# EXHIBIT 38
# Part 1 of 2

# In The United States Patent and Trademark Office

**Before the Board of Patent Appeals and Interferences**

**Interference No. 102,334**

FRITSCH

v.

LIN

**Examiner-in-Chief Marc L. Caroff**

**BRIEF FOR THE SENIOR PARTY LIN**

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**INTERFERENCE NO. 102,334**
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## I. STATEMENT OF ISSUES PRESENTED FOR CONSIDERATION

(A) Should the interference be terminated in favor of Lin, and unfavorably to Fritsch, in view of the Federal Circuit decision which was favorable to Lin on the priority issue raised by Fritsch et al?

(B) Is Lin entitled to priority award in this interference?

(C) Are the Lin claims corresponding to the count patentable to Lin under 35 USC 102(b)?

(D) Are the Lin claims enabled by Lin's disclosure?

(E) Is Lin entitled to his earlier filing dates?

(F) Should Fritsch et al be permitted to change their inventorship?

(G) Should other Fritsch et al claims be designated as corresponding to the count?

## II. STATEMENT OF THE FACTS

### (A) The Subject Matter

The invention involved in this interference relates to in vivo biologically active recombinant human erythropoietin ("EPO") obtained by expression using a mammalian host cell transformed or transfected with an isolated DNA sequence encoding human EPO.

### (B) The Parties

This interference involves U.S. application Serial No. 06/824,688 filed on December 3, 1985 by Edward Fritsch, Rodney M. Hewick and Kenneth Jacobs ("Fritsch et al") and U.S. application Serial No. 113,178, filed October 23, 1987 by Fu-Kuen Lin. The Lin application is a division of U.S. Patent 4,703,008 (the '008 patent) which was filed on November 30, 1984. The Fritsch et al application is a continuation-in-part of Serial No. 06/693,258, filed January 22, 1985.

The Fritsch et al application is assigned to Genetics Institute, Inc. ("GI"). The Lin application is assigned to Amgen Inc. ("Amgen").

Fritsch et al have been given the benefit of Serial No. 06/693,258 and an earlier U.S. application Serial No. 688,622, filed January 3, 1985 while Lin has been given the benefit of his '008 patent filing date (November 30, 1984) and three earlier filings as follows:

U.S. Serial No. 561,024, filed December 13, 1983

U.S. Serial No. 582,185, filed February 21, 1984

U.S. Serial No. 655,841, filed September 28, 1984

Each of Lin's earlier applications is prior to the initial Fritsch et al filing (January 3, 1985) and Lin is the senior party by virtue of these earlier filings.

## (C) The Count

The interference involves a single count as set out in Appendix 1 and reading as follows:

> Count 1
>
> A non-naturally occurring glycoprotein product of the expression in a non-human eucaryotic host cell of an exogenous DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin, said product possessing the in vivo biological property of causing human bone marrow cells to increase production of reticulocytes and red blood cells and having an average carbohydrate composition which differs from that of naturally occurring human erythropoietin.

## (D) Related Interferences

There are two other closely related interferences involving the same parties. These interferences are Interference Nos. 102,096 and 102,097. The first of these interferences (No. 102,096) is directed to the purified and isolated DNA sequence encoding human EPO which is used in the process which is the subject matter of Interference No. 102,097 to produce the in vivo biologically active human EPO of the present interference. A single Rule 608(b) showing by Fritsch et al is the basis for the declaration of all three interferences.

The close relationship of these interferences is acknowledged by Fritsch et al in their briefs at final hearing herein and in Interference No. 102,097 by the statement:

> "Accordingly, as in the '096 interference, priority turns upon the first conception of the purified and isolated EPO gene".[1]

Fritsch et al thus admit that the priority issue in all three interferences is the same.

**(E) Related Litigation**

Lin's assignee (Amgen) and the Fritsch et al assignee (GI) and the latter's licensee (Chugai Pharmaceutical Co. Ltd.) have been involved in extensive litigation regarding erythropoietin. See the decision of the United States Court of Appeals for the Federal Circuit in Amgen Inc. v. Chugai Pharmaceutical Co. Ltd. and Genetics Institute, Inc., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) (hereinafter referred to as the "Federal Circuit decision"). This decision affirmed in relevant part a decision of the United States District Court for the District of Massachusetts, No. 87-2617-Y, Amgen Inc. v. Chugai Pharmaceutical Co. Ltd. and Genetics Institute, Inc., 13 USPQ2d 1737 (E.D. Mass 1989) (hereinafter the "District Court decision").

The Federal Circuit decision is thought to be dispositive of any basis for this interference as noted later.

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[1] See page 23 of Fritsch et al brief at final hearing in this interference and page 24 of Fritsch et al brief in Interference No. 102,097.

Proceedings prior to the District Court decision are briefly summarized under the heading "III Procedural History" beginning at page 1739 of the District Court decision.[2] The litigation has included action before the International Trade Commission (ITC) wherein validity of Lin's '008 patent was put in issue. The District Court and Federal Circuit decisions addressed priority and patentability issues involving Lin's '008 patent claims. These proceedings have involved many depositions and documents and extensive trial testimony. The District Court trial itself extended through 38 trial days. In both the ITC proceedings and the District Court action, invalidity and unenforceability defenses were raised against Lin's '008 patent. These defenses variously included alleged prior invention by Fritsch under 35 USC 102(g), obviousness over the prior art under 35 USC 103, failure to satisfy best mode requirements (35 USC 112) and inequitable conduct. Except for an issue of enablement with respect to Lin's claim 7, which is not relevant here, all invalidity and enforceability defenses against the '008 patent were rejected by the ITC, the District Court and most recently, the Federal Circuit. The Federal Circuit has denied rehearing and its mandate has recently issued.

The Federal Circuit decision stands as the law of the case insofar as issues decided by the Court are concerned. The Examiner-in-Chief, apparently

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[2] All page references herein to the District Court and Federal Circuit decisions are based on the 13 USPQ2d and 18 USPQ2d report, respectively.

referring to M.P.E.P. § 706.03(w), has noted this on the record (FR 1029-1030)[3] as follows:

> *... and we are bound by any decision of the Federal Circuit so that any issues here that might be identical as to ones that are decided by the Court of Appeals in the Federal Circuit would bind us as far as those issues go.*

The Federal Circuit decision is discussed in detail later in this brief. However, it is useful to preliminarily note that the Federal Circuit specifically affirmed the District Court's ruling that, in view of the state of the art concerning EPO, a conception of the purified and isolated DNA sequence encoding EPO (at issue in Interference No. 102,096, and used to obtain the product of the present count) required its reduction to practice. In other words, based on the same record before the PTO in this interference, the District Court and Federal Circuit found that Lin's conception of the invention claimed, namely, "a purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin" occurred simultaneously with reduction to practice so that there could be no conception of the sequence until it was reduced to practice. This is the controlling law on the issue of priority in this interference and the related interferences by Fritsch et al's own admission.

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[3] The references FR, FB, LR are used to refer to the Fritsch et al record, Fritsch et al brief and Lin record, respectively.

The District Court decision, which was affirmed by the Federal Circuit,[4] includes a very helpful background discussion regarding EPO (Section V, pages 1741-1745) and in Section VI (pages 1745-1754) sets out the facts relevant to the efforts by Lin (Amgen), Fritsch[5] (Genetics Institute) and others to clone and express EPO. The prior art is also discussed at pages 1753-1754. The facts as set out in the District Court decision, including the activities of Lin and Fritsch to clone and express EPO, have not been challenged and, therefore, stand established as the factual background for this interference.

The District Court decision considered in detail priority of invention as between Lin and Edward Fritsch with a holding in favor of Lin based on simultaneous conception and reduction to practice (13 USPQ2d at pages 1759-1764). This ruling was affirmed by the Federal Circuit (18 USPQ2d at 1020-1022). The District Court also considered the same question of prior conception, as proposed by Fritsch et al in this interference, that is, on the assumption that conception could occur prior to reduction to practice, and held against Fritsch based on the same facts before the PTO (pages 1762-1764). The Court further considered the question of Fritsch's diligence (assuming prior conception) and again found against Fritsch (pages 1763-1764).

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[4] Except for the District Court's ruling as to validity of Genetics Institute's Hewick et al U.S. Patent No. 4,677,195, which is not here involved.

[5] As discussed infra with respect to the deferred Fritsch et al motion to change inventorship, at trial in the District Court, Edward Fritsch's co-inventors here (Rodney Hewick and Kenneth Jacobs) were not identified as participants in the alleged prior conception (which the Courts found inadequate). One (Jacobs) did not even begin working for GI until July, 1983.

While the product of the present count was not expressly at issue in the litigation, it is clear that the product was directly involved in the priority determination. This is acknowledged by Fritsch et al in the portion quoted from their brief (FB 23), supra. It is also significant to note that the District Court's 102(g) determination addressed not only the DNA claims of the Lin '008 patent but also addressed the claims to host cell such as involved in obtaining the product of the count herein.

**(F) The Interference History**

This interference was declared after the District Court decision on the basis of the same showing under Rule 608(b) that Fritsch et al relied on in the other related interferences purporting to establish prior conception by Fritsch, based on the alleged knowledge of a probing technique, with diligence up to reduction to practice. The Rule 608(b) evidence was, for all intents and purposes, the same as that relied on by the defendants in the District Court action and rejected by both the District Court and Federal Circuit. The Federal Circuit decision regarding priority is final. Fritsch et al are now presenting the same arguments, for a third time, at final hearing.

In the declaration of the interference, Lin claims 76-83 and Fritsch et al claim 8 were identified as corresponding to the count.

The count is identical to Lin's claim 76. The other Lin claims corresponding to the count are dependent on claim 76 and specify the use of a cDNA sequence (claim 77); a genomic DNA sequence (claim 78); mammalian host cell (claim 79); or a CHO cell (claim 80); a pharmaceutical composition including the product of

claim 76 (claim 81); and a method of providing EPO therapy using the product of claim 76 (claims 82 and 83).

As the interference was declared, Fritsch et al claim 8 read as follows:

> *8. A pharmaceutical composition comprising a therapeutically effective amount of erythropoietin produced by the method of claims 2-7 in a pharmaceutically acceptable vehicle.*

However, because claims 3, 4 and 5 had been cancelled, claim 8 was amended, pursuant to the Examiner-in-Chief's decision on motions, to depend from only claims 2, 6 and 7.

Fritsch et al claims 2, 6 and 7 read as follows:

> *2. A method for the production of erythropoietin comprising culturing in a suitable medium mammalian host cells containing a DNA sequence substantially as shown in Figure 3B operatively linked to an expression control sequence, and separating the erythropoietin so produced from the cells and the medium.*
>
> *6. A method of claim 2 wherein the mammalian cells are CHO cells.*
>
> *7. A method of claim 2 wherein said DNA sequence is contained in a vector also containing bovine papilloma virus DNA.*

Fritsch et al claims 2, 6 and 7, or the equivalents thereof, correspond in essence with the Fritsch et al claims that are currently involved in Interference No. 102,097.[6] The remaining elected claims in Fritsch et al Serial No. 824,688 (claims 18-21, 23-25, 32) are drawn to the subject matter of Interference No. 102,096.

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[6] The DNA sequence called for in Fritsch et al claim 2 and mammalian cells transformed by said sequence are claimed in Fritsch et al Serial No. 06/693,258 in claims which are designated as corresponding to the count in Interference No. 102,096. See, for example, claims 46, 48, 50 and 52 in Serial No. 06/693,258.

The Fritsch et al application as placed in this interference was not subject to any substantive examination by the PTO as to the claimed subject matter corresponding to the present count. In fact, the Fritsch et al claims to recombinant EPO and pharmaceutical compositions containing the same (Fritsch et al claims 8, 13, 17 and 28-31) were non-elected in the Fritsch et al application Serial No. 824,688 here involved. The claims which were prosecuted by Fritsch et al corresponded to those prosecuted in Serial No. 693,258 which, as noted, are involved in Interferences No. 102,096 and No. 102,097. It is undisputed, however, that the recombinant product here at issue is obtained by the expression process of Interference No. 102,097 using the DNA sequence of Interference No. 102,096.

Fritsch et al filed no motions attempting to distinguish the EPO product described by their claim 8 from the EPO defined by the count. Fritsch et al also did not attempt to distinguish either their claimed DNA sequence from the DNA sequence defined by the count in Interference No. 102,096 or their expression process from the process defined by the count of Interference No. 102,097. It stands acknowledged by Fritsch et al, therefore, that their DNA sequence, expression process and recombinant EPO product correspond to the counts of the respective interferences and are the same as Lin's.

Both parties filed preliminary statements and motions. With respect to motions, Lin filed the following:[7]

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[7] The various motions are identified by number designations corresponding to those used by the Examiner-in-Chief in his decision on motions (Paper No. 42).

(1) to designate Fritsch et al claims 17 and 28-31[8] as corresponding to the count;

(2) to deny Fritsch et al benefit of Serial No. 677,813 which was filed in the name of Kaufman;

(3) to add Hewick patent 4,677,195 to the interference;

(4) for judgment of unpatentability of Fritsch et al claim 8 under (A) 35 USC 112 and (B) 35 USC 102(f);

(5) to substitute a count which omitted some unnecessary language of the existing count; and

(6) for benefit of earlier applications (contingent on granting of motion 5).

Lin also filed a contingent motion (7) for interference with the Hewick '195 patent in case his motion (3) was denied.

Fritsch et al filed the following motions:

(8) for unpatentability of the Lin claims under (A) 35 USC 102(b) and (B) 35 USC 112;

(9) to strike Lin's application for inequitable conduct;

(10) to deny Lin benefit of his earlier applications.

Other motions which were filed included a motion (11) by Lin for judgment of unpatentability of claim 8 to Fritsch et al on the basis of an apparent

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[8] These claims are set out in Appendix 2 to this brief. Fritsch claim 13 should be included with this group of claims and is also set out in Appendix 2.

admission by Fritsch et al; motion (12) by Fritsch et al to correct inventorship of the Kaufman application Serial No. 677,813; and motion (13) by Fritsch et al to correct their claim 8.

The Examiner-in-Chief (EIC), in his decision on motions (Paper No. 42), ruled as follows:

(1) Motions 4A, 6, 7, 9 and 11 were dismissed;

(2) Motions 1, 3, 5, 8(A) and (B), 10 and 12 were denied;

(3) Motion 2 was granted and motion (13) was provisionally granted subject to Fritsch et al claim 8 being amended to depend only from claims 2, 6 and 7; and

(4) Motion (4)(B) was deferred to final hearing.[9]

Of these motions, Fritsch et al are requesting reconsideration at final hearing of their motions identified as (8) and (10), i.e. patentability to Lin under Section 102(b) and Section 112 (enablement) and earlier filing date entitlement. Lin is requesting reconsideration of Motion (1), i.e., designation of Fritsch et al claims as corresponding to the count.

Both parties have presented their priority evidence in the form of deposition and declaration testimony and 37 CFR §1.682 submissions. Additionally, during their testimony time, Fritsch et al filed a motion to amend the inventorship of their application to list Fritsch as sole inventor, i.e., to delete Hewick and Jacobs as

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[9] Lin does not propose to pursue the issue raised by this motion at final hearing.

joint inventors, with a companion motion to correct their preliminary statement. Lin has opposed these motions and consideration thereof has been deferred to final hearing.

The Federal Circuit decision was issued during Lin's testimony period and pursuant to Commissioner's Memorandum and Order dated April 5, 1991, Lin filed a motion for entry of judgment in favor of Lin. This motion has been opposed by Fritsch et al and has also been deferred for consideration at final hearing.

As briefed, the case comes on for final hearing to consider Lin's motion for entry of judgment, priority, the previously denied Fritsch et al motions listed as (8) and (10) supra, relating to Section 102(b) and Section 112 patentability of Lin's claims and Lin's entitlement to his earlier filing dates. Also for consideration is the deferred Fritsch et al motion to change inventorship. An additional issue relates to the denial of Lin's motion listed as (1) supra.

**(G) Lin's Priority Evidence**

Lin accepts, for priority purposes, the District Court's undisputed summary of Amgen's activities as set out at pages 1746-1750 of the District Court decision. The District Court summary of the Lin position is quoted in Appendix 3.

Additional evidence presented on Lin's behalf includes declaration testimony by Drs. Jeff Browne, Joan Egrie, Peter Dukes, Robert Yu, their assistants (Ralph Smalling, Geri Traill, Jeri Lane, Cheryl Bradley, Curtiss Polk and Toshio Ariga), Dr. Thomas Strickland and Dr. Lin himself. These witnesses testified as follows:

**Dr. Jeffrey Browne**

Dr. Browne, an Amgen employee whose education and experience are outlined at LR 9-10 and Lin Exhibit 200, testified (LR 9-33) that he was responsible for the expression of recombinant human EPO (rHuEPO) in 293 cells, COS cells and CHO cells as set out in the District Court decision (LR 12) and that these expressions were carried out at Dr.Lin's request. He also confirmed that radioimmunoassays (RIA) were conducted which demonstrated the presence of rHuEPO in test samples of his culture medium and that Dr. Joan Egrie was responsible for confirming that the expressed product was biologically active in vitro and in vivo (LR 12).

Browne testified as to the expression work which he and his assistants (Ralph Smalling and Geri Trail) did in cultured mammalian cells at Lin's request (LR 12-27) using human and monkey EPO clones obtained from Dr. Lin. Initially, this involved using 293 and COS cells but later CHO cells were used which contained either the human or monkey EPO gene (LR 12, 13).

The first expression vector which was prepared under Dr. Browne's supervision contained Dr. Lin's monkey EPO DNA clone. This vector was introducted into in COS cells. This work was done by Ralph Smalling working under Dr. Browne's direction (LR 12, 14). Culture media from the transformed COS cells was collected and given to Dr. Joan Egrie on December 7, 1983 to analyze for the presence of EPO. Dr. Egrie reported on December 8, 1983 that the isolates designated H and L, tested positive for recombinant monkey EPO (LR 14).

Further expression work using COS cells and Lin's monkey EPO clones was carried out in December, 1983 and January, 1984 (LR 15, 16) and on January 10, 1984, Dr. Browne transfected 293 cells with a plasmid containing Dr. Lin's human EPO genomic clone HE 1, which Dr. Lin had identified as carrying the complete human EPO gene coding sequence. Media was harvested after culturing and sent to Dr. Egrie who as of January 24, 1984 reported the presence of rHuEPO in the samples (LR 16, 17). The results indicated (LR 17) that the cloned fragment provided by Dr. Lin contained the complete coding portion of the human EPO gene (LR 17, Lin Exhibit 206).

Dr. Browne and his assistant Mr. Smalling continued their expression work with the human EPO gene and 293 and COS cells in the period January 9, 1984 to February 14, 1984 sending isolates to Dr. Egrie for assay with positive results reported (LR 18-20). Expression work with CHO cells was also carried out, first with monkey EPO clone and then with the human EPO clone with the results showing in vivo biological activity for the expression products (LR 20-27). Highlights of the expression work Dr. Browne did, or which were done under his direction in the period December, 1983 to May, 1984, included the successful expression of rHuEPO using 293 cells in the period January 10-17, 1984 with Dr. Egrie reporting positive results on January 18, 1984. This followed earlier expression of monkey EPO using COS-1 cells which also were reported favorably by Dr. Egrie on December 8, 1983 (LR 28, 29; Lin Exhibit 204).

Additionally, in the period April 3, 1984 to May 22, 1984, successful expression of rHuEPO in CHO cells was carried out (LR 26, 28, 29). CHO cells were transfected with DNA from 2 isolates designated H3 and B11, both containing the complete coding

portion of the human EPO gene (LR 25-26, 986). Isolated samples of culture medium from pools of the H3 and B11 transformed CHO cells were given to Dr. Egrie (LR 988) and she reported that rHuEPO was present in the samples (LR 27-29).

Dr. Browne also testified as to the importance of carbohydrate moieties for in vivo biological activity of human EPO and his expectation that rHuEPO produced in a mammalian eucaryotic host cell would probably have a different carbohydrate composition from that of human urinary EPO (LR 30). Additionally, he noted that Dr. Egrie and others showed that as of May 1984, in vivo biologically active rHuEPO expressed in CHO cells had a different average carbohydrate composition from that of a partially purified pooled source of human urinary EPO (LR 30).

Additionally, Dr. Browne confirmed that the expressions of rHuEPO in CHO cells by May 1984 gave a product having the properties and characteristics recited in the count (LR 32). He noted that while publications refer to rHuEPO and urinary derived human EPO as similar, there are average carbohydrate differences which are discernible with sensitive analytical techniques (LR 32).

Dr. Browne's expression work is summarized in Appendix 4.

**Dr. Joan Egrie**

Dr. Egrie, an employee of Amgen with the background and experience indicated at LR 40-41 (see also Lin Exhibit 110), testified in detail (LR 40-72) and confirmed that she was responsible for the assay and determination of in vivo biological activity of the rEPO expressed by Dr. Browne as referred to in the District Court summary (LR 40,

42). She also testified that in vivo biological activity for the expressed rEPO was determined working with Dr. Peter Dukes of Children's Hospital, Los Angeles (LR 42, 43).

She knew that Dr. Lin had isolated EPO clones in late 1983 (LR 43, 44) and she was aware that Dr. Browne had been asked by Lin to use the clones for expression (LR 43, 44). She extensively discussed (LR 44-67) her assay work on rEPO samples received from Dr. Browne's group. She described the method used for determining in vivo bioactivity of recombinant human EPO expressed in COS and CHO cells (LR 50, 51). She also testified as to tests carried out by Dr. Dukes in the period February-March, 1984 showing that COS-cell expressed samples received from Browne's group and identified as E3 and E7 contained in vivo biologically active rHuEPO (LR 51, 52). A further in vivo bioassay on E7 by Dr. Dukes conducted March 26-March 30, 1984 confirmed the in vivo biological activity of this sample of human recombinant EPO (LR 52-53).

Dr. Egrie also testified as to a further experiment which was carried out beginning March 5, 1984 which showed that the COS cell-expressed rHuEPO (designated as E3) elevated the hematocrit of mice (LR 53, 54). This indicated to Dr. Egrie that the rHuEPO possessed the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells (LR 53, 54).

Dr. Egrie also testified as to assays done in the period May-June, 1984 on samples of CHO cell-expressed rHuEPO designated H3 and B11 which she received from Dr. Browne's group (LR 55, 56). These were obtained by transfecting CHO cells

with Lin's human genomic clone, culturing and collecting the cell cultured media. RIAs and in vitro assays were positive and tests by Dr. Dukes confirmed that these samples (H3 and B11) were active in vivo (LR 56, 57).

Egrie included in her testimony other work on recombinant monkey EPO expressed in COS and CHO cells by Dr. Browne's group which showed that this too was found to be in vivo biologically active. See LR 57-67. Dr. Dukes reported in vivo biological activity for COS cell media samples as early as December 23, 1983 (LR 59-61) and again on March 19, 1984 (LR 60) and for the CHO cell expressed samples in April, 1984 (LR 63-65). It was also shown that the COS and CHO cell-expressed monkey EPO was able to increase red blood cells in the period March 5, 1984 to June 6, 1984 (LR 65-67).

Dr. Egrie also discussed her work towards determining the size of recombinant EPO in relation to natural EPO in a partially purified pooled source human urinary EPO preparation provided by Dr. Goldwasser (LR 67-69). She found that COS cell-expressed recombinant EPO and the pooled human urinary EPO migrated identically on SDS-PAGE, while CHO cell-expressed recombinant EPO moved differently (LR 68, 69). However, after treatment with Endo F, an enzyme which removes carbohydrate chains, the CHO-derived recombinant human EPO migrated to the same extent as the ENDO F digestion products of the partially purified human urinary EPO (LR 68, 69). This indicated that the difference in apparent molecular weight between the pooled source of human urinary EPO and CHO-derived recombinant human EPO was the result of differences in the carbohydrate portions of the molecules (LR 69).

Dr. Egrie also considered the count and confirmed that the recombinant human EPO expressed by Dr. Browne's group possessed the characteristics recited in the count as to biological properties and that the CHO cell-expressed recombinant EPO had an average carbohydrate composition different from Dr. Goldwasser's partially purified human urinary EPO (LR 70).

**Dr. Peter Dukes**

Dr. Dukes, Director of Research, Childrens Hospital of Los Angeles, testified (LR 78-89) as to test work to determine in vivo biological activity which was carried out under his direction by his assistant Curtis Polk, at Dr. Egrie's request. He summarized his test results which showed in vivo activity for the samples received from Dr. Egrie in the period December, 1983 to June 1, 1984 with specific reference to Egrie samples H and L (December 1983), E3 and E7 (March 1984), H and L (March 1984), A and pure, A (April 1984), and H3 and B11 (June 1984) (LR 88).

The test work by Drs. Egrie and Duke's summarized in Appendix 5. Of the samples tested by Dr. Dukes for in vivo biological activity, E3 and E7 were samples of culture media obtained by expression from COS cells transfected with Lin's human EPO gene. Samples H3 and B11 were media obtained by expression from CHO cells transfected with Lin's human EPO gene. The other samples H, L and A were obtained by expression from COS or CHO cells transfected with the monkey EPO gene. All of these samples were found to be in vivo biologically active by Dr. Dukes. Accordingly, the Lin evidence shows that by March, 1984, it was established that COS cell

expression using Lin's purified and isolated DNA sequence encoding human EPO gave in vivo biologically active recombinant human EPO (samples E3 and E7) and by June, 1984 that CHO cell expression gave an in vivo biologically active recombinant human EPO which had a different average carbohydrate composition from that of naturally occurring human EPO.

**Dr. Fu-Kuen Lin**

Dr. Lin confirmed that he was the inventor of the subject matter and that the invention was the result of extensive experimental work which he did or which was done by others at his request, as set out by the District Court and Federal Circuit decisions (LR 1, 2). He testified that the disclosure in his application regarding the difference in average carbohydrate composition between his rHuEPO and a partially purified pooled source of human urinary EPO was based on work done by Dr. Egrie and other work done by Dr. Yu at his request (LR 3). He indicated that he expected that the rHuEPO would have a different carbohydrate composition (LR 4) and that Dr. Egrie's work with Western blot analysis and SDS-PAGE indicated such a difference for CHO cell produced rHuEPO (LR 4). He also noted that Egrie's work is referred to in his Example 10 (LR 4).

Dr. Lin also discussed the work done for him by Dr. Yu (LR 5, 6) regarding carbohydrate analysis. The Yu and Egrie work indicated to Dr. Lin that the carbohydrate composition of CHO cell-expressed rHuEPO was different from that of pooled human urinary EPO product obtained from Dr. Goldwasser (LR 6).

Lin also confirmed that the rHuEPO produced by Dr. Browne using CHO cells met all of the limitations of the count (LR 3). This was also confirmed by Dr. Egrie (LR 70) and, as noted, by Dr. Browne.

Dr. Lin also noted with respect to papers that he co-authored with Egrie and Browne that, while these papers refer to the carbohydrate composition of rHuEPO as very similar to that determined for urinary EPO, they do not say the EPOs are the same and the products are, in fact, different (LR 95). He additionally testified that, while the hexose value given in his application had been questioned, he believed the value was correct when he filed the application (LR 94).

**Dr. Thomas Strickland**

Dr. Strickland testified (LR 96-106) in support of his earlier declaration (LR 133-148) confirming that Lin's rHuEPO had a different average carbohydrate composition from that of naturally occurring human EPO.

**Dr. Robert Yu**

Dr. Yu. Professor and Chairman, Department of Biochemistry and Molecular Biophysics, Medical College of Virginia, testified as to carbohydrate analysis that he and his assistant Toshio Ariga carried out at Dr. Lin's request (LR 149 FF-HH).

**Assistants**

Ralph Smalling and Geri Trail, who assisted Dr. Browne, testified in confirmation of Browne's work (LR 34-39) while Jeri Lane and Cheryl Bradley confirmed Egrie's work (LR 73-78). Curtiss Polk, Dr. Dukes' assistant, confirmed Dr. Dukes testimony (LR 90-93) and Toshio Ariga confirmed his work with Dr. Yu (LR 149 II, JJ).

**(H) The Fritsch Priority Evidence**

Fritsch et al have alleged conception of the invention, based on the concept of a probing strategy in December, 1981 with an actual reduction to practice in September, 1984.

The evidence presented by Fritsch tracks closely with the factual history recorded by the District Court under the heading "c. Genetics Institute" in its decision (1750-1752). There is some added evidence amplifying Fritsch et al's alleged diligence in the period 1981 to 1983. However, as discussed infra, this is of no relevance in view of the Federal Circuit's holding that conception of the purified and isolated DNA sequence encoding human EPO was simultaneous with its reduction to practice. Fritsch et al make no claim in their brief to have reduced the invention to practice before Lin. No new evidence concerning Fritsch et al's conception from that considered in the litigation has been presented.

It is also noted that Fritsch et al have presented no adequate evidence to establish that the product they ultimately expressed had in vivo biological activity as required by the count. Dr. Dukes, who allegedly did some in vivo testing for Fritsch et

al, did not testify as to any results. Fritsch et al have referred to activity data received from Japan (from GI's exclusive license Chugai). However, this work was done outside the U.S. and cannot be relied on for priority purposes. (35 USC 104). Furthermore, no one involved with the Chugai work testified. Accordingly, the in vivo activity requirement of the count remains unproven in the evidence presented by Fritsch et al. Hence, Fritsch et al have not established any actual reduction to practice of the invention defined by the count.

## III. ARGUMENT

### (A) The Fritsch et al Brief Ignores the Federal Circuit Decision

This interference needs to be considered in the context of the law and facts established by the related infringement litigation which culminated in the Federal Circuit decision. The Fritsch et al brief at final hearing totally ignores the implications of that decision and treats the priority issue presented herein as though this had not been the subject of judicial analysis. The Board's consideration is greatly simplified when one takes into account the Federal Circuit's decision. Particularly significant in this respect is the determination referred to earlier that conception of the invention at issue in the litigation (the purified and isolated DNA sequence encoding human EPO as defined in Lin's '008 patent claim 2) required reduction to practice, i.e. simultaneous conception and reduction to practice. See, for example, the Federal Circuit decision, 18 USPQ2d at 1021. See also the District Court's holding

> "if any fact situation triggers the simultaneous conception and reduction to practice doctrine, this is it" (13 USPQ2d at 1760).

Fritsch et al admit that "priority turns upon the first conception of the purified and isolated gene". Since that conception required reduction to practice, Fritsch et al have, in essence, acknowledged Lin's entitlement to priority in these proceedings. Thus, the arguments and evidence presented by Fritsch et al attempting to establish priority by showing a "conception" prior to Lin's concededly earlier reduction to practice of the purified and isolated EPO DNA sequence, are totally irrelevant. The priority issue was thoroughly considered by the District Court and Federal Circuit. Fritsch et al have made no effort in their brief to differentiate the facts pertinent to priority from the facts considered by the District Court and Federal Circuit and they clearly cannot do so.

**(B) Summary of Lin's Position**

The Lin position can be summarized as follows:

(a) The Lin April 25, 1991 motion for judgment should be granted. The Federal Circuit has decided the fundamental issue regarding priority between the parties as raised by Fritsch et al for final hearing.

(b) The Federal Circuit affirmed the District Court opinion that the invention of a purified and isolated DNA sequence encoding EPO required simultaneous conception and reduction to practice. The undisputed findings are that Lin purified and isolated the EPO gene and carried out

expression using mammalian host cells transformed with this gene to produce in vivo biologically active human EPO before Fritsch et al even conceived the gene. The arguments by Fritsch et al that they conceived earlier than Lin, on the basis of their goal for obtaining the isolated EPO gene, whatever its identity, and their proposal of a possible probing method for finding the gene, and that they were diligent to reduction to practice of this proposal, were dealt with and dismissed by the Courts. Fritsch did not conceive a purified and isolated DNA sequence for EPO and a viable method for obtaining it until after Lin.

(c) The Lin claims corresponding to the count are patentable. These claims define a novel product and, therefore, are not anticipated under 35 USC 102(b).

(d) The Lin claims are enabled by the Lin disclosure. One skilled in the art would have no problem in practicing the invention and obtaining Lin's product on the basis of Lin's disclosure.

(e) Lin is entitled to benefit of his earlier filings because these disclosures are enabling. However, the question of priority benefit is really a moot point since Lin has an actual

reduction to practice the claimed invention before Fritsch et al even conceived the invention.

(f) Fritsch et al should not be permitted to change inventorship or correct their preliminary statement. They have not shown that the original inventorship was inadvertently designated. They have also not proceeded diligently with the proposed amendment.

(g) Other Fritsch et al claims, which are drawn to the invention of the count but have not been so designated, should be designated as corresponding to the count.

**(C)** Discussion of the Issues

**(a) The Lin Motion for Judgment Should Be Granted**

The Federal Circuit decision should be dispositive of this interference and is res judicata as to the priority issue. In re Katz, 167 USPQ 487, 488 (CCPA 1970). Accordingly, the Motion for Judgment by Lin filed on April 25, 1991, and incorporated herein by reference, should be granted in favor of Lin with a holding that Lin is entitled to his claims corresponding to the count in interference and that Fritsch et al are not entitled to their claims corresponding to the count.

In the Commissioner's Memorandum and Order dated April 5, 1991, Lin was asked to explain why it was appropriate to grant relief prior to the time the "Amgen decision" (i.e., the Federal Circuit decision) became final and why the decision governs

the "application v. application" interferences, i.e. the present interference and Interference No. 102,097. Since then, however, the Court has denied a petition for rehearing and has issued its mandate.

As to why the Federal Circuit decision should govern in an application v. application interference, as here, Lin notes that the Courts' findings on the priority evidence considered in the litigation established that Lin is the prior inventor of not only the DNA sequence at issue in Interference No. 102,096, but of the use of that sequence to produce in vivo biologically active recombinant human EPO. Fritsch et al agree that priority turns upon the first conception of the purified and isolated EPO gene (FB 23). The Federal Circuit found for Lin in this regard. Accordingly, Lin submits that the Court findings establish priority for Lin as to the present count and show that the subject matter at issue is not patentable to Fritsch et al under 35 USC 102(g) because of Lin's acknowledged prior work. Since the subject matter at issue cannot be patentable to Fritsch et al because of Lin's Section 102(g) standing, the Fritsch et al Rule 608(b) showing stands nullified and Fritsch et al have no valid basis for being in interference.

The decision of the Federal Circuit is manifestly binding on the PTO with respect to issues considered by the Court. In re Katz, supra. See also, for example, Henning v. Hunt, 223 F.2d 926, 106 USPQ 307, 313 (CCPA 1955) where the Court stated:

> *The appeal, Civil Action 20,023, was taken for the purpose of reviewing the action of the Board of Appeals of the Patent Office, and the court reversed the board's decision, as noted in the above-cited conclusions of law. The court found that Hunt was*

> *entitled to the claim forming the count of the interference. The commissioner (and the Patent Office tribunals) cannot question the court's decisions; their failure or refusal to execute it by appropriate action would undoubtedly be corrected by judicial process; the decree of the court is the final adjudication on the question of right. Butterworth v. Hoe, 112 U.S. 50. If the Patent Office tribunals did not follow the court's decision, it would be tantamount to reversing the appellate court.*

As noted by the Commissioner in In re Pearne, 212 USPQ 467 (Comm'r Pat & TM 1981), "[in] appropriate circumstances, it may also be proper to consider the effect of any known litigation which the patent may have been involved." Id. at 468. The rationale of the Commissioner was clear:

> *the federal courts and the PTO are jointly responsible for the overall administration of the patent system. ...[T]he maximum benefit to the system occurs when the PTO and the federal courts act in harmony. Accordingly, it scarcely seems appropriate for the PTO to relitigate in a reexamination proceeding an issue of patentability which has been resolved by a federal court on the merits after a thorough consideration of the prior art called to its attention in an adversary context.* Id. at 4 68-469.

Clearly, the effect of the Federal Circuit decision is that Lin has been determined to be prior to Fritsch et al under 35 USC 102(g) as to the product in issue (as well as to the subject matter of the related interferences). The Court's determination forecloses patentability of the subject matter at issue to Fritsch. Paraphrasing Pearne, it scarcely seems appropriate for the PTO to relitigate in an interference proceeding issues which have been decided by a federal court on the merits after thorough consideration of matters called to its attention in an adversarial context by the same parties.

The Fritsch opposition to the Lin motion is without merit. The decisions referred to by Fritsch et al were all decided before the formation of the Federal Circuit as the sole Appellate Court having jurisdiction over priority determinations by the Patent Office and the various district courts. Judge Learned Hand's notations in the 1943 Second Circuit Sinko decision[10] concerning the statutory change to the Patent Office to determine priority of invention must be viewed in the context of the statutory charge to the Federal Circuit to review such decisions for errors in fact and law. Fritsch et al's reference to the unpublished opinion in Piher Sociedad Anomina v. CTS Corp., No. S. 78-174 (N.D.Ind. 1979) as "following" Sinko is without significance to the issues involved here. In that decision, the Indiana District Court, ruling in an action under 35 U.S.C. 146, remanded the case to the Patent Office for a decision on 102(g) issues which the Board had refused to determine on collateral estoppel grounds even though the parties had stipulated in an earlier district court action that 102(g) issues were to be determined in the first instance by the Patent Office.

Likewise, Fritsch et al's citation to Childers Foods, Inc. v. Rockingham Poultry Co-Op, Inc., 203 F.Supp. 794, 133 USPQ 648, 650 (W.D.Va. 1962) is both inapt and misleading. That case involved the denial of a stay of an infringement action pending interference proceedings. In quoting from the district court decision, Fritsch et al purposely cropped the court's notation that it was the moving party's counsel who commented on the lack of influence of a district court determination on the conclusion to be reached in the interference. Moreover, in quoting the court's notation

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[10] Sinko Tool & Manufacturing Co. v. Automated Devices Corp., 136 F.2d 186, 189-90, 57 USPQ 356, 359-360 (2d Cir. 1963)

on the "particular expertise" of the Patent Office in determination of priority of invention, Fritsch et al failed to quote the very next sentence wherein the court denied any binding effect of such a determination, stating:

> *[t]he conclusion reached on this question in the Interference Proceeding, while not binding on this court, would certainly be most helpful.*

Fritsch et al's argument that, "[i]n this proceeding, however, Fritsch will prevail if he can prove prior conception by a preponderance of evidence" is legally unsound. It disregards the law established by the Federal Circuit. The law of the case is that the invention of a purified and isolated DNA sequence encoding human EPO involved simultaneous conception and reduction to practice. Fritsch et al admit that this DNA sequence was not reduced to practice in their hands until long after Lin's reduction to practice. Thus, a "conception" of the DNA sequence prior to Lin's cannot be shown by any evidence, regardless of the standard of proof.

Furthermore, Fritsch et al's arguments on the evidentiary showing which purportedly would allow them to prevail in this proceeding wholly ignore the District Court's evidentiary findings concerning priority of invention if it could have been possible to form a conception of the purified and isolated EPO gene without actually reducing it to practice, i.e., if conception of a possible cloning strategy amounted to conception of the gene. The District Court specifically found a corroborated conception of the same cloning strategy by Lin in October, 1981, two months before any date of conception alleged for Edward Fritsch (13 USPQ2d at page 1763). Thus, Fritsch et al cannot here present a preponderance of evidence, prior conception when

Edward Fritsch did not develop the idea of his cloning strategy until after Lin's corroborated conception of the same. Moreover, the District Court specifically found that, even in the absence of proof of Lin's earlier conception of a cloning strategy, plaintiff (Lin's assignee) had proven lack of diligence by Edward Fritsch in reducing the strategy to practice (pages 1763-1764). Fritsch et al cannot establish diligence towards reduction to practice by a preponderance of evidence where it has already been proven that Edward Fritsch was guilty of lapses in diligence virtually throughout the period between December 1981, through to contracting with Miyake for additional EPO protein in May of 1984, long after Lin had cloned the EPO gene (see again pages 1763-1764, 13 USPQ2d). While Fritsch et al have provided some additional evidence regarding the proposed diligence by Fritsch, they have failed to provide any evidence to rebut the lapses in diligence found by the District Court.

In presenting the motion for judgment, Lin is mindful of the holding in Perkins v. Kwon, 886 F.2d 325, 12 USPQ 1308 (Fed. Cir. 1989). However, the present situation is fundamentally different from that in the Kwon case. A key difference is that Kwon involved the issue of whether or not priority should be determined at final hearing after the subject matter had been found unpatentable to a party. Disregarding priority in Kwon would have meant that the later inventor would obtain a patent because of an on-sale bar against the first inventor. In the present case, the Courts have already determined priority favorably to Lin. The present position is, therefore, the exact reverse of the Kwon situation. The issues dealt with and determined in the litigation should not be relitigated in the present proceedings. In re Katz, supra. See

also Amoco Oil Company v. Zarb, 402 F.Supp. 1001, 1008 (D. D.C. 1975); Nixon v. Richey, 513 F.2d 430, 438 (note 75) (D.C. Cir. 1975); IB Moore's Federal Practice, ¶ 0.416[3] at 523 (2nd Ed.).

Fritsch et al also note in their opposition that the present interference raises patentability issues which the Federal Circuit did not determine. However, the motions relating to these issues were denied by the Examiner-in-Chief in his decision on motions and Fritsch et al have not shown any manifest error in the motion decision warranting a change in the earlier ruling on reconsideration at final hearing. Hence, these issues do not warrant maintaining the interference. Furthermore, it is noted that Fritsch's EPO of claim 8 is defined as the product made by using the host cells at issue in Interference No. 102,096 and which the Federal Circuit has ruled Lin invented first. Thus, the carbohydrate feature of the count gives no basis for distinguishing the priority issue in this interference from that addressed by the Federal Circuit.

Lin's motion for judgment should be granted.

**(b) Lin Is the Prior Inventor of the Subject Matter at Issue**

Since the Federal Circuit has found that Lin was the first to have a conception of the purified and isolated gene (upon its reduction to practice) and it has not been questioned that Lin obtained in vivo biologically active recombinant human EPO product before Fritsch et al even obtained the gene, it follows that Lin is entitled to priority on the record as to the present count.