In The United States Patent and Trademark Office

Before the Board of Patent Appeals and Interferences

Interference No. [illegible]

FRITSCH [illegible]

LIN [illegible]

Examiner-in-Chief [illegible]

BRIEF FOR THE SENIOR PARTY LIN

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INTERFERENCE NO. 102,097
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OTHERS

I. STATEMENT OF ISSUES PRESENTED FOR CONSIDERATION

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

(3) Has Lin satisfied best mode requirements?

(4) Are the Lin claims corresponding to the count patentable to Lin under 35 USC 103?

(5) Is Lin the inventor of the subject matter at issue?

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

II. STATEMENT OF THE FACTS

(A) The Subject Matter

The invention involved in this interference relates to a process for producing in vivo biologically active recombinant erythropoietin ("EPO") by growing a mammalian host cell transformed or transfected with an isolated DNA sequence encoding EPO and isolating the EPO product.

(B) The Parties

This interference involves U.S. application Serial No. 693,258 filed on January 22, 1985 by Edward Fritsch, Rodney M. Hewick and Kenneth Jacobs ("Fritsch et al" or "Fritsch") and U.S. application Serial No. 113,179, 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 assigned to Genetics Institute, Inc. ("GI"). The Lin application is assigned to Amgen Inc. ("Amgen").

Fritsch et al have been given the benefit of 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 and Lin is the senior party by virtue of these earlier filings.

(C) The Count

The interference involves a single count which is set forth in Appendix I. In essence, the count defines a process for the preparation of an in vivo biologically active glycosylated polypeptide (recombinant EPO) by growing a mammalian host cell which is transformed or transfected with an isolated DNA sequence encoding EPO and isolating the recombinant EPO product.

In the declaration of the interference, Fritsch et al claims 72 and 73 and Lin claims 65-69 were identified as corresponding to the count. Lin's claim 65 is identical to the count.

None of the Fritsch et al claims is identical to the count. The Fritsch et al claims 72 and 73 are more general in nature and read:

> *72. A method of producing human erythropoietin comprising culturing the cell line of claim 50 in a suitable culture medium and isolating erythropoietin from said medium.*
>
> *73. A method of producing human erythropoietin comprising culturing the cell line of claim 52 in a suitable culture medium and isolating erythropoietin from said medium.*

Fritsch et al claims 50 and 52, from which claims 72 and 73 depend, themselves refer back to claim 48 and then to claim 46. These claims (claims 50, 52, 48 and 46 read as follows:

> *50. A mammalian cell line transformed with the vector of claim 48.*

> *52. The mammalian cell line of claim 50 wherein said mammalian cells are CHO cells.*
>
> *48. A recombinant DNA vector comprising a heterologous promoter and the cDNA sequence of claim 46.*
>
> *46. A cDNA sequence comprising a DNA sequence encoding the amino acid sequence 1-166 as shown in Figure 3B.*

Fritsch et al claims 46, 48, 50 and 52, which are drawn to DNA sequence encoding EPO or host cells transformed therewith, are listed as corresponding to the count in Interference No. 102,096. Thus, in essence, Fritsch et al claims 72 and 73 call for producing human EPO by culturing a host cell transfected with DNA according to the count of Interference No. 102,096 and isolating the product.

The culturing and isolating steps recited in Fritsch et al claims 72 and 73 are the counterparts of steps (a) and (b) of the count. Step (a) is inherent in the culturing step of the Fritsch et al claims. Step (b) is accomplished when the expressed product is separated as media from the cells themselves, for example, for assay to determine in vivo biological activity.

(D) Related Interferences

There are two other closely related interferences involving the same parties. These interferences are Interference No. 102,096, which has already been referred to, and which was declared concurrently with the present interference, and Interference No. 102,334. As indicated, Interference No. 102,096 is directed to a purified and isolated DNA

sequence encoding human EPO which is used in the process which is the subject of the present interference. The count of Interference No. 102,334 is directed to an in vivo biologically active human EPO product. A single Rule 608(b) showing by Fritsch et al is the basis for the declaration of all three interferences.

Papers common to all three proceedings have been filed and the evidentiary presentation has been consolidated.

The close relationship of the three interferences has been acknowledged by Fritsch et al in preliminary motions and in their Briefs at Final Hearing in this interference and in Interference No. 102,334. Thus, Fritsch et al in earlier motions urging the combination of Interference Nos. 102,096 and the present interference characterized these two interferences as "different manifestations of the same invention"[1]. Additionally, in their briefs at final hearing in this interference and Interference No. 102,334, Fritsch et al state:

> *Accordingly, as in the '096 interference, priority turns upon the first conception of the purified and isolated gene.*[2]

Fritsch et al thus admit that the priority issue is identical in all three interferences. Moreover, the prior art references relied on in support of the Fritsch et al obviousness arguments in the present interference (including Toole et al U.S. Patent No. 4,757,006) are the same references relied upon in the Fritsch et al brief arguing

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[1] See Fritsch et al Motion G in Interference No. 102,096 at page 86 and Motion Q in Interference No. 102,097 at page 159.

[2] See Fritsch et al brief page 24 in this interference and page 23 of their brief in Interference No. 102,334.

obviousness of Lin's claims to the purified and isolated DNA sequence in Interference No. 102,096[1]. Likewise, the Fritsch et al allegations of best mode violation in this interference and in Interference No. 102,096 are identical.

[1]Compare Fritsch et al brief pages 48-50 in the present interference with pages 40-43 of the Fritsch et al brief in Interference No. 102,096.

(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 (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 (hereinafter the "District Court decision").

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

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.[4] This has included action before the International Trade Commission (ITC) wherein the validity of Lin's '008 patent was put at issue. The District Court and Federal Circuit decisions addressed priority and patentability issues directed towards 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

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

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 including Toole et al U.S. Patent 4,757,006 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 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 referring to M.P.E.P. § 706.03(w), has noted this on the record (FR 1029-1030)[5] 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 at this stage to note that the Federal Circuit specifically affirmed the District Court's ruling, in view of the state of the art concerning EPO, that a conception of the purified and isolated DNA sequence encoding EPO and host cells transfected therewith (at issue in Interference No. 102,096, and used in the process of the present count) required reduction to practice of the sequence. In other words, based on the

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

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 DNA sequence until it was reduced to practice. This is the controlling law on the issue of priority in this interference and, by Fritsch et al's own admissions, the related interferences.

The District Court decision, which was affirmed by the Federal Circuit[a], 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[b] (Genetics Institute) and others to clone and express EPO. The prior art including the Toole et al U.S. patent 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 the following issues which Fritsch refers to in his brief:

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

[b] 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 herein (Rodney Hewick and Kenneth Jacobs) were not identified as participants in the alleged prior conception by Fritsch (which the Courts found inadequate). One (Jacobs) did not even begin working for GI until July, 1983.

(1) Priority of invention as between Lin and Edward Fritsch with the holding of simultaneous conception and reduction to practice favorable to Lin (pages 1759-1764). The District Court also considered essentially the same question of prior conception as proposed by Fritsch et al in this interference, that is, the assumption that conception could occur prior to reduction to practice, and held against Fritsch based on the same facts now before the PTO (pages 1762-1763). The Court further considered the question of Fritsch's diligence (assuming prior conception) and again found against Fritsch (pages 1763-1764).

(2) Obviousness of the subject matter under Section 103 with the finding of unobviousness over the prior art (pages 1764-1769); and

(3) Best mode, with a finding favorable to Lin (pages 1769-1774).

The Federal Circuit affirmed the District Court on each of items (1), (2) and (3). See pages 1020 to 1022, 1022 to 1023 and 1023 to 1026, respectively, of the Federal Circuit decision.

While the process of the present count was not expressly at issue in the litigation, it is clear that the issues of priority and patentability of the process were directly addressed. Central to the process is the use of the DNA sequence encoding human EPO and host cells transfected therewith at issue in the litigation, to express in vivo biologically active human EPO. Fritsch et al have acknowledged this in admitting that priority with respect to the present count turns on conception of the purified and isolated gene (FB

24). The Section 112 issue raised here is identical to that raiased at trial. The obviousness issue raised here, as reflected by the Fritsch et al briefs, is not substantively different. Hence, the Federal Circuit decision is directly applicable to the issues in the present case.

(F) **The Interference History**

This interference was declared on May 9, 1989, prior to the District Court decision (December 11, 1989), concurrently with the declaration of Interference No. 102,096. As noted earlier, the interferences were declared on the basis of a showing under 37 CFR 1.608(b) ("Rule 608") by Fritsch et al purporting to establish prior conception, based on knowledge of a probing technique, with diligence up to reduction to practice. The 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.

Both parties filed preliminary statements and Fritsch et al filed ten preliminary motions generally on the lines of those filed in Interference No. 102,096. The Fritsch et al preliminary motions[8] included:

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[8] The motions are identified by the letters used by the Examiner-in-Chief in his decision on motions (Paper No. 35).

(H) for judgment of unpatentability of Lin's claims corresponding to the count under 35 USC 102(e) and/or 103 based on the Toole et al U.S. Patent 4.757.006;

(I) for judgment of alleged failure to meet written description, enablement and/or best mode requirements of 35 USC 112, first paragraph;

(J) to deny benefit accorded to Lin as to earlier filings on written description or enablement grounds;

(K) to deny benefit accorded to Lin as to earlier filings on best mode grounds;

(L) for judgment of unpatentability to Lin under Section 102(g);

(M) for judgment of unpatentability to Lin under Section 102(f);

(N) to substitute or add a later-filed continuation-in-part application based on a probing technique described in the Toole et al patent which did not relate to EPO;

(O) to substitute a proposed method count directed towards the probing technique referred to in the later-filed continuation-in-part mentioned in (N);

(P) to be accorded the benefit of earlier Toole et al applications; and

(Q) as in motion (G) in Interference No. 102,096, to combine the two interferences because the two interferences represent "different manifestations of the same invention."

Subsequent to the filing of these motions, and Lin's oppositions thereto, the District Court issued its decision as reported at 13 USPQ2d 1737. As a consequence, Lin filed a motion to terminate (Paper No. 33) these proceedings.[9]

In his decision on motions (Paper No. 35), the Examiner-in-Chief ("EIC") dismissed the Lin motion to terminate. He also dismissed Fritsch et al motions (L), (O), (N) and (Q); deferred action on Fritsch et al motions (H) (Section 102/103 patentability), (I) (best mode only), (K) (Lin's priority benefit) and (M) (Section 102(f) patentability) and denied motions (P) (Fritsch et al priority benefit), and (I) and (J), as directed to "description" and "enablement".

Fritsch et al requested reconsideration of the motions decision with respect to motion (J) but this was denied, the Examiner-in-Chief (E-I-C) noting that Fritsch et al had taken no issue with Lin's assertion that a correlation between glycosylation and in vivo biological activity of EPO was art-recognized (Paper No. 44, sentence bridging pages 2-3).

Both parties have since presented their priority evidence in the form of deposition and declaration testimony and 37 CFR 1.682 submissions. Additionally, during the Fritsch et al testimony time, Fritsch et al filed a motion to amend the inventorship of their application here involved Serial No. 693,258 to list Fritsch as sole inventor, i.e. to delete Hewick and Jacobs as joint inventors. A companion motion to correct their

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[9] Lin also filed a contingent motion (Paper No. 34 1/2) proposing a substitute count in view of the District Court's position regarding claim 7 of Lin's '008 patent but this motion was dismissed (Paper No. 41).

preliminary statement was also filed. Lin has opposed these motions and consideration thereof has been deferred to final hearing.

The Federal Circuit decision, on appeal from the District Court decision, was issued during Lin's testimony period and, pursuant to Commissioner's Memorandum and Order dated April 5, 1991, Lin has filed a motion for entry of judgment in favor of Lin. This motion has been opposed by Fritsch et al and has been deferred for consideration at final hearing (Paper No. 157).

The inteference thus comes on to final hearing to consider (1) Lin's motion for entry of judgment; (2) priority; (3) Fritsch et al motions relating to best mode, Section 103 patentability and the inventorship; and (4) Fritsch et al motion to change inventorship. Fritsch et al have not briefed their deferred Motion K regarding Lin's priority benefit and this is not, therefore, an issue at final hearing.

(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 ("Amgen") position is quoted in Appendix 2.

Additional evidence presented on Lin's behalf included declaration testimony by Dr. Jeff Browne and his assistants, Ralph Smalling and Geri Trail; Dr. Joan Egrie and her assistants, Jeri Lane and Cheryl Bradley; Dr. Peter Dukes and his assistant Curtiss Polk; Dr. Randolph Wall 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 7-8 and Lin Exhibit 200, testified (LR 7-31) 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 10) and that these expressions were carried out at Dr.Lin's request (LR 10). He also confirmed that Dr. Joan Egrie was responsible for conducting radioimmunoassays (RIA) which demonstrated the presence of recombinant human erythropoietin (rHuEPO) in test samples of his culture medium and that Dr. Egrie was responsible for confirming that the expressed product was biologically active in vitro and in vivo (LR 10).

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 10-25) 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 10, 11).

The first expression vector which was prepared under Dr. Browne's supervision contained Dr. Lin's monkey EPO cDNA clone. This vector was introduced into COS cells. This work was done by Ralph Smalling working under Dr. Browne's direction (LR 11, 12). Culture media from the transformed COS cells was isolated 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 12).

Further expression work using COS cells and Lin's monkey EPO clones was carried out in December, 1983 and January, 1984 (LR 13, 14) 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 14, 15). The results indicated (LR 15) that the cloned fragment provided by Dr. Lin contained the complete coding portion of the human EPO gene (LR 15, Lin Exhibit 206).

Dr. Browne and his assistant Mr. Smalling continued their expression work with the human EPO gene in 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 16-18). Expression work with CHO cells was also carried out in the period December, 1983 to May, 1984, 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 18-25). Highlights of the expression work Dr. Browne did, or which was 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 24, 1984 (LR 26, 27; Lin Exhibits 205, 206). These were the 293 cells transfected with a 5.4 kb BAMHI-HindIII subfragment including Lin's human EPO genomic gene clone HE1 which included the complete coding portion of the human EPO gene. This followed the earlier expression of monkey EPO using COS-1 cells which also were reported favorably by Dr. Egrie on December 8, 1983 (LR 26; 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 24, 26, 27; Lin Exhibits 208, 211, 212). CHO cells were transfected with DNA from these two isolates H3 and B11, both of which contained the complete coding portion of the human EPO gene (LR 23, 24). Isolated samples of culture medium from pools of the H3 and B11 transformed CHO cells were given to Dr. Egrie on May 22, 1984 (LR 25) and she reported on May 24, 1983 that rHuEPO was present in the samples (LR 25, 26, 27).

Dr. Browne described how CHO cells and other mammalian cells (293, COS) synthesized recombinant human EPO and secreted it into the culture medium (LR 28, 29). He also testified that expression in CHO cells or other mammalian cells proceeded via steps (a(i)(ii)(iii) of the count (LR 28-29). He acknowledged familiarity with the count and confirmed that the expression which he carried out using COS and CHO cells transfected with the DNA sequence encoding EPO from Dr. Lin represented a process exactly according to the count (LF 29, 30). He noted that he was able to express biologically active rHuEPO using the EPO gene clones which Dr. Lin had isolated and provided for expression, successful expression of an in vivo biologically active product being shown by the in vivo results obtained by Dr. Egrie (LR 30).

Dr. Browne's expression work is summarized in Appendix 3.

Dr. Joan Egrie

Dr. Egrie, an employee of Amgen with the background and experience indicated at LR 38-39 (see also Lin Exhibit 110), testified in detail (LR 38-69) 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 39, 40). 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 40, 41).

She knew that Dr. Lin had isolated EPO clones in late 1983 (LR 41) and she was aware that Dr. Browne had been asked by Lin to use the clones for expression (LR 41, 42). She extensively discussed (LR 42-65) 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 48, 49), noting that the carbohydrate portion of EPO, particularly sialic acid content, affects in vivo activity (LR 49).

Egrie 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 49, 50). A further in vivo bioassay on E7 by Dr. Dukes conducted March 26 - March 30, 1984 confirmed the in vivo biological activity for this sample of human recombinant EPO (LR 50-51).

She also testified as to a further experiment which was carried out beginning March 5, 1984 which showed that the COS cell-expressed rHuEPO designated E3 elevated the hematocrit of mice (LR 51, 52). 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 51, 52).

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 53, 54). RIAs and in vitro assays were positive and tests by Dr. Dukes confirmed that these samples (H3 and B11) were active in vivo (LR 54, 55).

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 55-65. Dr. Dukes reported in vivo biological activity for COS cell media samples as early as December 23, 1983 (LR 57-59) and again on March 19, 1984 (LR 58) and for the CHO cell expressed monkey EPO samples in April, 1984 (LR 61-63). 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 63-65).

Dr. Egrie also confirmed the testimony of Drs. Browne and Lin that the indicated expression by Dr. Browne's group of in vivo biologically active recombinant using a mammalian host cell transfected with an isolated DNA sequence encoding human EPO involved each of the steps specified in the count (LR 67, 68).

Dr. Peter Dukes

Dr. Dukes, who is Director of Research, Children's Hospital of Los Angeles with the background and experience noted at LR 76-77 (see also Lin Exhibit 1) testified (LR 76-87) 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 85).

The test work by Drs. Egrie and Dukes is summarized in Appendix 4. 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 the 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 the effective carrying out of the process of the count to obtain rHuEPO with a determination of in vivo biological activity by March, 1984 for the COS cell-expressed EPO and by June, 1984 for the CHO cell-expressed EPO.

Dr. Randolph Wall

The declaration evidence of Dr. Randolph Wall, Professor in the Department of Microbiology and Immunology at UCLA, was also presented by Lin (LR 91-102). This declaration was earlier filed in the motion period. The declaration includes Dr. Wall's comments distinguishing the invention at issue from Toole U.S. 4,757,006 and supports Lin's position on patentability (LR 95-100) and best mode (LR 100, 101).

Dr. Fu-Kuen Lin

Dr. Lin (LR 1-6) confirmed that he was the inventor of the subject matter claimed in his application (LR 1) and that the experimental work on which the invention is based was done by himself or others, including Drs. Browne and Egrie, at his request (LR 1, 2). He specifically confirmed that the expression of EPO in 293, COS and CHO cells was done on his behalf (LR 3). This included expression with the approximately 5.4 kb BamHI-Hind III DNA subfragment within a lambda bacteriophage clone he called HE1 and which carried the complete human EPO coding sequence (LR 3). He confirmed that the expression of in vivo biologically active rHuEPO by culturing mammalian host cells transformed with a DNA sequence encoding EPO was shown to be successful by Dr. Egrie's determination that the expressed rHuEPO was biologically active in vivo (LR 3, 4). He also confirmed that the expression carried out by Dr. Browne and his assistant satisfied all features and limitations of the count (LR 5).

Assistants

Ralph Smalling and Geri Trail, who assisted Dr. Browne, testified in confirmation of Browne's work (LR 32-36) while Jeri Lane and Cheryl Bradley confirmed Egrie (LR 70-75) and Curtiss Polk, Dr. Dukes' assistant, confirmed Dr. Dukes testimony (LR 87-90).

(H) The Fritsch et al Priority Evidence

Fritsch et al have alleged a conception of the invention, based on the concept of a probing strategy in December, 1981.

The evidence presented by Fritsch et al 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 towards isolating the DNA sequence in the period 1981 to 1983. However, this is of no relevance in view of the Federal Circuit's holding that conception of the purified and isolated DNA sequence encoding EPO must be simultaneous with its reduction to practice. No new evidence concerning conception has been presented. As GI's counsel succinctly stated the issue at trial day 7:

> *"there is no way on this God's earth that Dr. Fritsch could make a showing that he cloned first."* (Tr. 7,125, lines 9-11, A7328)

It is also noted that Fritsch et al have presented no adequate evidence to establish that the recombinant product they ultimately expressed in the latter half of 1984[10]

[10] Fritsch et al make no claim that they obtained in vivo biologically active recombinant human EPO before Lin. Their only argument is the alleged prior conception (December 1981) with diligence to a reduction to practice after Lin's reduction.

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 GI's exclusive Japanese licensee (Chugai). However, this data cannot be relied on as whatever work was done to obtain the data was done outside the U.S., i.e. in Japan (35 USC 104). Furthermore, no one directly involved with the Chugai work testified. Accordingly, the in vivo activity requirement of the count remains unproven by Fritsch et al. Hence, Fritsch et al have not established any actual reduction to practice.

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 Fritsch et al "Issues Presented for Decision" Nos. (1), (3) and (4) therein as though they had never been the subject of judicial analysis. The Board's consideration of these "issues" 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 and host cells including this sequence) requires reduction to practice i.e. that the claimed

invention involves 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", and, as conception requires reduction to practice, Fritsch et al have in essence acknowledged Lin's entitlement to priority in the present proceedings. Thus the arguments and evidence presented by Fritsch et al attempting to establish priority by showing a "conception" prior to Lin's acknowledged earlier reduction to practice of the purified and isolated EPO DNA sequence, are totally irrelevant. The same is true with respect to the Fritsch et al arguments regarding Section 103 patentability of Lin's claims and Lin's best mode. These issues were thoroughly considered by the District Court and Federal Circuit. Fritsch et al have made no effort in their brief to distinguish the facts pertinent to the priority and patentability issues (Section 103 and best mode) they present for final hearing 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:

(i) The Lin April 25, 1991, motion for judgment should be granted. The Federal Circuit has decided all of the fundamental issues between the parties as submitted by Fritsch et al for final

hearing. The requested inventorship correction is mooted because the subject matter at issue is not patentable to either Fritsch et al as joint inventors or to Fritsch as sole inventor.

(ii) 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 obtain in vivo biologically active human EPO before Fritsch et al have 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 in reduction to practice of this proposal, were dealt with and dismissed by the Courts because Fritsch did not conceive a purified and isolated DNA sequence for EPO and a viable method for obtaining it until after Lin.

(iii) While the count is directed to a process for preparing in vivo biologically active EPO using a mammalian host cell transfected or transformed with an isolated DNA sequence

encoding human EPO, and the litigation was directed to the purified and isolated DNA sequence and host cells transfected or transformed thereby, it is evident that these are only different manifestations of the same invention as acknowledged by Fritsch et al in their Motion Q herein (and in Motion G in Interference No. 102,096). Clearly, the whole purpose and intent of the purified and isolated DNA sequence encoding human EPO (and host cells transfected therewith) at issue in the litigation was to express in vivo biologically active human EPO. Stated otherwise, the process language of the Lin patent claims at issue in the litigation ("encoding human EPO") is, for all intents and purposes, a description of the present count. One cannot be sure he has the sequence until he has successfully expressed in vivo biologically active human EPO. This involves culturing the transfected cells and isolating the expression product to determine whether or not it has the required in vivo activity. Hence, the priority holding in the litigation is directly on point, notwithstanding the different statutory class of claims involved.

(iv) Lin's disclosure satisfies best mode requirements. The only arguments advanced by Fritsch et al in this interference are identical to those raised by Fritsch et al in the '096

Interference. With respect to those agruments, the Federal Circuit affirmed the District Court ruling that Lin has satisfied best mode requirements.

(v) The Lin claims are patentable over the prior art for the reasons noted in the District Court and Federal Circuit decisions. The Courts found Lin's EPO purified and isolated DNA sequence and host cells transformed with the same, to be patentable over the same prior art. The Courts' ruling applies with equal force to Lin's process claims.

(vi) Lin is the inventor of the invention at issue. The inventor of the isolated EPO DNA sequence is clearly the inventor of the process for producing EPO involved in this interference. Fritsch et al admit as much by confirming that "priority turns upon the first conception of the purified and isolated human EPO gene." The process for producing EPO using Lin's purified and isolated gene was done at Lin's request.

(vii) 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.

(C) DISCUSSION OF THE ISSUES

(a) The Lin Motion for Judgment Should Be Granted

The Federal Circuit decision is dispositive of all issues raised by Fritsch et al for determination in this interference and the decision in res judicata as to those issues. In re Katz, 167 USPQ 487, 488 (CCPA 1970). Of the five "issues" proposed by Fritsch et al in their brief at final hearing, issue No. 1 (priority), No. 3 (best mode) and No. 4 (Section 103 patentability), which depend on exactly the same arguments raised in the '096 Interference and previously presented to the Courts, have been finally decided by the Federal Circuit adverse to Fritsch et al. Issue No. 2 (inventorship change) is mooted by the Federal Circuit decision as it does not matter whether Fritsch et al are joint inventors or Fritsch is the sole inventor. The invention at issue is not patentable to either entity under 35 USC 102(g).

This leaves Fritsch et al issue No. 5 (which challenges Lin's inventorship under 35 USC 102(f)). However, this is not a real issue, particularly with the Fritsch et al admissions referred to supra.

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. 102,334. Since then, however, the Court has denied both a petition for rehearing and a suggestion for rehearing en banc 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 and host cells transformed therewith at issue in Interference No. 102,096, but that he had used this sequence and transformed mammalian host cells to produce in vivo biologically active recombinant human EPO. Fritsch et al agree that the conception of the invention is dependent upon the conception of the DNA sequence. Thus, the litigation directly involved an essential feature of the process, i.e. the purified and isolated DNA sequence encoding EPO. The findings of the District Court, affirmed by the Federal Circuit, clearly show that Lin carried out the expression process using the DNA sequence to produce in vivo biologically active recombinant human EPO before Fritsch et al even conceived the DNA sequence. 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. In the circumstances, the District Court's findings as affirmed by the Federal Circuit are dispositive of the priority issue, as well as other issues represented by the present interference, as discussed in the Lin motion for judgment. Since the subject matter at issue cannot be patentable to Fritsch et al because of Lin's 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, 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 process in issue

(as well as to the subject matter of the related interferences). The Court's determination forecloses priority award and 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 et al opposition to the Lin motion is without merit. The arguments by Fritsch et al are misplaced and the authorities they have cited relate to situations fundamentally different from the present case which is unique because of the involvement of the Federal Circuit in its determination of the priority, Section 103 patentability and best mode issues. There is clearly nothing analogous to the present situation in the authorities Fritsch et al rely on. Nor is it reasonable for Fritsch et al to suggest that this matter should be reconsidered on the basis that different standards of proof are involved. There can only be one standard of proof as to priority evidence, patentability and best mode, namely, the standard used by the Federal Circuit to decide these issues.

Furthermore, the decisions relied on by Fritsch et al were all decided before the formation of the Federal Circuit as the sole Appellate Court having jurisdiction over priority and patentability determinations by the Patent Office and the various district courts. Judge Learned Hand's notations in the 1943 Second Circuit Sinko decision[11]

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