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[6], 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[7] (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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[6] 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.

[7] 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).

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CONFIDENTIAL
SUBJECT TO PROTECTIVE ORDER

(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).