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. DOUGLAS A. RICE UNDER 37 C.F.R. § 1.132

1. I am a citizen of the United States and reside in Leawood, Kansas.

2. I am the same Douglas A. Rice who provided a Declaration in connection with Reexamination No. 90/007,542 on November 25, 2005.

3. As I indicated in my earlier Declaration, I have been retained to provide my scientific opinions on certain matters that have been raised in the reexamination proceedings involving 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 $450 per hour.

4. My background and experience are essentially unchanged relative to how I described them in my earlier Declaration.

5. I reviewed the following references which were identified by the Patent and Trademark Office (PTO) in the course of preparing this Declaration:

   - Cabilly *et al.*, U.S. Patent No. 4,816,567 ("the '567 patent");
   - Cabilly *et al.*, U.S. Patent No. 6,331,415;
   - Axel *et al.*, U.S. Patent No. 4,399,216 ("*Axel*");

- Rice *et al.*, *PNAS* 79:7862-7865 (1982) ("*Rice*" or "1982 *PNAS* paper");
- Kaplan *et al.*, European Patent No. 0 044 722 ("*Kaplan*");
- Accolla *et al.*, *PNAS* 77:533-536 (1980) ("*Accolla*");
- Builder *et al.*, U.S. Patent No. 4,511,502 ("*Builder*");
- Valle *et al.*, *Nature* 300:71-74 (1982) ("*Valle II*");
- Valle *et al.*, *Nature* 291:338-340 (1981) ("*Valle I*");
- Deacon *et al.*, *Biochemical Society Transactions* 4:818-820 (1976) ("*Deacon*");
- Dallas, PCT Application Publication No. WO 82/03088 ("*Dallas*");
- Ochi *et al.*, *Nature* 302:340-342 (1983) ("*Ochi*"); and
- Oi *et al.*, *PNAS* 80:825-829 (1983) ("*Oi*").

6. I also reviewed documents associated with this reexamination proceeding including all of the materials identified in my earlier Declaration, and the following materials:

- 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.

7. In this Declaration, I have been asked to address: (i) the expectations a person of ordinary skill in the art would have had in early April of 1983 regarding production of an immunoglobulin by transforming a single host cell with exogenous DNA sequences encoding both immunoglobulin chains; (ii) the comments made by the PTO in the Second Office Action regarding three scientific publications relating to expression of exogenous light chain genes in lymphoid cells, specifically the 1982 *PNAS* paper that I co-authored with Dr. David Baltimore in 1982, *Ochi*, and *Oi*; (iii) additional comments set forth in the Second Office Action concerning various other references; and (iv) the Declaration signed by Dr. Baltimore that was included with the Second Request for Reexamination.

8. The analysis I provided in my earlier Declaration, and the analysis provided in this Declaration, reflect the views I believe a person of ordinary skill in the art would have had in early April of 1983. I believe that a person of ordinary skill in the art in the field of the '415 patent as of early April of 1983 would have the following qualifications: a Ph.D. in molecular biology or a related field, and about two years of post-doctoral experience in a lab working with recombinant DNA.

Observations on the Expectations of a Person of Ordinary Skill in Early April of 1983

9. The Second Office Action contains a number of statements concerning what the PTO believes a person of ordinary skill in the art would have reasonably expected in early April of 1983 based on findings we reported in our 1982 *PNAS* paper and other publications from that time frame, including the *Ochi* and *Oi* references.

10. As an initial comment, I believe individuals working in this field would not have considered these three papers in isolation. Instead, they would have also considered what was known in early April of 1983 about how B-lymphocytes produce immunoglobulins. In particular, their expectations would have been shaped by numerous reports in the literature documenting the types of factors that affect the ability of B-lymphocytes to produce immunoglobulins.

11. B-lymphocytes are specialized cells that have the specific function of producing immunoglobulins. They derive from precursor cells, called "pre-B" cells, found in bone marrow and fetal liver. B-lymphocytes undergo a characteristic sequence of development and maturation, resulting in the terminally developed circulating B-lymphocyte (which is called a plasma or memory B-lymphocyte) found in the bloodstream. Only the circulating B-lymphocyte produces and secretes intact immunoglobulin tetramers in significant quantities.

12. The process of immunoglobulin gene assembly and expression is complex and unique. Immunoglobulin genes are assembled from discrete immunoglobulin gene fragments during the process of maturation of the B-lymphocyte. *See, e.g.*, Brack *et al.*, *Cell* 15:1-14 (1978) (attached as Exhibit A). The timing of expression of the individual

immunoglobulin genes is also linked to the stage of development of the B-lymphocyte. For example, the heavy and light chain genes are expressed at different points in time during the development and maturation of the B-lymphocyte. *See*, *e.g.*, Siden *et al.*, *PNAS* 78:1823-7 (March 1981) (attached as Exhibit B).

13. Although all of this was known by early April of 1983, the processes that control immunoglobulin gene rearrangement and expression were not understood at that time, as we indicated in our 1982 *PNAS* paper (*see*, page 7862, left column). The unusual complexity of this system would have caused a person of ordinary skill in the art at that time to question whether one could achieve successful expression of exogenous light and heavy chain DNA sequences in a B-lymphocyte without disrupting the ability of that cell to properly express the introduced sequences, or carry out post-transcriptional events, such as immunoglobulin polypeptide folding, assembly or secretion.

14. Similarly, the 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. For example, at that time there were numerous reports in the literature of hybridoma and myeloma cell lines that, during the passage of these cell lines over time, spontaneously lost the ability to express their immunoglobulin genes, produce individual heavy or light chains, or secrete immunoglobulin tetramers. *See*, *e.g.*, Coffino *et al.*, *PNAS* 68:219-223 (1971) (attached as Exhibit C). Some researchers also reported that excess amounts of free heavy chain in mutant hybridoma lines often was toxic to these cell lines. *See*, Kohler, *PNAS* 77:2197-2199 (1980) (attached as Exhibit D). Excess free heavy chain can result from loss of the light chain gene, inadequate expression of the light chain gene or imbalances in amounts of the individual immunoglobulin chains caused by factors in the cellular environment.

15. In light of these observations, 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. This was consistent with reports in the literature that suggested that specialized proteins may be involved in the control of expression of immunoglobulin genes, and possibly in the assembly and secretion of immunoglobulin. *See*, *e.g.*, Wabl *et al.*, *PNAS* 79:6976-6978 (1982) (attached as Exhibit E). 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.

16. As a result, in early April of 1983, I believe a person of ordinary skill in the art who was familiar with the scientific literature would have expected that the ability of a transfected B-lymphocyte cell (or for that matter any other type of cell) to produce immunoglobulin tetramer would depend on several known and unknown but interrelated factors: (i) whether the immunoglobulin genes had been properly assembled in the cell, (ii) the timing and levels of expression of the light and heavy chain genes, (iii) the state of development of the cell, (iv) the amounts of the free light and heavy chain polypeptide proteins produced by and present in the cell, and (v) the presence of the appropriate translational machinery and various "helper" agents that are found in native B-lymphocytes that produce immunoglobulins.

17. The three publications reporting successful expression of a light chain gene in lymphoid cells (*i.e.*, our *1982 PNAS* article, the *Ochi* article and the *Oi* article) described useful techniques for exploring the mechanisms governing immunoglobulin gene expression. These publications, however, did not answer the questions that existed in early April of 1983 about how B-lymphocyte cells arrange or express immunoglobulin genes, regulate the production of the light and heavy chains, assemble the chains into immunoglobulin tetramers, or ultimately secrete functional immunoglobulins. In my opinion, the constrained experimental design of these experiments and the limited results they reported would not have created the general expectations that the PTO has suggested.

18. Each of these publications documents efforts to introduce a functionally rearranged light chain gene into differentiated cell lines of the B-lymphocyte lineage. Most of the cell lines used also had previously produced both chains, but had lost the capacity to produce

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