EXHIBIT F

30

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#30

Applicant(s): LIN, F.

Serial No.: 07/113,178

Filed: 10/23/87

Title: PRODUCTION OF ERYTHROPOIETIN

Group Art Unit: 186

4300

Board of Int.

NOTICE OF CHANGE OF ADDRESS

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

RECEIVED
MAR 19 1993
GROUP 130

Sir:

Please note the new firm name, address and telephone number for the undersigned attorney of record effective March 1, 1993:

Marshall, O'Toole, Gerstein, Murray & Borun
6300 Sears Tower
233 South Wacker Drive
Chicago, IL 60606-6402

Telephone: (312) 474-6300

Correspondence in this application should be directed to the undersigned at the new address effective March 1, 1993.

Respectfully submitted,

MARSHALL, O'TOOLE, GERSTEIN,
MURRAY & BICKNELL

Date: February 22, 1993

Michael F. Borun
Registration No. 25,447
Attorney for Applicant(s)

Two First National Plaza
Chicago, Illinois 60603
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CP181 #31 12/14/93

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	F.K. Lin	Art Unit:
Serial No.	:	07/113,178	Examiner:
Filed	:	October 23, 1987	
Title	:		

812 187

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 recombinant analog 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

"Express Mail" mailing label number IB 550002156
Date of Deposit: July 23, 1993
I hereby certify under 37 CFR 1.10 that this correspondence is being deposited with the United States Postal Service as "Express Mail Post Office to Addressee" with sufficient postage on the date indicated above and is addressed to the commissioner of Patents and Trademarks, Washington, D.C. 20231.

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, Frisch 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 USPQ2d 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 publicly 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 550002167 and IB 550002178, 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.

Name: Por-Hsiung Lai

Address:

2001 Richard Drive
Broomall, PA 19008-2742

Date: July 23, 1993

EXHIBIT A

TITLE First Tryptic Digestion of EPO, E.G. Project No.____

From Page No.__ K No.____

083183 Received 15 Fractions from E.G. and a chromatogram of #21, 18, 16, 13, 4 (#13 = RP HPLC of the ...
#39, 38, 35, 33, 31

PLF______ DEFT ✓ #30, 28, 27, 26, 25

EXHIBIT 15.1 DATE 5/8/02

JOAN LAVALLEY

Tryptic fragments were obtained from 20 nmoles of intact EPO with trypsin
EPO: 120 µg ≈ 3.75 nmoles

090183 #35 which does not contain any ^3H radioactivity.
20% to be sequenced 20 µl / 5 µl H₂O + 5 µl HCOOH

090583 #38 30 µl / 5 µl H₂O + 5 µl HCOOH sequenced

090783 #31 30 µl / 5 µl H₂O + 5 µl HCOOH

26 091183
33 091483 70%
30 091683 24%

091383 #26 30 µl / 5 µl + 5 µl HCOOH

091483 #33 30 µl / 5 µl + 5 µl HCOOH

091683 #30 20 µl / 5 µl H₂O + 5 µl HCOOH

100783 #28 30 µl / 5 µl H₂O + 5 µl HCOOH

101083 #27 30 µl / 5 µl H₂O + 5 µl HCOOH

101983 #21 30 µl / 5 µl H₂O + 5 µl HCOOH

102083 #16 30 µl (5 µl H₂O + 5 µl HCOOH

102383 #13 30 µl / 5 µl H₂O + 5 µl HCOOH

102583 #18 30 µl / 5 µl H₂O + 5 µl HCOOH

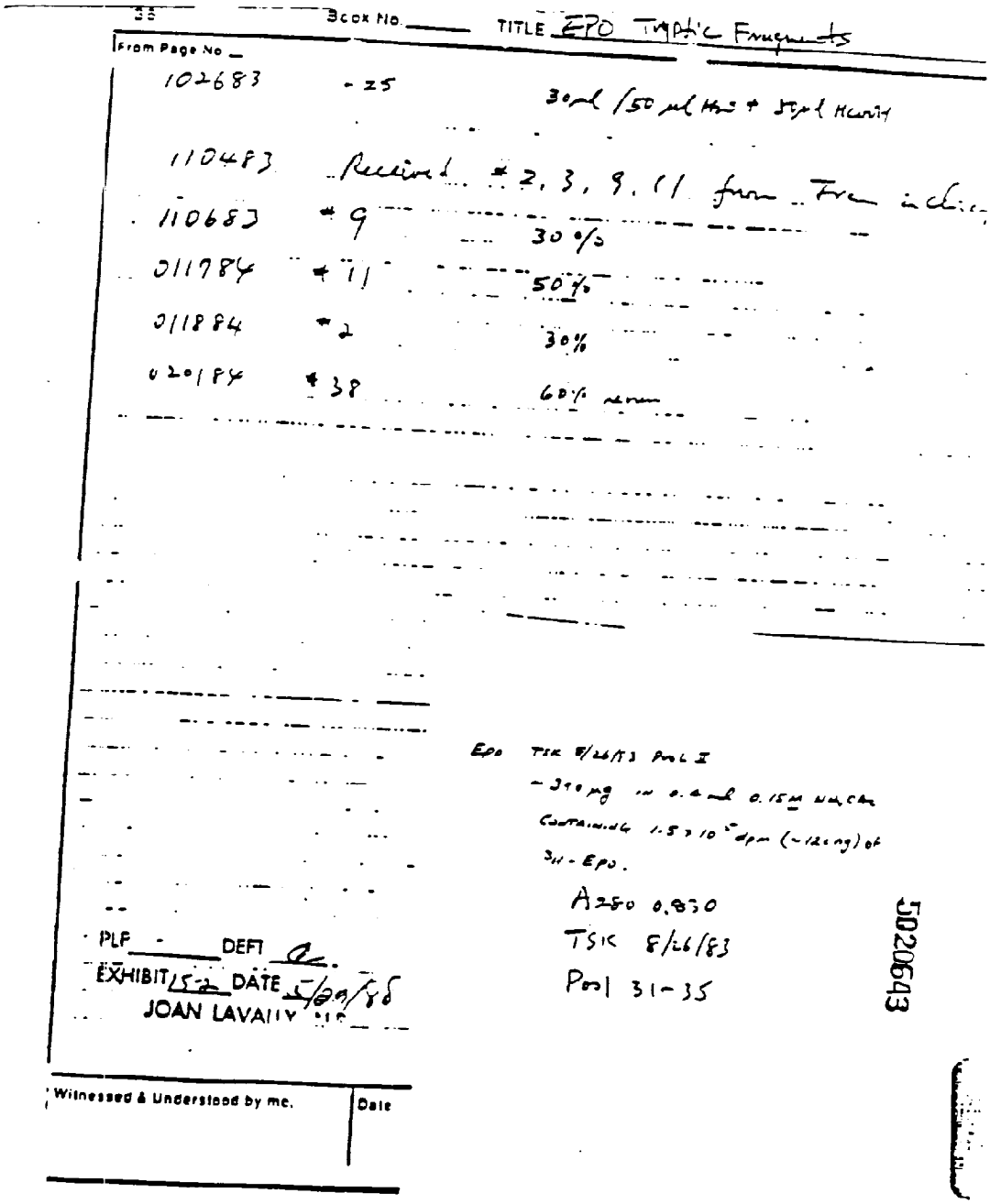
Witnessed & Understood by me.	Date	Invented by	Date
		Recorded by [signature]	10-25-83

To Page No.__

1-2

DEFENDANT'S DEPOSITION EXHIBIT LDX-36 2-8-01

302



38 Book No. ____ TITLE EPO Tryptic Fragments

From Page No. ____

102683 - 25 30ml /50 ml Hex + Styrl Hexane

110483 Received #2, 3, 9, 11 from Fran in clinic

110683 #9 30%

011784 #11 50%

011884 #2 30%

020184 #38 60% serum

EPO TSK 8/26/83 Pool II
~300 mg in 0.4 ml 0.15M NH4Cl
Containing 1.5 x 10^8 dpm (~12 mg) of
3H-EPO.
A280 0.830
TSK 8/26/83
Pool 31-35

5020643

PLF ____ DEFT ____
EXHIBIT 15-2 DATE 5/20/88
JOAN LAVALLY

Witnessed & Understood by me. | Date

303

Sample Number P3183 #35 Sample submitted by E. G.

Laboratory _____ Phone Ext. _____ Date 09028?

Sequence analyzed by RE/PHL Report prepared by PHL

Amount of sample sequenced 10% nmoles _____ ug

Total cycles run 22

Manual sequencing _____ Automatic sequencing AOI 470A

Pretreatment at protein laboratory Protocol before sample loading.

Amino acid sequence via HPLC 1 2 3 4 5 6 7
V-N-F-Y-A-W-K

@ The residue before V may be Arg or Lys.

Amino acid sequence via other methods _____

CONFIDENTIAL BUSINESS INFORMATION
SUBJECT TO PROTECTIVE ORDER

Comments on sequence analysis No questions could be answered after 7.

Comments on sample preparation This sequence information is only distributed to F.K. Lin, F. Martin, D. Vapnek. If not necessary, please don't identify source of sequence

DEFT
EXHIBIT 9 DATE 5-22-98
JOAN LAVAILY, NP

HPLC chromatograms attached? ____ yes ✓ no

DEFENDANT'S DEPOSITION EXHIBIT LDX-38 1-8-90 DM

304

AMINO ACID SEQUENCE REPORT

Sample Number 083/83-38 Sample submitted by E.G AMGen

Laboratory _____ Phone Ext. _____ Date 09/13/83

Sequence analyzed by RE/PHL Report prepared by PHL

Amount of sample sequenced 30 nMoles Pmoles
nmoles _____ ug
mg

Total cycles run 29

Manual sequencing _____ Automatic sequencing ABI 470A

Pretreatment at protein laboratory Sample was dissolved in 100 uL of solubilizing solvent, 50uL were injected Sequenced

Amino acid sequence via HPLC G-Q-A-L-L-V-X-S-S-Q-P-W-E-P-L-Q-X-X-

Trp 2 4 Cl. 4

X: unidentified residues. #: residue 7 may be Asn. Q: Offline Residue 16 no amino acid assigned can be confirmed.

Amino acid sequence via other methods _____

Comments on sequence analysis ① This sequence contains the second Trp residue identified ② Unambiguous sequence analysis ③ Sequence information is distributed to F.K. Lin, J. Eppler, and D. Vapnek.

Comments on sample preparation _____ PLF DEFT d

EXHIBIT 11 DATE 5/29/98
JOAN LAVALLY, N.P.

HPLC chromatograms attached? ____ yes ✓ no available at P.S.L.

DEFENDANT'S DEPOSITION EXHIBIT LDX-40 12-8-90 MM

305

Sample Number 053183 SUMMARY Sample submitted by AMGen

Laboratory _____ Phone Ext. _____ Date 11/06/83

Sequence analyzed by DHL Report prepared by DHL

Amount of sample sequenced _____ Pmoles / nmoles _____ ug / mg

Total cycles run _____ ~1.3 nmoles

Manual sequencing _____ Automatic sequencing _____

I, N-terminal

~~Predominant or protein isolated~~ A-P-(P)-R-L-I-(N)-D-S-R-V-L-E-R-Y-L-E-A-K-E-A-E-(N)-I-T-T-G-A-(A)-H-(H)-S-L-N-N-(N)-I-T-V-P

II,

Amino acid sequence via HPLC E-A-I-S-P-D-A-A-M-A-A-P-L-R-T-I-T-D-T-E-R

III, K-A-V-S-E-L-R-(C)-A-E

IV, V-Y-S-N-F-L-R

V, N-L-S-S-L-L-R

~~Amino acid sequence via other methods~~ VI, K-V-N-F-Y-A-W-K

VII, G-Q-A-L-L-V-(N)-S-S-Q-P-W-E-P-L-Q-X-(H)-V

VIII, K-L-F-R

~~Comments on sequence analysis~~ IX, R-V-L-L-E

This is the only submitted copy of the summary
124 residues are included in this summary.

CONFIDENTIAL BUSINESS INFORMATION
SUBJECT TO PROTECTIVE ORDER

Comments on sample preparation _____

16.77 -LKMQXR- (?)

HPLC chromatograms attached? ____ yes ____ no

EXHIBIT 14 DATE 5/25/88

DEFENDANT'S DEPOSITION EXHIBIT LDX-42 11:59 AM

306