Amgen Inc. v. F. Hoffmann-LaRoche LTD et al Doc. 502

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

AMGEN INC., Plaintiff, v. F. HOFFMANN-LA ROCHE LTD., a Swiss Company, ROCHE DIAGNOSTICS GmbH, a German Company and HOFFMANN-LA ROCHE INC., a New Jersey Corporation, Defendants.	)	Civil Action No.: 05-12237 WGY

DECLARATION OF HARVEY F. LODISH, Ph.D. IN SUPPORT OF AMGEN INC.'S MOTION FOR SUMMARY JUDGMENT OF NO OBVIOUSNESS-TYPE DOUBLE PATENTING

684715

Dockets.Justia.com

I, Harvey F. Lodish, declare that:

1. I am a Professor of Biology and Professor of Biomedical Engineering at the Massachusetts Institute of Technology (MIT) and a Member of the Whitehead Institute for Biomedical Research. I am submitting this declaration in support of Amgen's Motion for Summary Judgment of No Obviousness-Type Double Patenting. If called to testify as to the truth of the matters stated herein, I could and would do so competently.

2. A copy of my curriculum vitae, reflecting my professional experience, affiliations, and work is attached as Exhibit A.

3. I received an A.B. degree summa cum laude from Kenyon College in 1962, and a Ph.D. from the Rockefeller University in 1966. I was a post-doctoral Fellow at the Medical Research Council Laboratory of Molecular Biology in Cambridge, England from 1966 to 1968. I held the positions of Assistant Professor and Associate Professor at the Massachusetts Institute of Technology (MIT) during the years 1968-71 and 1971-76, respectively. Since 1976, I have been a full Professor of Biology at MIT and since 1999 Professor of Bioengineering. In 1982, I became a Founding Member of the Whitehead Institute for Biomedical Research.

4. Since 1961, I have authored or co-authored more than 500 scientific publications, in a variety of peer- reviewed scientific journals, as detailed in Exhibit A.

5. I was elected to the National Academy of Sciences in 1987. In 2004, I was President of the American Society for Cell Biology, an international organization of more than 10,000 scientists. I have also served on a variety of external advisory boards and grant review panels. A complete list is provided in Exhibit A.

6. As described in detail in my curriculum vitae, I have been a researcher, a teacher, a writer, and an editor in the fields of molecular and cellular biology for over 35 years.

Adherence to the scientific method is the common thread that runs through all the aspects of my career. Excellence is achieved in the field of science through application of the logical principles and philosophies shared by the scientific community. Like other scientists, through study and practice I have collected a set of analytical tools that I use to address all scientific problems. For example, I apply these tools when I evaluate others' work. If others do not rigorously apply scientific methodology, I properly discount their assertions.

7. In the course of my career, I have taught many M.I.T. undergraduates, Ph.D. students, and post-doctoral fellows. Imparting an understanding of proper scientific method is one of my major goals. More specifically, I teach students how to formulate testable hypotheses; how to design and perform well-controlled, repeatable experiments to validate hypotheses; and to evaluate experimental outcomes objectively. It is only by understanding and applying the scientific method rigorously that students can develop into scientists whose work will withstand the scrutiny of the scientific community and advance scientific knowledge.

8. I have served on the Editorial Boards for many peer-reviewed scientific journals. For example, I was a member of the Board of Reviewing Editors of the journal *Science* from 1991 to 1999, and a Member of the Editorial Board of the journal *Proceedings of the National Academy of Sciences* from 1996 to 2000. Furthermore, I have reviewed hundreds of articles for publication in many different journals. When I review papers for potential publication, I must consider critically whether the work is well conceived, controlled, and performed in order to establish whether its scientific conclusions are correct. Additionally, I consider whether the work is sufficiently described such that other workers in the field can repeat, confirm, and extend the reported findings.

9. I am the principal editor and author of the textbook *MOLECULAR CELL BIOLOGY*, now in its Fifth Edition.[1] The Sixth Edition has just been published. In addition to my seven co-authors, literally dozens of our scientific colleagues from around the world have contributed to chapters, and reviewed and commented on the manuscripts. This textbook has been relied upon by scientific researchers, undergraduate students, and graduate and medical students all around the world since the publication of our First Edition in 1986. The Fifth Edition has been translated into six languages. It is considered one of the most authorative resources on the fields of molecular and cellular biology. The textbook presents a comprehensive, authoritative review of the fields of molecular and cellular biology, and is intended for advanced undergraduates and graduate and medical students. In the course of preparing my book over the past 20 years, I have comprehensively studied, in detail, the published literature to determine what experimental work is new, significant, and sufficiently credible to merit reliance by the scientific community at large.

10. In the course of my career as a researcher, I have personally applied the scientific method to many different avenues of research, including cell signaling, protein synthesis, cell membranes and their formation, cell death, fat cell biology, and, most relevant here, blood cell differentiation. One example of my experience in blood cell differentiation is my work concerning the characterization of the murine erythropoietin ("EPO") receptor, the protein on the surface of red blood cell precursors that binds to EPO and that mediates the activity of EPO in cells and *in vivo* (in the body).

11. I have been studying glycoprotein synthesis and function in mammalian cells since about 1976. My laboratory has made several significant contributions to the understanding

---

[1] *See* Lodish *et al.*, *Molecular Cell Biology*, 5th Ed. W.H. Freeman Co., New York.

of the glycosylation process. Prominent examples of our work include first establishing that the addition of oligosaccharides (or "glycans") to asparagines on glycoproteins occurs during the synthesis of the polypeptide and its translocation into the endoplasmic reticulum, and purifying and characterizing the hepatocyte asialoglycoprotein receptor, a major component of the system of clearance of glycoproteins from the circulation.

12. Representative examples of my pre-1983 publications in the field of glycosylation include: Lodish, H.F., *et al.*, "Membrane assembly: synthesis and intracellular processing of the vesicular stomatitis viral glycoprotein," *Birth Defects Orig Artic Ser.* 14(2):155-75 (1978); Rothman, J.E., and Lodish, H.F., "Synchronised transmembrane insertion and glycosylation of a nascent membrane protein," *Nature* 269(5631):775-80 (1977); Lingappa, V.R. *et al.*, A signal sequence for the insertion of a transmembrane glycoprotein. Similarities to the signals of secretory proteins in primary structure and function," *J Biol Chem.* 253(24):8667-70 (1978); Rothman, J.E. *et al.*, "Glycosylation of a membrane protein is restricted to the growing polypeptide chain but is not necessary for insertion as a transmembrane protein" *Cell* 15(4):1447-54 (1978); Schwartz, A.L. *et al.*, "Difficulties in the quantification of asialoglycoprotein receptors on the rat hepatocyte," *J Biol Chem.* 255(19):9033-6 (1980); Schwartz, A.L., *et al.*, "Identification and quantification of the rat hepatocyte asialoglycoprotein receptor," *Proc Natl Acad Sci U S A.* 78(6):3348-52(1981); and Lodish, H.F., and Kong, N., "Glucose removal from *N*-linked oligosaccharides is required for efficient maturation of certain secretory glycoproteins from the rough endoplasmic reticulum to the Golgi complex," *J Cell Biol.* 98(5):1720-9. I have continued to research and publish in this field to the present day.

13. I was also very involved in cloning genes from several eukaryotic cells, including human and other mammalian cells, beginning in 1980 and continuing throughout the 1980s to the present day.

14. Moreover, in the early 1980s, I was also particularly interested in the production of recombinant proteins for therapeutic and industrial purposes. In particular, I was interested in how it would be possible to recapitulate the complex processing of mammalian proteins in heterologous expression systems. In 1981, I published a review article on this subject. Lodish, H.F., "Post-translational modification of proteins," *Enzyme Microb Technol.* 3(3):177-188 (1981). This article demonstrates that I am uniquely qualified to opine on the knowledge and understanding of an ordinarily skilled artisan in the fields pertinent to the claims-at-issue during the 1983-84 time period.

15. During the course of prior litigation involving the patents-in-suit between Amgen and Transkaryotic Therapies and Hoechst Marion Roussel, I reviewed in detail the patents-in-suit, portions of the prosecution histories, and related scientific publications. I testified at trial in connection with that action and prepared several expert reports.

16. Before making this declaration, I reviewed documents that are referred to herein and others listed in Exhibit B.

I. THE CLAIMS IN DR. LIN'S '933, '349, AND '422 PATENTS FALL WITHIN GROUPS I, IV, AND V OF THE RESTRICTION REQUIREMENT IN DR. LIN'S '298 APPLICATION

17. I understand that during the prosecution of Dr. Lin's U.S. Patent Application No. 675,298, the Examiner issued a "restriction requirement" on July 3, 1986. The restriction requirement identified six different categories of claimed inventions. The July 1986 restriction requirement stated:

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-13, 16, 39-41, 47-54 and 59, drawn to polypeptide, classified in Class 260, subclass 112.

II. Claims 14, 15, 17-36, 58 and 61-72, drawn to DNA, classified in Class 536, subclass 27.

III. Claims 37-38, drawn to plasmid, classified in Class 435, subclass 317.

IV. Claims 42-46, drawn to cells, classified in Class 435, subclass 240.

V. Claims 55-57, drawn to pharmaceutical composition, classified in Class 435, subclass 177.

VI. Claim 60, drawn to assay, classified in Class 435, subclass 6.[2]

18. The language of the claims assigned to Groups I-VI of the Examiners' restriction requirement is depicted in the chart attached as Exhibit C.

19. I have been asked to compare the subject matter of each of the claims of U.S. Patent Nos. 5,547,933 ("the '933 patent"), 5,955,422 ("the '422 patent") and 5,756,349 ("the '349 patent") with the six categories of invention determined by the examiner in the July 3, 1986 restriction requirement, and to offer my opinion as to which category, if any, each of the claims would fall within the scope of applying the perspective of an ordinarily skilled artisan. An "ordinarily skilled artisan" or "person of ordinary skill" in the field relevant to Dr. Lin's claims would have been a research scientist with a Ph.D. or M.D. and at least two years of postdoctoral research experience in the field of molecular biology, cellular biology, or protein expression.

20. I am informed that the claims of the '933, '349, and '422 patents-in-suit are said to be "consonant" with the 1986 restriction requirement if they fall within the scope of the

---

[2] '298 Prosecution, Paper 8 at 2 (Exhibit E-1).

groups that were not selected for further examination in the '298 application following the restriction requirement (i.e., Groups I and III-VI), and do not fall within the scope of the group that was selected for further examination in the '298 application (i.e., Group II). I am informed that the claims in the '933, '349, and '422 patents-in-suit are not consonant if they "cross the line of demarcation drawn around the invention elected in the restriction requirement."[3]

Restriction Group II

21. The Examiner described Group II as "drawn to DNA." Based on the subject matter of the claims assigned to Group II, I agree with this characterization. The claims assigned to Group II included both process and non-process claims. The common feature of claims 14, 15, 17-36, 58, and 61-72 is that each claim requires a specific, purified, and isolated DNA sequence, encoding either human or monkey erythropoietin or an analog polypeptide related to erythropoietin in both structure and function. While some of these claims are directed to host cells containing or processes using such purified and isolated DNAs, none are directed to erythropoietin polypeptides or erythropoietin pharmaceutical compositions. Nor do any of these claims relate to host cells or processes for use defined by characteristics of either the cells or the resultant polypeptides. Additionally, these claims do not relate to cells or processes defined by a required production level for any polypeptide. Therefore, based on the subject matter of the claims assigned to Group II, it is my opinion that the focal point of Group II was the recited DNA.

Restriction Group I

22. The Examiners described Group I as "drawn to polypeptide." Based on the subject matter of the claims assigned to Group I, I agree with this characterization. The common

[3] *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1579 (Fed. Cir. 1991).

feature of claims 1-13, 16, 39-41, 47-54 and 59 is that each claim is drawn to a protein (or "polypeptide"). Some of these proteins are characterized by the process by which they are produced, and others are characterized by their structure. For example, claim 1 is directed to EPO analogs defined by the process by which they are produced. Specifically, they are products "of procaryotic or eucaryotic expression of an exogenous DNA sequence." On the other hand, claim 40 is defined by its structure and function: a polypeptide with at least some of erythropoietin's biological characteristics, but which has "an average carbohydrate composition which differs from that of naturally-occurring erythropoietin." Lastly, claims 51-54 are directed to anti-erythropoietin antibody polypeptides. Therefore, based on the subject matter of the claims assigned to Group I, it is my opinion that the focal point of Group I was the recited polypeptides.

Restriction Group IV

23. The Examiner described Group IV as "drawn to cells." Based on the subject matter of the claims assigned to Group IV, I agree with this characterization. The common feature of claims 42-46 is that each claim requires a vertebrate cell that produces the large quantities of erythropoietin polypeptide required for the practical use of the protein. Moreover, the cells in Group IV are distinct from the cells in Group II because the Group IV cells do not require that they be transfected or transformed with exogenous EPO DNA. Therefore, based on the subject matter of the claims assigned to Group IV, it is my opinion that the focal point of Group IV was the recited cells.

Restriction Group V

24. The Examiner described Group V as "drawn to pharmaceutical composition." Based on the subject matter of the claims assigned to Group V, I agree with this characterization.

The common feature of claims 55-57 is that each claim requires a pharmaceutical composition of a polypeptide with erythropoietic biological and therapeutic properties. It is common sense that therapeutic methods of using such pharmaceutical compositions would be linked together with the therapeutic compositions themselves. Therefore, based on the subject matter of the claims assigned to Group V, it is my opinion that the focal point of Group V was the recited pharmaceutical compositions.[5]

A. THE '008 CLAIMS FALL WITHIN RESTRICTION GROUP II

25. I understand that in response to the July 3, 1986 restriction requirement in Dr. Lin's '298 application, Amgen chose to pursue the claims assigned to Group II, and that the Examiners withdrew all other claims from further examination in the '298 application. Dr. Lin and Amgen then pursued the Group II claims in the '298 application, which ultimately issued as U.S. Patent 4,703,008 ("the '008 patent") (Exhibit E-2). Having compared the issued claims of the '008 patent to the claims in the '298 application assigned to Group II, it is my opinion that, consistent with Amgen's election to have the Group II claims examined in the '298 application, all of the '008 patent claims fall within the scope of restriction Group II.

B. THE '933 CLAIMS FALL WITHIN RESTRICTION GROUPS I AND V

26. Each of the claims of the '933 patent is directed to an EPO glycoprotein, an EPO pharmaceutical composition, or a method of using same. Having compared the claims of the '933 patent to the claims in the '298 application that were assigned to the various restriction groups in the July 1986 restriction requirement, from the perspective of one of ordinary skill in

---

[5] I have also analyzed the subject matter of the claims in Dr. Lin's '298 application that the Examiners assigned to Groups III and VI, and I agree with the Examiner's characterization of Group III as "drawn to plasmid" and Group VI as "drawn to assay." Because, as discussed below, the claims of the '933, '349, and '422 patents-in-suit fall within the scope of Groups I, IV, and/or V (and not Group II), I do not focus on Groups III and VI.

the art, it is my opinion that the '933 claims fall within the scope of either Group I, "drawn to polypeptide," or Group V, "drawn to pharmaceutical composition." None of the claims of the '933 patent cross the line of demarcation drawn around restriction Group II, "drawn to DNA."

27. As shown in the table attached as Exhibit D-1, both claims 1-8 of the '933 patent and original claims in the '298 application assigned to restriction Group I claim EPO glycoproteins. It is clear that the Examiner made no distinction in the restriction requirement between an EPO "polypeptide" and an EPO "glycoprotein," considering the inclusion of original claim 40 directed to "a glycoprotein product" in restriction Group I. Some of the original claims assigned to Group I as well as '933 claims 1-8 make reference to use of an exogenous DNA sequence to produce EPO erythropoietin polypeptides. But like the original claims assigned to Group I, none of '933 claims 1-8 is directed to DNA or a host cell transfected with DNA. Thus, based on my substantive analysis of the claims, it is my opinion that an ordinarily skilled artisan would recognize and understand that there are no material differences between original claims 1-13 of the '298 application and '933 claims 1-8 (EPO glycoproteins) which thus would fall within the scope of the Group I category of claims — "Claims 1-13, 16, 39-41, 47-54 and 59, drawn to polypeptide, classified in Class 260, subclass 112" — and would not fall within the scope of the Group II category of claims, "drawn to DNA."

28. As shown in the table attached as Exhibit D-2, both claims 9-14 of the '933 patent and the original claims in the '298 application assigned to restriction Group V claim EPO pharmaceutical compositions and methods of using same. Because the original Group V claims (original claims 55-57) each depend on claims of Group I, they similarly may or may not require use of exogenous EPO DNA, but each are not directed to such a DNA or host cell transformed or transfected with such a DNA. None of '933 claims 9-14 are directed to either an EPO DNA or a

host cell transformed or transfected with an EPO DNA. Thus, based on my substantive analysis of the claims, it is my opinion that an ordinarily skilled artisan would recognize and understand that '933 claims 9-14 (EPO pharmaceutical compositions and methods of using same) fall within the scope of the Group V category claims — "Claims 55-57, drawn to pharmaceutical composition, classified in Class 435, subclass 177" — and would not fall within the scope of the Group II category of claims, "drawn to DNA."

C. THE '349 CLAIMS FALL WITHIN RESTRICTION GROUP IV

29. Each of the claims of the '349 patent is directed to vertebrate cells which make EPO or a process of making EPO using such cells. Having compared the claims of the '349 patent to the claims in the '298 application that were assigned to the various restriction groups in the July 1986 restriction requirement, from the perspective of one of ordinary skill in the art, it is my opinion that the '349 claims fall within the scope of restriction Group IV, "drawn to cells." None of the claims of the '349 patent cross the line of demarcation drawn around restriction Group II, "drawn to DNA."

30. As shown in the table attached as Exhibit D-3, the cell claims of Dr. Lin's '349 patent are very similar to the Dr. Lin's original cell claims that were assigned to restriction Group IV in the '298 application. Both sets of claims cover the same types of cells (vertebrate cells), and require the same EPO production capabilities. The difference between the '349 cell claims and the original cell claims assigned to restriction Group IV is that original cell claims (numbered 42-46) did not include any structural limitation regarding the contents of the cells. Although '349 claims 1-3 recite "DNA encoding human erythropoietin" they do not cross the line of demarcation drawn around the EPO DNA inventions of restriction Group II because the '349 claims do require that the EPO DNA in the vertebrate cells be isolated or purified at any time. Rather, the DNA encoding human EPO in these vertebrate cells merely needs to be

transcriptionally controlled by "non-human DNA sequences." This interpretation is confirmed by the Federal Circuit's holding that '349 claims 1-7 are infringed by a process using "gene activated" EPO DNA, wherein the EPO DNA was never purified or isolated. *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 457 F.3d 1293, 1317 (Fed. Cir. 2006). Therefore, based on my substantive analysis of the claims, it is my opinion that an ordinarily skilled artisan would recognize and understand that '349 claims 1-7 (vertebrate cells for producing EPO and process for using same) fall within the scope of Group IV — "Claims 42-46, drawn to cells, classified in Class 435, subclass 240" — and do not fall within the scope of Group II, "drawn to DNA."

D. THE '422 CLAIMS FALL WITHIN RESTRICTION GROUP V

31. Each of the claims of the '422 patent is directed to an EPO pharmaceutical composition. Having compared the claims of the '422 patent to the claims in the '298 application that were assigned to the various restriction groups in the July 1986 restriction requirement, from the perspective of one of ordinary skill in the art, it is my opinion that the '422 claims fall within the scope of restriction Group V, "drawn to pharmaceutical composition." None of the claims of the '422 patent cross the line of demarcation drawn around restriction Group II, "drawn to DNA."

32. As shown in the table attached as Exhibit D-4, consistent with the original claims assigned to restriction Group V, '422 claim 1 is drawn to a pharmaceutical composition comprising human EPO. '422 claim 1 does not include any limitation concerning or invoking the purified or isolated EPO DNA of restriction Group II. This is confirmed by the Federal Circuit's holding that '422 claim 1 is infringed by a pharmaceutical composition comprised of human EPO produced by a process using "gene activated" EPO DNA, wherein the EPO DNA was never purified or isolated. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F3d. 1313, 1348-49 (Fed. Cir. 2003). The limitation "purified from mammalian cells grown in culture" was

not present in the original claims assigned to restriction Group V in the '298 application. This subject matter, however, bears no relationship to the EPO DNA and transfected host cell subject matter of restriction Group II.

33. '422 claim 2 is also drawn to a pharmaceutical composition comprising human EPO consistent with the original claims assigned to restriction Group V. The limitation "wherein human serum albumin is mixed with said erythropoietin" was not present in the original claims assigned to restriction Group V in the '298 application. This subject matter, however, bears no relationship to the EPO DNA and transfected host cell subject matter of restriction Group II.

34. Thus, based on my substantive analysis of the claims, it is my opinion that an ordinarily skilled artisan would recognize and understand that the '422 claims (pharmaceutical compositions) fall within the scope of restriction Group V — "Claims 55-57, drawn to pharmaceutical composition, classified in Class 435, subclass 177" — and do not fall within the scope of restriction Group II, "drawn to DNA."

II. A PERSON OF ORDINARY SKILL IN THE ART WOULD NOT HAVE FOUND THE CLAIMS OF THE PATENTS-IN-SUIT TO BE OBVIOUS IN LIGHT OF CLAIM 10 OF THE LAI '016 PATENT GIVEN THE STATE OF THE ART, THE LACK OF REASONABLE EXPECTATION OF SUCCESS, AND MATERIAL DIFFERENCES IN THE CLAIMED INVENTIONS

A. THE APPROPRIATE LEGAL TEST

35. I have been instructed that there are two legal tests for obviousness-type double patenting that may be applied to determine whether the claims of the patents-in-suit are patentably distinct from the claims of U.S. Patent No. 4,667,016 ("the Lai '016 patent"). I have

been instructed that, under the "one-way" double patenting test, the claims of the patents-in-suit are patentably distinct from the claims of the Lai '016 patent unless they would have been obvious to a person of ordinary skill in the art in light of the claims of the '016 patent, at the time of the inventions claimed in the patents-in-suit. I am further informed that, under the "two-way" double patenting test, the claims of the patents-in-suit are patentably distinct from the claims of the Lai '016 patent unless (1) they would have been obvious to a person of ordinary skill in the art in light of the claims of the '016 patent, at the time of the inventions claimed in the patents-in-suit, and (2) the claims of the '016 patent would have been obvious to a person of ordinary skill in the art in light of the claims of the patents-in-suit, at the time of the '016 inventions.

36. I have been asked to consider whether the claims of the patents-in-suit are invalid for obviousness-type double patenting over the claims of the Lai '016 patent under both the "two-way" and "one-way" tests. As discussed below, under both tests, I find that the claims of the patents-in-suit are patentably distinct from the claims of the Lai '016 patent, and are therefore not invalid for obviousness-type double patenting over the Lai '016 claims.

B. CLAIM 10 OF THE LAI '016 PATENT

37. Claim 10 of the Lai '016 patent states:

> 10. A process for the efficient recovery of recombinant erythropoietin from a mammalian cell culture supernatant fluid, said process comprising the following steps in sequence:
>
> (1) subjecting the fluid to ion exchange chromatographic separation at about pH 7.0, thereby to selectively bind erythropoietin in said sample to a DEAE agarose cationic resin;

(2) stabilizing materials bound to said resin against degradation by acid activated proteases through treatment with urea;

(3) selectively eluting bound materials having a pKa greater than that of erythropoietin by treatment with aqueous acid at a pH of about 4.3.

(4) selectively eluting erythropoietin by treatment with an aqueous salt at a pH of about 7.0;

(5) subjecting erythropoietin-containing eluent fractions to reverse phase liquid chromatographic separation involving an immobilized C4 resin, thereby to selectively bind erythropoietin in said fluid to said resin;

(6) selectively eluting bound erythropoietin from said resin with an aqueous ethanol solution of about 60 percent at a pH of about 7.0; and,

(7) isolating erythropoietin-containing fractions of the eluent.

38. Importantly, '016 claim 10 recites a process for purifying erythropoietin produced in an unspecified way, but the claim is not itself a process for the production of erythropoietin. Therefore, a person of ordinary skill in the art would not have looked to Claim 10 of the '016 patent to prepare an *in vivo* biologically active erythropoietin because it provides no indication of how to do so. For this reason, it is nonsensical to consider the purification procedure of '016 claim 10 as a basis for obviousness of a process of preparing "recombinant erythropoietin," or of an *in vivo* biologically active erythropoietin product. In fact, '016 claim 10 does not even acknowledge the importance of *in vivo* biological activity, let alone recite how to make an erythropoietin glycoprotein possessing it.

39. I also note that '016 claim 10 does not mention many of the characteristics of Dr. Lin's inventions claimed in the patents-in-suit. '016 claim 10 does not mention: the steps to take for the production of an *in vivo* biologically active erythropoietin glycoprotein; the structure of any mammalian host cells that might be used for such production; any *in vivo* biologically active

erythropoietin glycoprotein products; any pharmaceutical compositions prepared from those products; or any methods of treatment using those products. '016 claim 10 simply describes a seven-step procedure for the purification of recombinant erythropoietin from a cell culture supernatant.

40. The '016 patent was filed in June of 1985 and claims a method for purifying EPO. This method is just one of many ways to purify EPO. For example, Miyake, Kung, and Goldwasser published a technique to substantially purify urinary EPO in 1977.[9] Likewise, the Lin patent specification also teaches a method for purifying recombinant EPO:

> The productivity of the EPO producing CHO cell lines described above can be improved by appropriate cell culture techniques. The propagation of mammalian cells in culture generally requires the presence of serum in the growth media. A method for production of erythropoietin from CHO cells in media that does not contain serum greatly facilitates the purification of erythropoietin from the culture medium. The method described below is capable of economically producing erythropoietin in serum-free media in large quantities sufficient for production.[10]
>
> Mammalian cell expression products may be readily recovered in substantially purified form from culture media using HPLC (C4) employing an ethanol gradient, preferably at pH7.[11]

41. Serum-free production as disclosed by Dr. Lin was an important advance for purifying EPO for use in pharmaceutical compositions. Mammalian cells are usually grown in growth medium containing about ten percent serum from animals (e.g., fetal calf serum). The serum in the growth medium contains a complex mix of proteins and other biomolecules,

---

[9] Miyake *et al.*"Purification of Human Erythropoietin," *J. Biol. Chem.* Aug. 10 252(15):5558-64 (1977) (Exhibit E-4).

[10] '933 Patent, col. 27:8-16 (Exhibit E-5).

[11] '933 Patent, col. 28:29-32 (Exhibit E-5).

including particular growth factors that are necessary for the health and growth of the cultured cells.

42. The high-pressure liquid chromatography "HPLC (C4)" step disclosed in Dr. Lin's specification is one of the steps in the multi-step procedure claimed in the '016 patent.

43. Purification of biomolecules such as proteins was a relatively straightforward technique in 1983. Many different techniques and strategies were well-known in the art. I agree with the characterization found in the background section of the '016 patent:

> Numerous techniques have in the past been applied in preparative separations of biochemically significant materials. Commonly employed preparative separatory techniques include: ultrafiltration, column electrofocusing, gel filtration, electrophoresis, isotachophoresis and various forms of chromatography. Among the commonly employed chromatographic techniques are ion exchange chromatography and adsorption chromatography.[12]

C. THE '016 CLAIMS DO NOT RENDER THE CLAIMS-IN-SUIT INVALID FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

1. The claims-in-suit are not invalid under the one-way test

44. The term "recombinant erythropoietin from a mammalian cell culture supernatant," which appears in '016 claim 10, ***standing on its own*** teaches nothing about the production of recombinant EPO from mammalian cells. Such an assertion would absurdly denigrate Dr. Lin's achievements. Many entities, including Genetics Institute, Biogen, Genentech, and academic scientists had the wish of producing "recombinant erythropoietin from a mammalian cell culture supernatant" but Dr. Lin was the first to achieve this long-desired and important advance. In order for such an assertion to hold, it would also have to be true that Dr. Lin's cloning of the EPO gene and expression of *in vivo* biologically active EPO was obvious in

[12] '016 Patent, col. 1:15-23 (Exhibit E-3).

light of the prior art. In my opinion, and as has been found by many courts, Dr. Lin's inventions were not obvious.

45. When Dr. Lin began his efforts to produce *in vivo* biologically active EPO using recombinant DNA techniques, he faced a daunting array of difficult problems. The DNA sequence of the EPO gene was unknown. The amino acid sequence of EPO was unknown. The particular cells in the kidney that made EPO were unknown. The post-translational modifications to EPO that might occur when produced in the human body were unknown. Additionally, the glycosylation structure of EPO was unknown. The EPO receptor was not known. The minute amounts of EPO protein available to study came from urine, and consequently, might vary significantly from natural, biologically active EPO protein found in the bloodstream.

46. Recombinant expression of biologically active human glycoproteins in cultured, mammalian cells was still in its infancy. In fact, prior to 1984, no one had reported successful production of any *in vivo* biologically active human glycoprotein in cultured mammalian cells. Scientists understood that glycosylation potentially played an important role in the function of glycoproteins like EPO, but they did not understand how EPO was glycosylated in the body, nor could they predict whether differences in glycosylation caused by production in different cell types might result in biologically inactive EPO.

47. To successfully produce *in vivo* biologically active recombinant EPO for the first time in history, in the midst of this uncertainty, it was necessary to, among other things: (a) "clone" the EPO gene by discovering its DNA sequence, (b) discover and select cell types that could successfully produce biologically active EPO in sufficient quantities for administering to patients, (c) genetically engineer and modify such cells to express biologically active EPO, and

(d) validate that the cells actually produced sufficient quantities of *in vivo* biologically active EPO. Each of these successive inventions was necessary to develop a protein that could be administered to patients to treat anemia. None of these inventions, standing alone, were sufficient to achieve that result.

48. With regard to the invention of the Lai '016 patent, I find the analogy made by Amgen's counsel during examination of the '933 patent particularly apt: "a method of purifying recombinant EPO cannot be modified to produce recombinant EPO any more than a method of washing a car can be modified to make a car."[14] The method of purifying EPO claimed in claim 10 of the Lai '016 patent presumes the availability of erythropoietin as a starting material, just as the invention of the automated car wash presumed the availability of cars to wash. Neither method teaches how to make the necessary starting material, whether EPO polypeptide or cars; they rely on the fact that someone else has already invented what is needed to practice the method.

49. Without the teachings of Dr. Lin's patents, the Lai '016 patent's method for purifying "recombinant erythropoietin from a mammalian cell culture supernatant fluid" is a mere hope or wish, as is "a method for purifying a drug which cures all forms of cancer" or "a method for washing a car that gets 200 miles per gallon." In order to have any hope of practicing claim 10 of the '016 patent one would have needed:

- The EPO protein sequence
- The EPO DNA
- The structure of the EPO gene
- DNA constructs designed to express EPO

[14] 1/11/90 Amendment Under Rule 116, at p.4 (Exhibit E-6).

- Transformed or transfected host cells capable of producing EPO protein in large quantities
- A means for growing the cells

50. None of these are taught by, or even implicit in, the '016 claim 10 claim language "recombinant erythropoietin from a mammalian cell culture supernatant fluid."

51. The question that resolves the issue of whether the claims of Dr. Lin's patents-in-suit are obvious in light of '016 claim 10 is: would '016 claim 10 render an ordinarily skilled artisan in 1983-84 — operating without the benefit of the teachings of the Lin or Lai patent specifications — any closer to achieving the products claimed in the '933 and '422 patents, or the processes claimed in the '868, '698, and '349 patents than she would have been otherwise? For the reasons explained above, it is my opinion that it clearly would not. In other words, '016 claim 10 would not provide an ordinarily skilled artisan a reasonable expectation of success in practicing Dr. Lin's claimed inventions. Since the '016 patent claims could not provide an ordinarily skilled artisan with the limitations of the claims-in-suit, nor instruct the artisan how to practice the claims-in-suit, the Lai '016 claims simply cannot render the claims-in-suit invalid for obviousness-type double patenting under the one-way double patenting test.

52. Further to my more general analysis, a comparison of '016 claim 10 to the claims in suit further establishes that there are significant differences between the claims that preclude a finding of obviousness-type double patenting.

53. The asserted claims of the '933 patent are each significantly different than '016 claim 10 because they each depend on claim 3, and thus specify: (1) a particular process of production of the erythropoietin glycoprotein, and (2) that the erythropoietin glycoprotein have a specific *in vivo* biological activity. Moreover, the dependent claims have further limitations that are also not suggested by '016 claim 10, col. 7:15-8:22 (Exhibit E-3):

- '933 Claim 7: additionally requires that the EPO glycoprotein be produced in a non-human mammalian cell.
- '933 Claim 8: additionally requires that the EPO glycoprotein be produced in a CHO cell.
- '933 Claims 9 and 12: additionally require that the EPO glycoprotein be part of a pharmaceutical composition.
- '933 Claims 11 and 14: additionally require that the EPO glycoprotein pharmaceutical composition be effective in increasing the hematocrit of kidney dialysis patients.

54. The asserted claim of the '422 patent is significantly different from '016 claim 10 because it specifies: (1) a human EPO pharmaceutical composition, and (2) that the erythropoietin be therapeutically effective.

55. The asserted claims 1 and 2 of the '868 patent are each significantly different from '016 claim 10 because each specifies: (1) a particular process for production of the erythropoietin glycoprotein in a host cell with a specific structure, and (2) that the erythropoietin glycoprotein have a specific *in vivo* biological activity. Moreover, dependent claim 2 has the further limitation of production in a CHO cell that is not suggested by '016 claim 10, col. 7:15-8:22 (Exhibit E-3).

56. The asserted claims of the '698 patent are each significantly different from '016 claim 10 because they each specify: (1) a particular process of production of the erythropoietin glycoprotein requiring vertebrate host cells with specific genetic structures (claim 4: an operatively linked non-EPO promoter, claim 6: amplified EPO DNA), and (2) that the erythropoietin glycoprotein have a specific *in vivo* biological activity. Moreover, the dependent claims have further limitations that are not suggested by '016 claim 10, col. 7:15-8:22 (Exhibit E-3):

- '698 Claim 5: additionally requires that the promoter DNA be viral promoter DNA.

- '698 Claim 7: additionally requires that there be amplified marker DNA in the host cell.
- '698 Claim 8: additionally requires that the amplified marker DNA be the DHFR gene.
- '698 Claim 9: additionally requires that the host cells be mammalian host cells.

57. Asserted claim 7 of the '349 patent is significantly different from '016 claim 10 because it specifies: (1) a particular process of production of the erythropoietin glycoprotein requiring host cells with specific genetic structures, and (2) that the erythropoietin glycoprotein be produced to certain high levels.

58. Furthermore, although I have been informed that the Examiner of the '178 application that issued as the '868 patent stated that the pending method (claims 70 and 71) "is an obvious variation of the process of Lai *et al.*," I disagree with the Examiner's (unsupported) conclusion. Claims 70 and 71 of the '179 application had no more subject matter in common with Lai than any of the issued claims that I have analyzed above. Claim 70 was identical to issued '868 claim 1. Claim 71 only differed in the description of the DNA that was transformed or transfected into the host cell. Thus my basic premise that the vague wishful language of Lai '016 claim 10 "recombinant erythropoietin from a mammalian cell culture supernatant fluid" no more describes or suggests these pending claims than any of the issued claims.

2. The claims-in-suit are not invalid under the two-way test

59. I understand that under the two-way test, there would be no obviousness-type double patenting if ***either*** (1) Dr. Lin's claims-in-suit would have been not obvious in light of Lai's claim 10, ***or*** (2) Lai's claims would have been not obvious in light of Dr. Lin's claims. I have already explained above why Dr. Lin's claims-in-suit would have been not obvious in light

of Lai's claim 10. It is also my opinion that Lai's claims would have been not obvious in light of Dr. Lin's claims.

60. As I have shown above, '016 Claim 10 is to a seven step procedure for the purification of "recombinant erythropoietin from a mammalian cell culture supernatant fluid." Of Dr. Lin's claims, only '422 claim 1 directly references the term "purified": "said erythropoietin is ***purified*** from mammalian cells grown in culture." This claim clearly does not make any reference to any specific purification technique. Nor does the specification specially define "purified" or "purification" to mean any particular technique, instead allowing isolation and purification by conventional means: "Isolation and purification of microbially expressed polypeptides provided by the invention may be by conventional means including e.g., preparative chromatographic separations and immunological separations involving monoclonal and/or polyclonal antibody preparations."[15] A number of the claims-in-suit use the closely related term "isolating," such as '698 claim 4: "b) isolating said glycosylated erythropoietin polypeptide expressed by said cells."[16] Dr. Lin's claims that use the term "isolating" also do not specifically define it or identify any particular technique. There are no other terms in any of Dr. Lin's claims-in-suit that address the seven particular steps recited by Lai '016 claim 10 in any way.

61. In my opinion, Dr. Lin's claims-in-suit would not have rendered Lai '016 claim 10 obvious. As I have explained, Dr. Lin's claims do not suggest or explain the particular combination of elements of different purification techniques that define Lai '016 claim 10. Reading Dr. Lin's claims-in-suit would have not provided the ordinarily skilled artisan with ***any*** teaching or information that was missing from the prior art. The Lai claims were issued by the

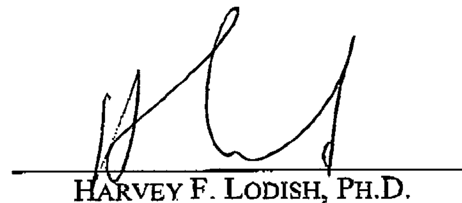
---

[15] '933 Patent, col. 11:14-19 (Exhibit E-5).

USPTO who examined them in light of this prior art. Finally, nothing about Dr. Lin's claims would have provided an ordinarily skilled artisan with a reasonable expectation of success in practicing Lai '016 claim 10.

62. I declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both (18 U.S.C. § 1001).

Executed this 13th day of June, 2007.



HARVEY F. LODISH, PH.D.

[16] *See also* '698 Claim 6 and '868 Claim 1 (Exhibit E-5).