CONTROL NOS. 90/007,542 AND 90/007,859 ATTORNEY DOCKET NOS. 22338-10230, -10231

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 MICHAEL BOTCHAN UNDER 37 C.F.R. § 1.132

I, Michael Botchan, do hereby declare and state:

1. I am a citizen of the United States, and reside in Kensington, California. 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. I am being compensated for my time at a rate of $550 per hour.

3. I am not now affiliated with either Genentech or City of Hope. I served as an expert for Genentech in *City of Hope Nat'l Med. Center v. Genentech, Inc.*, Case No. BC215152 (Los Angeles Co. (Cal.) Super. Ct.), and provided deposition testimony in that litigation.

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

- Cabilly *et al.*, U.S. Patent No. 6,331,415 (the '415 patent)
- Cabilly *et al.*, U.S. Patent No. 4,816,567 (the '567 patent)
- Moore *et al.*, U.S. Patent No. 5,840,545 (the '545 patent)
- Moore *et al.*, U.S. Patent No. 4,642,334;
- Moore *et al.*, U.S. application no. 06/358,414 (the '414 application)
- Boss *et al.*, U.S. Patent No. 4,816,397

CONTROL NOS. 90/007,542 AND 90/007,859 ATTORNEY DOCKET NOS. 22338-10230, -10231

- Axel *et al.*, U.S. Patent No. 4,399,216
- Rice *et al.*, *Proc. Nat'l Acad. Sci. USA* 79: 7862-65 (1982)
- Kaplan *et al.*, EP 0044722
- Builder *et al.*, U.S. Patent No. 4,511,502
- Accolla *et al.*, *Proc. Nat'l Acad. Sci. USA* 77: 563-66 (1980)
- Dallas, WO 82/03088
- Deacon *et al.*, *Biochem. Soc. Trans.* 4: 818-20 (1976)
- Valle *et al.*, *Nature* 291: 338-40 (1981)
- Valle *et al.*, *Nature* 300: 71-74 (1982)
- Ochi *et al.*, *Nature* 302: 340-42 (1981)
- Oi *et al.*, *Proc. Nat'l Acad. Sci. USA* 80: 825-29 (1983)

5. I have also reviewed the documents associated with the two reexamination proceedings, including the PTO communication dated February 16, 2007 (the Office Action).

6. I understand that patentability is to be 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., in this case, 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 postdoctoral experience. 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 I worked with many people at that time with these qualifications.

7. I understand that the '545 patent issued in 1998 from an application filed on June 5, 1995. I also understand that there were several earlier applications filed between 1982 and 1995, and that the first of these was the '414 application, which was filed in March of 1982. I understand that the question of what is described in the '414 application (the 1982 application) relative to what is described in the '545 patent is an issue in this reexamination proceeding.

8. I have been asked to explain the techniques described in the '414 application and whether there is a description of a host cell that produces two different polypeptide chains or a

CONTROL NOS. 90/007,542 AND 90/007,859 ATTORNEY DOCKET NOS. 22338-10230, -10231

process which produces two different polypeptide chains in a single host cell in that application. I have also been asked to address what a person of ordinary skill in the art in early April of 1983 would have taken away from the information in a variety of patents and publications, and whether that information would have made the coexpression procedures in the '415 patent claims obvious at that time.

Analysis of the '414 Application and the '545 Patent

9. The '414 application describes procedures for cloning DNA that were conventional in early April of 1983. At that time, it was known that to "clone" a DNA sequence, you would:

- isolate or prepare desired DNA;
- insert the DNA into a vector;
- insert the vector into a host cell, and grow the host cell;
- isolate the copies of the DNA (within the vector) from the host cell culture (which now contains multiple progeny of the cells, and therefore multiple copies of the vector containing the desired DNA).

10. The '414 application describes cloning procedures having these steps at pages 5, line 16, to page 9, line 20.

11. The process for isolating DNA encoding the individual immunoglobulin chains is described at page 6, line 14 to page 8, line 7 of the '414 application. First, an mRNA extract is produced from a hybridoma that is making a desired antibody. This mRNA extract will contain many different mRNA "transcripts" corresponding to the messengers of the genes being expressed in the cell. Each of the mRNA transcripts is a discrete molecule containing a sequence corresponding to the amino acid sequence of a single polypeptide encoded by the DNA in the cell. The mixture of mRNA transcripts isolated from the hybridoma in the '414 application will contain mRNA transcripts produced during transcription of the immunoglobulin light chain gene, and different mRNA transcripts produced during transcription of the immunoglobulin heavy chain gene. There will be no mRNA transcripts in the extract that contain sequences from both heavy

and light chain genes, because the mRNAs for the chains are encoded by different genes expressed from separate promoters at different chromosomal positions.

12. The mRNA extract is then purified and used to prepare a cDNA library. The process as described is standard for the time, as described at page 7, line 37 to page 8, line 7. It involves using the "reverse transcriptase" enzyme that produces a complementary DNA (cDNA) molecule corresponding to each mRNA transcript in the purified mRNA extract. Again, because no mRNA transcript will contain sequences for both heavy and light chains, no individual cDNA in this cDNA library will contain heavy and light chain sequences.

13. The next step described in the application is amplification of the cDNA library. Amplification involves incorporating all of the cDNA molecules in the cDNA library into individual plasmids, and then inserting the plasmids into cells in culture by a transformation process. This procedure is specified at 8, line 12, to page 9, line 19. The procedures being described make it absolutely clear that each plasmid incorporates a single cDNA encoding a light or heavy immunoglobulin chain, and that each bacterial cell transformed will contain one plasmid.

- At page 8, lines 15-18, the application states that "the ds cDNA obtained from the reverse transcription of the mRNA" is being used. As I explained above, each discrete ds cDNA molecule in the cDNA library encodes only one immunoglobulin polypeptide sequence because it is produced from individual mRNA transcripts in the mRNA extract.
- The design of the plasmid indicates that one cDNA insert will be incorporated into each plasmid. *See* page 8, lines 20-24 ("... the vector will have a unique restriction site in one of multiple markers so that transformants may be selected by the expression of one marker and the absence of expression of the other marker"). Certainly, this is the desired outcome.

CONTROL NOS. 90/007,542 AND 90/007,859 ATTORNEY DOCKET NOS. 22338-10230, -10231

- The selection of screening techniques for bacterial clones indicates that each clone has one plasmid with one cDNA in it. The descriptions of these techniques could not be clearer in stating that each clone contains one plasmid with one cDNA encoding only one of the two immunoglobulin chains. Specifically, at page 9, lines 10-13, the '414 application states:

> The host colonies, usually bacterial, which have DNA which hybridizes to either the light or heavy chain probes are picked and then grown in culture under selective pressure.

14. After each clone has been propagated in culture, the bacterial cells are lysed, and the copies of the plasmid are isolated, sequenced, and subjected to restriction mapping. The sites for specific restriction enzyme hydrolysis are mapped on the genome of the plasmid. The sequencing and restriction mapping techniques in the application indicate that individual cDNA sequences encoding the light or heavy immunoglobulin chain are being used in the process. For example, at page 9, lines 22-31, the application states:

> These analyses insure that the isolated cDNA clones completely encode the variable region and, optionally, the leader sequences for the light or heavy chain of the desired immunoglobulin. Furthermore, by having a restriction map of the variable regions and leader sequences, as well as the flanking sequences, one can determine the appropriate restriction sites for excising a DNA fragment which will allow for appropriate modification of the DNA sequence for insertion into a vector and expression of the polypeptide of interest. (emphasis added)

15. Someone who was familiar with basic molecular biology principles would know that unless special steps were taken to culture the bacterial cells under "selective pressure," those cell cultures will become uniform with respect to plasmid content within each cell. Specifically, if a bacterial cell is transformed with a plasmid that contains an antibiotic resistance gene, copies (clones) of that bacterial cell can be selectively cultivated by adding the relevant antibiotic to the cell culture (i.e., the antibiotic kills the cells that have not incorporated the plasmid). This concept of selective pressure is central to the design of genetic engineering experiments. In the case of the '414 application, the procedures employ cell culture techniques that use only a single source of selective pressure (i.e., a single antibiotic is used to exert selective pressure on transformed cells).

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