Patent

Control Nos. 90/007,542; 90/007,859 Attorney 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
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Patent Owner:	Genentech, Inc. and City of Hope			

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

DECLARATION OF STEVEN LANIER MCKNIGHT UNDER 37 C.F.R. § 1.132

I, Steven Lanier McKnight, do hereby declare and state

1. I am a citizen of the United States and reside in Dallas, Texas. My c.v. is attached as Exhibit A.

2. I have been retained by Genentech and City of Hope to provide my opinion on certain issues in the patent reexamination proceedings involving U.S. Patent No. 6,331,415 ("the '415 patent"). I am being compensated for my time at a rate of $750.00 per hour.

3. I have reviewed the following documents in the course of preparing this declaration:

- U.S. Patent No. 5,840,545 ("the '545 patent");
- U.S. Application No. 06/358,414 ("the '414 application");
- The '415 patent;
- U.S. Patent No. 4,816,567 ("the '567 patent");
- U.S. Patent No. 4,399,216 ("Axel");
- Deacon & Ebringer, BIOCHEMICAL SOCIETY TRANSACTIONS 4: 818-820 (1976) ("Deacon");
- European Patent No. 0 044 722 ("Kaplan");
- Ochi *et al.*, NATURE 302: 340-342 (1983) ("Ochi");

- Oi *et al.*, PROC. NATL. ACAD. SCI. 80: 825-829 (1983) ("Oi");
- Rice & Baltimore, PROC. NATL. ACAD. SCI. 79: 7862-7865 (1982) ("Rice");
- Valle *et al.*, NATURE 300: 71-74 (1982) ("Valle 1982");
- Valle *et al.*, NATURE 291: 338-340 (1981) ("Valle 1981");
- WO 82/03088 ("Dallas");
- The Declaration of Richard Axel filed during prosecution of U.S. Application No. 08/422,187;
- Opposition Request of European Patent No. 0120694 filed in the European Patent Office on behalf of Genentech, Inc.

4. I have also reviewed documents associated with the two reexamination proceedings, including:

- The PTO Office Action dated February 16, 2007;
- The PTO Office Action dated August 16, 2006;
- A Request for Ex Parte Reexamination dated December 23, 2005, including attachments to that Request;
- The Declaration of David Baltimore submitted in connection with the December 23, 2005 Request for Ex Parte Reexamination;
- The Declarations of Dr. Rice, Dr. Colman, and Dr. Harris filed with the responses of the patent owner to the two office actions

5. I understand that patentability is evaluated using the perspective of a person of ordinary skill in the technical field of the invention just prior to the filing date of the patent (*i.e.*, early April of 1983). A person of ordinary skill in the field of the '415 patent would have had a Ph.D. in molecular biology or a comparable scientific discipline, and two to three years of practical experience, such as that gained through a post-doctoral appointment or comparable assignment. I believe I am well-qualified to express an opinion on what a person of ordinary skill in the art of the '415 patent would have believed or expected in early April of 1983, because at that time I was a person who had a level of experience in line with this definition and worked with people who met this definition.

6. I understand that the '545 patent issued from an application filed on June 5, 1995. I also understand that there were several earlier applications filed between 1982 and 1995 related to the '545 patent. I understand that the first of these applications was the '414 application filed in March of 1982, and that the contents of this application are to be the

focus of my analysis. In particular, I have been asked to determine if the '414 application describes a host cell that produces two different immunoglobulin chain polypeptides or a process where two different polypeptides are expressed in a single host cell. I understand that the requirements of the host cell and process are outlined in the claims of the '545 patent.

7. I also have been asked to determine if there is any description in the '414 application of procedures for coexpressing two different polypeptides in a single host cell. Finally, I have been asked to provide my views on the observations of the PTO contained in the Final Office Action dated February 17, 2007.

General Observations On The '414 Application

8. The '414 application describes procedures for making what it calls an rFv binding composition, or rFv. An rFv consists of two polypeptides, each with an amino acid sequence that corresponds to the variable region sequence of an immunoglobulin chain. An "L-rFv" polypeptide contains a variable region sequence from a light chain immunoglobulin, and an "H-rFv" contains a variable region sequence from a heavy chain immunoglobulin.

9. The '414 application indicates that an rFv can contain two polypeptides with the same amino acid sequence, or with different amino acid sequences. *See*, p. 3, line 37 to p. 4, line 2 ("the L- and H- designations will normally mean light and heavy respectively, but in some instances the two chains [of the rFv] may be the same and derived from either the light or heavy chain sequences.").

10. Pages 5 to 18 of the '414 application provide a general description of procedures for producing L-rFv and H-rFv polypeptides, and rFv binding compositions. The '414 application also provides an example of using these procedures on pages 19-42 ("Example 1"). These procedures can be summarized as follows:

    a. Produce a hybridoma that makes an antibody with a desired specificity. *See*, p. 5, line 32 to p. 6, line 18.

    b. Prepare a purified whole cell mRNA extract from the hybridoma, and use this to prepare a cDNA library using a reverse transcriptase. *See*, p. 6, line 19 to p. 8, line 7. This produces cDNA molecules with sequences that are complementary to each of the discrete mRNA sequences (mRNA transcripts) in the mRNA extract.

    c. Amplify the cDNA library. This is done by inserting the cDNA molecules into plasmids, transforming a bacterial host cell culture with the plasmids, and growing the transformed bacterial host cells under selective pressure (*i.e.*, in the presence of an agent that causes bacterial cells that did not incorporate a plasmid to die). This produces a collection of bacterial clones, each containing a plasmid with one of the cDNA molecules from the cDNA library in it. *See*, p. 8, line 12 to p. 9, line 1.

d. Identify colonies of transformed bacterial cells that contain plasmids with cDNA encoding either the heavy or the light chain using a nucleotide probe corresponding to the constant domain of the heavy or the light chain. Then, select these colonies and grow the colonies under selective pressure to produce a population of identical copies (clones) of the bacterium with the desired heavy or light chain cDNA sequence. *See*, p. 9, lines 1-19.

e. Extract the cDNA from the individual clone selected by colony hybridization, and use it to produce a "tailored" cDNA that encodes the variable region of either the heavy or the light chain polypeptide. *See*, p. 9, line 20 to p. 14, line 15.

f. Insert the modified cDNA into an expression vector (*i.e.*, a plasmid containing an origin of replication, a promoter, and an insertion site), and transform another bacterial host (*E. coli*) with the plasmid. *See*, p. 14, line 16 to p. 16, line 23.

g. Express either the light or heavy chain variable region polypeptide by growing a transformed bacterial host cell, and then isolate, purify, and renature the polypeptide. *See*, p. 17, line 1 to p. 18, line 14. Repeat the process with the other immunoglobulin chain.

h. Combine the individually produced chains *in vitro* to form the rFv binding composition. *See*, p. 16, lines 24-28.

11. If these procedures are followed as they are written, individual L-rFv and H-rFv polypeptides will be produced in separate cell cultures and these individually prepared polypeptides will be isolated, renatured, and combined in a test tube to form an rFv. I did not find any description of procedures in the '414 application of a "coexpression" strategy (*i.e.*, where two polypeptides with different amino acid sequences would be produced in a single transformed cell culture).

12. All of the processes described in the '414 application relate to bacterial expression systems. There are some references to the use of yeast cell cultures to amplify DNA sequences, but there are no procedures described in the '414 application for expressing proteins in yeast-based systems. There is also no description of using mammalian cell lines to produce rFv polypeptides in the '414 application.

The '414 Application Does Not Describe Or Suggest Coexpression Of L-rFv And H-rFv Polypeptides In A Single Host Cell

13. I could find no description in the '414 application of a single host cell that produces two different polypeptides, or a process where two different polypeptides are expressed in a single host cell. As such, I do not believe there is any description in the '414 application of a host cell meeting the requirements of claim 1 of the '545 patent, or a process meeting the requirements of claim 2 of the '545 patent as these claims have been interpreted by the PTO.

14. The '414 application clearly states that an rFv is to be made by producing the L-rFv and H-rFv polypeptides in separate cells and combining them in a test tube after expression and purification. For example, on page 16, lines 24-28, the '414 application plainly states:

> The resulting construct [*i.e.*, a cDNA insert encoding the L-rFv or H-rFv polypeptide in an appropriate expression vector] is then introduced into an appropriate host to provide expression of the heavy or light polypeptide members of the rFv and the polypeptides isolated. The heavy and light polypeptide members of the rFv are then combined in an appropriate medium to form the rFv. (emphasis added).

15. This clearly indicates that each of the L-rFv and H-rFv polypeptides will be produced in separate cells. The "appropriate medium" being referred to is the test tube environment where the two expressed and purified polypeptide chains are finally mixed together after they have been separately produced and isolated. An appropriate medium is not referring to a transformed bacterial host cell.

16. All of the techniques and options in the '414 application for producing L-rFv and H-rFv polypeptides are consistent with this approach. For example, page 17, lines 35-38, indicates that "[w]here the light or heavy chain is not secreted, the transformed microorganisms containing the appropriate ds cDNA for either light or heavy chains are grown in liquid culture and cleared lysates prepared." (emphasis added). This again makes clear that each of the L-rFv and H-rFv polypeptides is being produced in a separate cell culture.

17. Similarly, page 18, lines 4-7, indicates that the "eluates from each of the heavy and light chain isolations are pooled, followed by treatment to renature the polypeptides to form L-rFv and H-rFv respectively." (emphasis added). These references to multiple isolations clearly indicate that separate cell cultures are being used to produce the two different polypeptides. A single isolate would be the result of lysing a single host cell that was producing both the L-rFv and H-rFv polypeptides.

18. As such, in my opinion, it is absolutely clear that, if the procedures described in the '414 application are followed as they are written, each of the polypeptides will be produced in separate cells. I do not believe any other reading of these sections of the '414 application would be rational, logical, or scientifically accurate.

The Procedures Described In The '414 Application Will Not Yield Genetic Constructs Encoding More than One Polypeptide Or Host Cells That Contain Multiple Plasmids

19. The procedures in the '414 application produce a "tailored" cDNA sequence by starting with a cDNA obtained from a cDNA library that encodes a full length heavy or full length light immunoglobulin chain polypeptide. *See*, p. 6, lines 19-34. These starting cDNA sequences are produced using mRNA transcripts isolated from a hybridoma that is producing an antibody with a desired specificity (*i.e.*, a cDNA library is produced

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