

Exhibit 1

1805 #28

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



Applicant : F.K. Lin
Serial No. : 07/113,179
Filed : October 23, 1987
Title :

Art Unit:
Examiner:

Handwritten initials and numbers

Commissioner of Patents and Trademarks
Washington, DC 20231

PROTEST BY POR-HSIUNG LAI
REGARDING INVENTORSHIP UNDER 37 C.F.R. SECTION 1.291

I, Por-Hsiung Lai, hereby declare:

1. Although my name is not listed as an applicant, I am indeed a co-inventor of the subject matter of the above-captioned application concerning a process for the preparation of the recombinant version of human erythropoietin (EPO) for the reasons stated below.

2. I was employed by Amgen, Thousand Oaks, CA, from October, 1982 to September, 1987, initially as a Research Scientist, and later, became Head, Protein Development in charge of protein structural chemistry and protein formulation.

3. My contributions to the subject matter of this application include (a) design of key protein chemistry approaches to obtaining previously unknown EPO protein structure, e.g., fast tryptic digestion of urinary EPO which gave the desirable EPO peptide fragments; (b) development of novel protein microsequencing

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techniques necessary for working with minutely available proteins such as urinary EPO and its tryptic fragments; (c) precise selection, from the EPO tryptic peptides, of the EPO fragments, T-35 and T-38 based on their HPLC profiles as the first two fragments for structural studies; (d) successful determination of the amino acid sequences of EPO T-35 and T-38 fragments, and suggestion of use of these critical, essential EPO protein sequence information for the construction of DNA probes which were required for cloning of the EPO genes; and (e) elucidation of the previously unknown sequence of the EPO protein structure which was also used for confirming the complete EPO gene structure. These contributions are evidenced by the documents collectively attached hereto as Exhibit A.

U.S. Patent no. 4,703,008 (the '008' patent), a case from which this application claims priority, is the subject matter of a legal action decided by the court of Appeals Federal Circuit. Amgen Inc. v. Chugai Pharmaceutical Co., Ltd., 18 USPQ2d 1016, 1021-22 (CAFC 1991). According to the Federal circuit, "[B]ased on the uncertainties of the method and lack of information concerning the amino acid sequence of the EPO protein, the trial court was correct in concluding that neither party had an adequate conception of the DNA sequence until reduction of practice had been achieved; Lin was first to accomplish that goal (emphases added)." [Id. at 1021-22 (CAFC 1991)], attached hereto as Exhibit B. Similarly, the Board of Patent Appeals and Interference has subscribed to a judicial conclusion that "[k]nowledge of appropriate erythropoietin amino acid sequence is necessary for complete conception of subject invention (emphases added),..." [21 USPQ2d at 1731, Erisch v. Lin, (BPAI 1991)], attached hereto as Exhibit C.

Note that the amino acid sequencing work was performed under my supervision, not Dr. F.K. Lin's. Dr. Lin's field of expertise was not related to protein structural researches, in particular, not related to protein sequence analysis. Dr. Lin's lack of knowledge of protein sequencing was evidenced by his incorrect testimony for



the US International Trade Commission case, Amgen Inc. v. Chugai Pharmaceutical Co., Ltd., Investigation No.337-TA-281. At the Findings of Fact No. 179, Dr. Lin testified that "A sequencing machine determines the amino acid sequence of the proteins. The machine will analyze the amino acid sequence starting at the first amino acid at the N-terminal of the protein. The machine identifies each amino acid using chromatography techniques." (Lin, Tr. 307-310). This testimony is incorrect. In September-October, 1983 when the EPO gene was successfully cloned at Amgen, no on-line PTH-amino acid analysis by HPLC was available for a sequencing machine. Therefore, the machine could not identify each amino acid using chromatography techniques. The machine only removed amino acid residues from a peptide/protein, sequentially, one by one, step by step. Subsequent identification of the PTH-amino acids by an HPLC machine was then performed separately.

In fact, I was instrumental in the discussion with Dr. Goldwasser about his supplying, to Amgen, of the EPO tryptic fragments in August 1983 for sequence analysis. Dr. Lin was not involved in the planning of these activities as evidenced by Dr. Vapnek's memo dated August 2, 1983 attached hereto as Exhibit D. The decision on selection of the critical EPO fragments, T-35 and T-38, for sequence analysis was also made by myself after I received the set of EPO fragments from Dr. Goldwasser's postdoctor, Dr. Wang on August 31, 1983 and reviewed the HPLC profile of the fast tryptic digest of EPO. This is evidenced by Dr. Wang's and my own lab note records attached hereto as Exhibits E and F, respectively. These evidences contradict Dr. Lin's testimony. Dr. Lin had falsely testified at the District Court case (District Court D. Massachusetts, Amgen Inc. v. Chugai Pharmaceutical Co., Ltd.) that he was the one who obtained additional tryptic EPO fragments from Goldwasser at the end of August 1983 (Tr. 4, 59). 13 USPQ2d at 1747 (attached hereto as Exhibit G). Dr. Lin also provided false information that had misled the court to conclude that "Dr. Lin was the one who selected the T-35 and T-38 fragments, designed the probes based on sequence

information obtained by his assistant Por Lai, under his direction, and screened the library (emphases added)." 13 USPQ2d at 1777 (attached hereto as Exhibit H). As shown by the dates of sample processing (090183 for #35, and 090683 for #38) recorded in Exhibit F, T-35 (#35) and T-38 (#38) were the first two fragments selected from the fragment set by myself, not by Dr. Lin, for sequence analysis. Immediately after I obtained the critical EPO amino acid sequence results using T-35 and T-38 fragments on September 2, 1983 and September 13, 1983, respectively, I gave these results to several Amgen people including Dr. Lin for probe construction (as shown in Exhibit A). Indeed, as evidenced in the documents attached hereto as Exhibit I, construction of the EPO DNA probes, i.e., EpV (V, single letter code for valine, stands for the N-terminal amino acid, Valine, of T-35) which is based on T-35, and EpQ (Q, single letter code for glutamine, stands for the N-terminus of the hexapeptide located in T-38) which is based on T-38, immediately began on September 2 and September 14, 1983, respectively. Furthermore, the statement that I was Dr. Lin's assistant, under his direction is simply untrue. I have never been Dr. Lin's assistant, or under his direction. Dr. Lin's only assistant was Chi-Hwei Lin as he had testified [(Tr. 4, 67), 13 USPO2d at 1746] (attached hereto as Exhibit J).

Dr. Lin further falsely testified at the District Court case that "He was project leader of the EPO project from 1981 through 1984" (Tr. 4, 46; 6, 66). Id. at 1746 (see Exhibit J). This untrue testimony had misled the district court to conclude that "In any event, Dr. Lin was the head of the EPO project at Amgen through 1984 with supervisory power over all aspects of the invention." Id. at 1761 (attached hereto as Exhibit K). In fact, the project leader of the EPO project at Amgen during the March 1983 - mid-1984 time frame was Dr. Vapnek, then Amgen's Director of Research, not Dr. Lin. This was evidenced by a number of documents attached hereto collectively as Exhibit L. In fact, Dr. Vapnek took over the EPO project leadership in early 1983, after Dr. Lin's failure to clone the EPO gene during August 1981-February

1983 due to lack of the necessary EPO amino acid sequence information. Dr. Vapnek had continued as the leader until late 1984 when the EPO project was split into two teams, namely, EPO Product Project Team and EPO Research Project Team. It should be mentioned that Amgen successfully cloned the EPO gene around September-October, 1983 when Dr. Vapnek was indeed the project leader. Why did Dr. Lin falsely testify that he was the EPO project leader from 1981 through 1984?

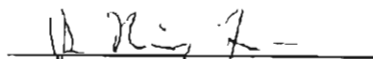
Based on my contribution in providing the critical EPO amino acid sequences, I am indeed a co-inventor of the subject matter claimed in the '008' patent. In fact, Amgen had also publically acknowledged, in its 1984 Annual Report, attached hereto as Exhibit M, that "Our isolation of the previously elusive EPO gene was made possible through superior protein microsequencing and proprietary genetic probe technology.", and that "Advanced microsequencing and other proprietary Amgen technology led to the isolation, cloning and expression of human erythropoietin." Since what is claimed in the above-captioned application is derived from that in the '008' patent, I am therefore also a co-inventor of the subject matter in the present case. Correction of the inventorship is hereby requested.

4. Sometime in 1985, soon after I learned that Dr. Lin was the sole inventor of the patent application concerning EPO gene cloning, I verbally questioned Dr. Vapnek, Dr. N. Stebbing (VP, Scientific Affairs, then my supervisor) and Mr. R. Weist (VP, Legal), about the merit of the sole inventorship, and was given no answer. Since then, I have made numerous correspondences to Amgen requesting correction of the inventorship of the '008' patent to include me as a co-inventor. Amgen has either rejected or ignored my requests. Although in a meeting with Mr. R. Weist, Mr. S. Odre and Dr. Vapnek on May 3, 1988, Mr. Weist, who departed from Amgen later, did mention the consideration of including me as a co-inventor in a separate EPO patent application. Examples of my related correspondence with Amgen are attached hereto as Exhibit N.

5. Attached hereto as Exhibit O to present more evidence of erroneous inventorship are the following documents: (1) a listing of publications and other information; (2) an explanation of the relevance of each listed item; and (3) a copy of each listed publication and other information. [Some of the documents in Exhibit O have been presented in Exhibits A through N.]

6. I hereby state that a copy of this protest, as well as all attachments thereto, has been served on Mr. Michael F. Borun of Marshall, O'Toole, Gerstein, who represents Applicant F.K. Lin, and Mr. Steve M. Odre of Amgen, on July 22, 1993 by Express Mail, mailing label number being IB 55000219X and IB 550002200, respectively.

7. All statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further 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, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.



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