oi").

7. I also reviewed the following documents (in addition to the materials I identified in paragraph 6 of my First Declaration):

- A PTO Office Action in Reexamination Nos. 90/007,542 and 90/007,859, dated August 16, 2006 ("Second Office Action");
- A PTO Order Granting *ex parte* reexamination of the '415 patent, dated January 23, 2006 ("Second Reexamination Order"); and
- A Request for Ex Parte Reexamination, dated December 23, 2005 ("Second Request for Reexamination"), including attachments to that Request.

8. In addition, I reviewed relevant literature from that general time period (*i.e.*, before April 8, 1983), as I had indicated in paragraph 7 of my First Declaration.

9. In my First Declaration, I explained why certain scientific findings or observations of the Office were inaccurate. I also explained why certain comments in the Office Action were inconsistent with how a person of ordinary skill in the art would have read certain references. In forming these opinions, I evaluated not only what each reference individually taught, but whether and how that reference would be considered in combination with U.S. Patent No. 4,816,567 ("the '567 patent") claims and the other references cited by the Office.

Observations on the New Rejections

10. Beginning on page 22 of the Second Office Action, there is a discussion of the '567 patent claims and various references. In this section, the Office identifies two specific reasons why claims of the '415 patent are believed to be obvious in view of prior art.

- At page 22, the Office states "(i) One of ordinary skill in the art would have been motivated to express, in a single host, light and heavy immunoglobulin chains (using one or two vectors) when viewing the reference Cabilly 1 patented invention in light of the prior art." The Office cites the Axel, Rice, Kaplan and Dallas references to support this point.
- At page 25, the Office states "(ii) The prior art provides further motivation to make active antibody with a reasonable expectation of success." The Office cites

the Deacon, Valle 1981 and Ochi papers to support this point. I note that the Office has also found the information in another paper by Valle (Valle 1982) to be cumulative to what is taught by the Deacon paper, and information in the Oi paper to be cumulative to what is taught by the Ochi paper.

11. I do not believe the Second Office Action accurately portrays what these references actually teach. I also do not believe these references would have been considered, individually or collectively, in the way the Second Office Action suggests they would have by a person of ordinary skill in the art in early April of 1983.

12. Certainly, by early April of 1983, there was interest within the industry of using recombinant DNA technology to produce proteins with known commercial value, including functional immunoglobulin molecules. However, the state of the art at that time and the experiences of those working in the recombinant DNA field, coupled with the information in the references cited by the Office, would not have led people to be particularly optimistic about achieving this goal, and did not provide any clear direction as to how to do so.

Overview of the Relevant Technological Field in April of 1983

13. In early April of 1983, the field of genetic engineering was still developing. It was nothing like the mature field it is today, over two decades later. A relatively small number of proteins had been made by recombinant DNA technology. Almost all of those were relatively simple monomeric (*i.e.*, one polypeptide chain) proteins.

14. In a review article I wrote that was published in April of 1983, I provided a list of eukaryotic proteins that had been produced in E. coli using recombinant methods. *See* Harris, Genetic Engineering, 4:127-85 (1983), attached as Exhibit B to my previous declaration, at pages 164 to 169. All but one of these examples concerned production of relatively simple monomeric proteins. The exception was insulin, which I reported had been produced by individually expressing each of the two chains of the insulin protein in different E. coli cell lines, or by expressing "preproinsulin" (a single polypeptide) which was enzymatically processed *in vitro* to form mature insulin. *See*, pages 137 to 138.

15. My 1983 review article provides a perspective on the types of recombinant DNA projects that had been published by early April of 1983 concerning the expression of recombinant proteins in E. coli. I note that all of the examples described in the review article involved production of one polypeptide in one transformed host cell.

16. I was not aware of any published reports as of early April of 1983 documenting production of a multimeric protein by independently expressing in a single cell recombinant DNA sequences corresponding to the constituent polypeptides of the multimeric protein. I also was not aware of any published reports at that time of production of a multimeric protein of the size (~150 kD) or structural complexity of an immunoglobulin tetramer.

17. As the '415 patent explains, the immunoglobulin tetramer is a large, complex multimeric protein made up of four polypeptides: two light chains and two heavy chains. The

structure of the tetrameric immunoglobulin molecule is generally maintained by a series of disulfide bonds between pairs of cysteine residues and non-covalent interactions between the four polypeptides. For example, in an IgG (depicted in Figure 1 of the '415 patent, reproduced below), pairs of heavy and light chains are linked through inter-chain disulfide bonds, and each pair is linked to the other pair through three disulfide bonds formed between cysteine residues within the heavy chains. In addition to these inter-chain disulfide bonds, each polypeptide subunit (*i.e.*, each heavy and each light chain) is stabilized by two or four intra-chain disulfide bonds. *See, e.g.*, '415 patent at col. 3, lines 19-38.

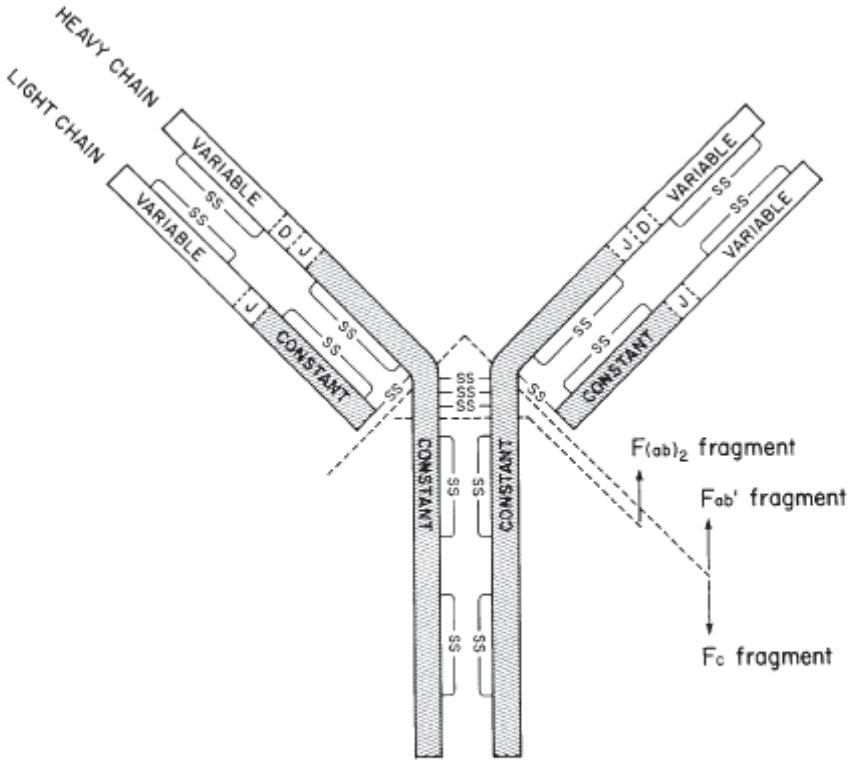

Fig. 1.

18. Based on these known structural characteristics of the tetrameric immunoglobulin molecule, I believe a person of ordinary skill in the art, in early April of 1983, would have expected that the production of an immunoglobulin tetramer using recombinant DNA techniques would have been a significantly more challenging undertaking than the types of projects described in my review article or the molecules described in Axel *et al*., U.S. Patent No. 4,399,216 ("Axel") (*i.e*., β–globin) and Rice & Baltimore, Proc. Nat'l.

Acad. Sci., 79:7862-7865 (1982) ("Rice") (*i.e.*, a recombinant immunoglobulin light chain gene).

The Reasonable Expectations of a Person of Ordinary Skill in the Art in Early April of 1983

19. I believe many of the scientific observations in the Second Office Action reflect an inaccurate description of the expectations of a person of ordinary skill in the art in early April of 1983.

20. As I previously indicated, in early April of 1983, I was not aware of any literature reporting the successful production of a multimeric protein by independently expressing in a single host cell recombinant DNA sequences encoding the constituent polypeptides of the multimeric protein. I also do not believe a person having ordinary skill at that time would have many expectations regarding a project of the scale of the '415 patent process based solely on their knowledge of general techniques for producing polypeptides in host cells transformed with recombinant DNA sequences.

21. The Office refers to the transfection experiments conducted in B-lymphoid cell lines in the Second Office Action. The Office apparently considers these types of experiments to be relevant to the '415 patent claims. In my view, these experiments provide little insight into the questions that would have influenced the expectations of a person of ordinary skill in the art contemplating production of an immunoglobulin tetramer or a fragment derived from it through expression of recombinant DNA sequences encoding the heavy and light chains in a single transformed host cell. However, to the extent that the Office does consider these experiments, they should also consider how a person of ordinary skill would have evaluated them in the context of what else was known about B-cells.

22. By early April of 1983, there was an extensive amount of literature documenting research on how B-lymphocytes produce immunoglobulins. That literature had shown that the native processes that govern immunoglobulin production in cells of the B-lymphocyte lineage were complicated and involved many variables.

23. For example, the literature had shown that the processes that govern the assembly and expression of immunoglobulin genes were unique compared to other types of genes. Immunoglobulin genes are assembled by rearrangement of gene fragments in the B-cell incidental to the cell's development into mature, immunoglobulin secreting plasma B-cells. The factors that controlled or influenced the processes of B-cell development as well as the assembly and expression of immunoglobulin genes, however, were not understood by early April of 1983.

24. For example, as Drs. Rice and Baltimore explained in the introduction of their 1982 *PNAS* paper:

> B-cell differentiation proceeds from the "pre-B" lymphocyte, which synthesizes μ immunoglobulin (Ig) heavy chains but no light chains, to the mature B lymphocyte, which synthesizes both heavy and light chains and expresses surface Ig, and finally to the Ig-secreting plasma cell (1-5). The availability of transformed cell analogs has allowed biochemical

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