IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Reexamination of Patent No. 6,331,415	)	
Shmuel CABILLY et al.	)	Group Art Unit: 3991
Control No. 90/007,542	)	Examiner: Bennett Celsa
Filed: May 13, 2005	)	Confirmation No.: 7585
For: METHODS OF PRODUCING IMMUNOGLOBULINS, VECTORS AND TRANSFORMED HOST CELLS FOR USE THEREIN	)	

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

I, Timothy John Roy Harris, do hereby declare and state:

1. I am a citizen of the United Kingdom, and reside in San Diego, California. My c.v. is attached as Exhibit A.

2. I am presently Chief Executive Officer of Novasite Pharmaceuticals. Prior to this position, I served in a variety of research and management positions in the biotechnology industry.

3. In early 1983, I was head of Molecular Biology at Celltech, Ltd., now part of UCB Pharma. Recombinant antibody production was a key research focus for the company, and its scientific advisors were experts in that field. Celltech is the same corporate entity that was involved in a protracted interference contest in the Patent and Trademark Office (PTO) with Genentech and City of Hope concerning recombinant antibody production.

4. I have been retained by Genentech and City of Hope to provide my views on certain issues that have arisen in connection with the reexamination proceeding of U.S. Patent No. 6,331,415 (the '415 patent)

5. I have reviewed the following patents and publications:

- Cabilly, U.S. Patent No. 4,816,567 (the '567 patent)
- Cabilly, U.S. Patent No. 6,331,415;
- Axel, U.S. Patent No. 4,399,216 (Axel)
- Rice, *PNAS* 79: 7862, 1982 (Rice)
- Kaplan, European Patent No. 0 044 722 (Kaplan)

- Accolla, *PNAS* 77: 536, 1980 (Accolla)
- Builder, U.S. Patent No. 4,511,502 (Builder)

6. I have also reviewed certain documents associated with the reexamination proceeding of the '415 patent, including:

   - A PTO Office Action in reexamination no. 90/007,542 dated September 13, 2005 ("Office Action");
   - A PTO Order granting ex parte reexamination of the '415 patent, dated July 7, 2005 ("Reexamination Order"); and
   - A Request for Ex Parte Reexamination dated May 13, 2005 ("Request for Reexamination").

7. In addition, in preparing this declaration, I reviewed literature I found relevant from the same general time period as the '567 and '415 patents.

8. In this declaration, I provide my opinions on the scientific observations found in the PTO Office Action concerning Axel, Rice, Kaplan, Accolla and Builder from the perspective of a person of ordinary skill in this art on or before the filing date of the '415 patent (i.e., April 8, 1983).

9. I understand that the '567 patent claims are directed to processes, vectors and host cells for producing chimeric immunoglobulin heavy or light chain polypeptides, and to a composition containing a chimeric immunoglobulin heavy or light chain polypeptide. The '567 patent method claims cover situations where only one chimeric immunoglobulin heavy or light chain polypeptide is produced in a single host cell.

10. The '415 patent claims differ from the '567 patent claims. One difference is that the method claims in the '415 patent require that DNA sequences encoding the heavy and the light immunoglobulin chain polypeptides be independently expressed by a single host cell. Another difference is that the method claims in the '415 patent require assembly of the heavy and light chain polypeptides into an immunoglobulin molecule or an immunologically functional fragment that comprises at least the variable domains of the heavy and light chain polypeptides.

Meaning of "Having Specificity for a Particular Known Antigen" in the '567 Patent Claims

11. The '567 patent claims use the phrase "having specificity for a particular known antigen… ." I have been asked to explain what that phrase would have meant to a person of ordinary skill in the art in view of the '567 patent disclosure in early April of 1983.

12. By this time, the physical structure and biological functions of immunoglobulins were fairly well known. The description of immunoglobulin structure in the '567 and '415 patents (e.g., '415 patent, col. 3, line 17 to col. 4, line 5) is consistent with what was generally understood about immunoglobulin structure and function. By this time, it also

was accepted that the antigen binding function of immunoglobulins was associated with the variable domains of the heavy and light chain polypeptides, and that an individual heavy or light chain polypeptide ordinarily would not bind to antigen very well, if at all.

13. I would rely on this general understanding of immunoglobulin structure and function to answer the question of what the phrase "having specificity for a particular known antigen" means as it is used in the claims of the '567 patent. I view that phrase as it is used in the claims of the '567 patent as referring to amino acid sequences within the variable domain of the individual chimeric heavy chain or light chain polypeptide that confer antigen binding specificity. In such a chimeric polypeptide, these sequences would be derived from the variable domains of an antibody or an antibody fragment exhibiting an antigen binding function.

14. I do not read this phrase as it is used in the '567 patent claims as requiring that the individual chimeric heavy chain or light chain polypeptide be assembled into a molecule that actually exhibits antigen-binding function, such as an immunoglobulin molecule or an immunologically functional fragment that includes the variable domains of the heavy and light chain polypeptides.

General Observations on State of the Art in 1983

15. I understand that the PTO has suggested that the inventions claimed in the '415 patent would have been considered obvious to a scientist working in this field in April of 1983. I also understand that this is based on their opinion of what the claims of the '567 patent would have suggested to a scientist at the time in view of Axel, Rice, Kaplan, Builder and Accolla. I do not agree with the conclusions or rationale offered by the PTO.

16. By early April of 1983, I was aware that a number of groups had successfully expressed polypeptides using recombinant techniques. These experiments generally involved expression of genes encoding relatively small polypeptides with simple tertiary structures (e.g., monomeric or dimeric proteins). The state of the art in this time frame is reflected in a review paper I authored (Harris, "Expression of Eukaryotic Genes in *E. coli*," *Genetic Engineering* 4: 127-85 (1983), attached as Exhibit B). In early April of 1983, I was not aware of any publications reporting the production of an active multimeric protein with a complexity comparable to an immunoglobulin by independent expression of the genes encoding the distinct constituent polypeptides of the protein in a single host cell.

17. Immunoglobulin molecules are large (approx. 150 kD) and complex tetrameric proteins. By early April of 1983, it was believed that the functional properties of immunoglobulins – particularly antigen binding – were dependent on specific covalent and non-covalent interactions within and between the heavy and light chains. For example, each pair of heavy and light chain polypeptides in an immunoglobulin is joined by several inter- and intra-chain cystine bonds. The immunoglobulin tetramer also has several inter-chain cystine linkages. These interactions between the heavy and light chain polypeptides were known to be important to antigen binding and other functions associated with

immunoglobulins. See, e.g., Edelman, G. M., *Ann. N. Y. Acad. Sci.* 190: 5-25 (1971), referenced in col. 3, lines 18-19 of the '415 patent and provided as Exhibit C.

18. Scientists working in this field at the time understood that mature B cells are able to assemble immunoglobulin tetramers out of the endogenous light and heavy immunoglobulin chain polypeptides naturally produced by those cells. However, I do not believe a scientist in this field, in early April of 1983, would equate this general understanding of B cell function as providing any particular insights into the challenge of recombinant production of an immunoglobulin molecule or immunologically functional fragment through expression of exogenous heavy and light chain genes in a single host cell.

19. I therefore do not agree with the suggestion of the PTO that, by early April of 1983, the patents and publications they identify demonstrate that the expression using recombinant DNA techniques of genes encoding complex multimeric proteins such as immunoglobulins had become routine.

The Axel Patent

20. The first publication the PTO identifies is U.S. Patent No. 4,399,216, to Axel, Wigler, and Silverstein ("Axel patent"). The PTO describes the relevance of the Axel patent as follows:

> Axel et al teaches a process for inserting foreign DNA into eukaryotic cells by co-transforming the cells with this foreign DNA and an unlinked DNA that codes for a selectable phenotype not otherwise expressed by the cell (see column 3, lines 21-27). Axel describes the process as particularly suited for the transformation of DNA into eukaryotic cells for making immunoglobulins (see column 3, lines 31 to 36). Axel thus demonstrates the predictability of expression of multiple heterologous proteins in a single host cell. Axel also suggests the desirability of expressing immunoglobulins in mammalian host cells, and as intact (assembled) proteins. Office Action, page 5.

21. The Axel patent describes a process for inserting a single heterologous gene ("DNA I") into a host cell co-transformed with a "selectable marker" gene ("DNA II"). Figure 1 in the patent provides an overview of the Axel process. In the Axel patent terminology, "DNA I" encodes a desired "proteinaceous material not associated with a selectable phenotype" that is to be isolated from the transformed host cell. See, col. 3, lines 31 to 36. The selectable marker is introduced by DNA II.

22. Two elements are essential to the process described in the Axel patent. First, the host cell must be co-transformed to contain DNA I and DNA II. Second, DNA II must impart into the transformed host cell a selectable marker associated with expression of DNA II by the cell. This enables a scientist to select transformed cells that are expressing DNA II from cells that are not expressing DNA II. This is done, according to the Axel patent, by introducing into the medium in which the cells are growing an agent that facilitates the selective removal of those cells that are not expressing DNA II.

23. The choices in Axel for DNA II are limited to genes that introduce selectable markers. As Axel explains at col. 5, lines 58-67:

> Although any DNA II coding for a selectable phenotype would be useful in the cotransformation process of the present invention, the experimental details set forth particularly concern the use of a gene for thymidine kinase obtained from herpes simplex virus and the use of a gene for adenine phosphoribosyl transferase. In addition, a DNA II which includes a gene coding for a selectable phenotype associated with drug resistance, e.g., a mutant dihydrofolate reductase gene which renders cells resistant to methotrexate, greatly extends the applicability of the process.

24. For the process described in the Axel patent to work, DNA II must encode a polypeptide that introduces a selectable phenotype not normally exhibited by the cell. A gene encoding an immunoglobulin heavy or light chain polypeptide cannot function in the role described in the Axel patent for DNA II, because its expression in a cell would not have introduced a "selectable marker" into the cell.

25. I do not find a description in the Axel patent for procedures where cells are transformed to express more than two distinct DNA sequences. Instead, the patent consistently states that one DNA (DNA I) encodes the polypeptide to be expressed by and isolated from the cell, and a second DNA (DNA II) encodes an introduced selectable marker. I also see nothing in the Axel patent describing or suggesting procedures where host cells are transformed with an additional, different DNA (a "DNA III") which would be necessary to use the Axel patent method to express genes encoding immunoglobulin heavy and light chain polypeptides in a single transformed host cell.

26. I also do not read the brief references to "antibodies" in the Axel patent as suggesting that genes encoding both heavy and light chain polypeptides can or should be expressed in a single host cell. These references are simply suggesting that antibody polypeptides might be a type of "proteinaceous material" that could be produced using the method described in the Axel patent.

27. I also do not find in the Axel patent any description of methods for producing a complex multimeric protein, such as an immunoglobulin, by independently expressing the genes encoding the individual polypeptide constituents of the multimeric protein in a single host cell. I note that the only examples in Axel concern small monomeric polypeptides (e.g., the rabbit β-globin polypeptide). In addition, none of the experiments described in the Axel patent actually show isolation of the polypeptides that were produced by the transformed host cells.

28. I do not agree with the Examiner that the Axel patent suggests the desirability of producing immunoglobulins as "intact (assembled) proteins." I am unable to find any mention in Axel of the desirability of producing "intact (assembled)" immunoglobulins, and nothing in the Axel patent provides any guidance on how to assemble "intact" immunoglobulins.

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