EXHIBIT 1
(Part 4 of 4)

Fritsch et al cannot validly argue the contrary. The isolation step (b) means nothing more than separating the expressed product from the cells (LR 229) and would obviously be necessary to determine the in vivo biological activity of the expression product. Any effort by Fritsch et al to argue that the isolation step of the Count means purification is nothing more than an afterthought which is inconsistent with Fritsch et al's own disclosure, as noted earlier.

Manifestly, the Lin evidence shows that Browne carried out the process of the count using COS cells transfected with Lin's isolated human EPO encoding gene and that Dukes should that the expressed product to be in vivo biologically active by March 1984 (expression products E3 and E7) and that Browne's CHO cell expressed human EPO (H3 and B11) was found to have in vivo activity by June 1984. All of this is prior to Fritsch et al's conception date.

Furthermore, it is noted that Fritsch et al have not proven an actual reduction to practice as they have not established that their expression product had in vivo biological activity. See discussion under "The Fritsch Priority Evidence".

In view of the foregoing, it is submitted that Lin is entitled to priority as to the count.

(c) Lin Has Satisfied Best Mode Requirements

The Fritsch et al argument (FB 35-44) that Lin has failed to meet best mode requirements is nothing more than a re-hash of the arguments which were met head on by Lin before the District Court and Federal Circuit and on which these Courts ruled

favorably for Lin. No new evidence has been adduced by Fritsch et al in this proceeding. Fritsch et al sought no discovery on this issue when their motion I was deferred for final hearing. The same record which prompted the District Court to observe that:

> *[T]here is no evidence that Dr. Lin knew of a better mode which he failed to disclose at all...*

and thus

> *those of ordinary skill in the art could produce mammalian cells with similar levels of [EPO] production identified in Example 10...*

is presented to the Board. The attempt by Fritsch et al to secure a different result from the Board must fail.

In affirming the District Court on best mode with respect to the same arguments as now urged by Fritsch, the Federal Circuit decision states (18 USPQ 2d at page 1023):

> *Defendants argue that the district court erred in failing to hold the '008 patent invalid under 35 U.S.C. §112, asserting that Lin failed to disclose the best mammalian host cells known to him as of November 30, 1984, the date he filed his fourth patent application.*
>
> *The district court found that the "best mode" of practicing the claimed invention was by use of a specific genetically-heterogeneous strain of Chinese hamster ovary (CHO) cells, which produced EPO at a rate greater than that of other cells. It further found that this strain was disclosed in Example 10 and that Lin knew of no better mode. GI argues that Lin's best mode was not adequately disclosed in Example 10 because one skilled in the art could not duplicate Lin's best mode without his having first deposited a sample of the specific cells in a public depository. The issue before us therefore is whether the district court erred in concluding that Example 10 of the '008 patent satisfied the best mode requirement as to the invention of the challenged claims and that a deposit of the preferred CHO cells was not necessary.*

After commenting on the relevant case law, the Court went on to state:

> *We agree that the district court did not err in finding that defendants have not met their burden of proving a best mode violation.*
>
> *As noted above, the district court found that the best mode of making the CHO cells was set forth in Example 10. As the district court stated, while it was not clear which of two possible strains Lin considered to be the best, the cell strain subjected to 1000 nanomolar MTX (methotrexate) or that subjected to 100 nanomolar MTX, the best mode was disclosed because both were disclosed.[6] Defendants argue that this disclosure is not enough, that a deposit of the cells was required.*
>
> * * * * *
>
> *The district court found that the claims at issue require the use of biological materials that were capable of being prepared in the laboratory from readily available biological cells, using the description in Example 10. The court also found that there were no starting materials that were not publicly available, that were not described, or that required undue experimentation for their preparation in order to carry out the best mode. The court noted that Lin testified that the isolation of the preferred strain was a "routine limited dilution cloning procedure[]" well known in the art. Dr. Simonsen, GI's own expert, testified that the disclosed procedures were "standard" and that: with the vectors and the sequences shown in Example 10, I have no doubt that someone eventually could reproduce -- well, could generate cell lines [sic, strains] making some level of EPO, and they could be better, they could be worse in terms of EPO production.*

The district court relied on this testimony, and, upon review, we agree with its determination. The testimony accurately reflects that the invention, as it relates to the best mode host cells, could be practiced by one skilled in the art following Example 10. Thus, the best mode was disclosed and it was adequately enabled.

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6 In its opinion, the district court stated that "the best way to express EPO was from mammalian cells ... and that a cell line derived from 11 possible clones from the CHO B11, 3.1 cell strain was to be used for Amgen's master working cell bank, which was expected to be started on November

> 26, 1984". 13 USPQ 2d at 1772. At another point, the court stated that Amgen "did disclose the best mode in Example 10 of the invention, when it described the production rates of the 100 nanomolar-amplified cells (the B11 3.1 cell strain) and one micromolar-treated cells." Id.

The Court then went on to distinguish the case from the situation where biological cells were obtained from unique soil samples, noting at page 1025:

> *On the other hand, when, as is the case here, the organism is created by insertion of genetic material into a cell obtained from generally available sources, then all that is required is a description of the best mode and an adequate description, not deposit of the cells. If the cells can be prepared without undue experimentation from known materials, based on the description in the patent specification, a deposit is not required. See Feldman v. Aunstrup, 517 F.2d 1351, 1354, 186 USPQ 108, 111 (CCPA 1975), ("No problem exists when the microorganisms used are known and readily available to the public"), cert. denied, 424 U.S. 912 [188 USPQ 720] (1976). Since the court found that that is the case here, we therefore hold that there is no failure to comply with the best mode requirement for lack of a deposit of the CHO cells, when the best mode of preparing the cells has been disclosed and the best mode cells have been enabled, i.e., they can be prepared by one skilled in the art from known materials using the description in the specification.*

The Court also dealt with the Fritsch argument regarding the possibility of "duplicating" Lin's example (at 1026-1027) as follows:

> *Defendants also assert that the record shows that scientists were unable to duplicate Lin's genetically-heterogeneous best mode cell strain. However, we have long held that the issue is whether the disclosure is "adequate", not that an exact duplication is necessary. Indeed, the district court stated that*
>
> > *[t]he testimony is clear that no scientist could ever duplicate exactly the best mode used by Amgen, but that those of ordinary skill in the art could produce mammalian host cell strains or lines with similar levels of production identified in Example 10.*
>
> *13 USPQ 2d at 1774. What is required is an adequate disclosure of the best mode, not a guarantee that every aspect of the specification*

> *be precisely and universally reproducible. See In re Gay, 309 F.2d 769, 773, 135 USPQ 311, 316 (CCPA 1962).*

Regarding Lin's deposits, the Court noted (at 1026):

> *Defendants finally argue that Lin's failure to deposit the transfected cells notwithstanding the fact that he was willing to deposit essentially worthless cell material was evidence of deliberate concealment. We have already stated that deposit of the host cells containing the rEPO gene was not necessary to satisfy the best mode requirement of Section 112. The best mode was disclosed and a deposit was not necessary to carry it out. Therefore, the fact that some cells were deposited, but not others, is irrelevant.*

Thus, each and every point argued in the Fritsch et al brief regarding Lin's best mode has already been fully dealt with and determined in Lin's favor by the District Court and Federal Circuit. There is no evidence, as pointed out by the District Court and affirmed by the Federal Circuit, that Lin held back or concealed information necessary for the practice of his invention as disclosed in each of his applications. To show that best mode requirements have not been satisfied, there must be clear evidence that the preferred mode contemplated by the inventor at the time of filing of the patent application was held back or concealed. There is no such evidence here.

As the Court stated in Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81, 94 (Fed.Cir. 1986):

> *Because not complying with the best mode requirements amounts to concealing the preferred mode contemplated by applicant at the time of filing, in order to find that the best mode requirement is not satisfied, it must be shown that the applicant knew of and concealed a better mode than he disclosed. (emphasis supplied)*

The Federal Circuit and District Court found Lin's Example 10 satisfied best mode requirements.[19] Lin viewed the Example 10 host cells as his best mode and Fritsch has offered no evidence that Lin contemplated a better mode of practicing or carrying out his invention than that disclosed in Example 10. Lin has satisfied best mode requirements, and Fritsch et al have not at all met their burden of establishing the contrary.[20]

(d) Lin's Claims Are Patentable Under 35 USC 103

The Fritsch argument (FB 44-51) is also, in essence, nothing more than a re-hash of the arguments against Lin's DNA and host cell claims advanced by Fritsch's assignee and dismissed by the Courts. The record before the Board is no different than that which prompted the District Court and the Federal Circuit to find that Lin's DNA and host cell inventions were unobvious. It is noteworthy that the Fritsch et al brief presents exactly the same argument on obviousness of the present count as was presented in its

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[19] The 11 clones developed as candidates for Amgen's prospective master working cell bank were from the CHO B11 3.1 cell strain, and Lin's knowledge as to these, was included in the Court's consideration. See District Court review (page 1772).

[20] Attention is also called to the footnote 5 of the Federal Circuit decision (18 USPQ2d at 1023) which reads:

> *Defendants assert that all the claims should be invalid for failure to disclose the best mode. We perceive that the best mode issue only relates to the host cell claims 4, 6, 23-27 and 29. Absent inequitable conduct, a best mode defense only affects those claims covering subject matter the practice of which has not been disclosed in compliance with the best mode requirement. See Northern Telecom, Inc. v. Datapoint Corp., 908 F2d 931, 940, 15 USPQ 2d 1321, 1328 (Fed. Cir.) cert. denied ____ U.S. ____, 111 S.Ct. 296 (1990).*

arguyment in the 102,096 interference except for two sentences beginning at the bottom of FB 49 and another two sentences in the penultimate paragraph of FB 49. The cryptic reference at FB 47 to "General Finding 2-3 et seq." simply invites attention to proposed findings III-36 to III-44 concerning Lin's prosecution. The FB 49 citation to proposed finding III-49 is an attempt to invest the Toole et al patent with significance.

Fritsch et al state (FR 46) that if the cloning approach was "obvious to try" and there was a reasonable chance of success, then the preparation of the host cells would be obvious. However, the Federal Circuit rejected this argument and affirmed that the EPO DNA sequence and host cells transformed therewith are not obvious from the prior art, including the Toole et al patent. Thus, the Federal Circuit, in agreeing with the District Court's position that the Lin '008 patent claims were valid over the prior art, including the Toole patent, stated (1022):

> *The district court specifically found that, as of 1983, none of the prior art references "suggest[s] that the probing strategy of using two fully-redundant [sic] sets of probes, of relatively high degeneracy [sic], to screen a human genomic library would be likely to succeed in pulling out the gene of interest." 13 USPQ2d at 1768. While it found that defendants had shown that these procedures were "obvious to try", the references did not show that there was a reasonable expectation of success. See In re O'Farrell, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1680-81 (Fed. Cir. 1988).*
>
> *Defendants challenge the district court's determination, arguing that, as of September 1983, one of ordinary skill in the art would have had a reasonable expectation of success in screening a gDNA library by Lin's method in order to obtain EPO. We agree with the district court's conclusion, which was supported by convincing testimony. One witness, Dr. Davies of Biogen, another biotechnology company that had worked on EPO, stated that he could not say whether Biogen scientists would have succeeded in isolating the EPO gene if Biogen had the EPO fragments that were available to Lin in 1983.*

> *Dr. Wall, a professor at UCLA, testified that it would have been "difficult" to find the gene in 1983, and that there would have been no more than a fifty percent chance of success. He said, "you couldn't be certain where in the genomic DNA your probe might fall". The court found that no one had successfully screened a genomic library using fully-degenerate probes of such high redundancy as the probes used by Lin. In the face of this and other evidence on both sides of the issue, it concluded that defendants had not shown by clear and convincing evidence that the procedures used by Lin would have been*
> *obvious in September 1983. We are not persuaded that the court erred in its decision.*

The Federal Circuit then summarized its opinion on the obviousness issue as follows:

> *Hindsight is not a justifiable basis on which to find that ultimate achievement of a long sought and difficult scientific goal was obvious. The district court thoroughly examined the evidence and the testimony. We see no error in its result. Moreover, if the DNA sequence was not obvious, host cells containing such sequence, as claimed in claims 4 and 6, could not have been obvious. We conclude that the district court did not err in holding that the claims of the patent are not invalid under Section 103.*

Clearly, in the circumstances, there is no merit whatsoever in the Fritsch argument under Section 103. The Primary Examiner recognized that the subject matter at issue was patentable and quite properly so. Significantly, Fritsch et al do not say that the process is unpatentable to them, only to Lin, and it is evident that their arguments are pitched primarily on the idea that obtaining the EPO DNA sequence was obvious (FB 47, 48). However, the Federal Circuit decision clearly confirms that the Fritsch et al position is incorrect and, in light of the Federal Circuit holding that the DNA sequence and host cells transfected therewith are unobvious, it follows that Lin's process claims should also define unobvious and patentable subject matter. The DNA sequence and host cells

transformed or transfected therewith were not available in the prior art and the process at issue could not be performed. Furthermore, it was not obvious that in vivo biologically active recombinant human EPO could be made by the claimed process. Until Lin obtained the sequence, Browne used it in expression and Egrie with Dukes found the product had in vivo biological activity, the process at best was only a wish.

While it is probably unnecessary to do so, it is noted for emphasis that the Toole et al patent (U.S. 4,757,006), on which Fritsch relies, is concerned with a fundamentally different protein (Factor VIII) and says nothing about EPO. The Toole patent was considered by the District Court on the arguments presented by Fritsch et al at, for example, FB 51 and properly dismissed. It is further noted that Fritsch et al were not able to isolate the EPO gene and prepare recombinant EPO without a great deal of work independent of, and notwithstanding, the availability of the Toole et al disclosure. All of this, of course, underscores the unobviousness of the invention.

Finally, it is noted that while the District Court addressed the Factor VIII work at GI in the context of representation in the Toole et al patent, the status of the patent as a 102(e)/103 prior art reference against Lin has not been established. The undisputed finding of the District Court was that, with respect to Lin, "[T]he successful cloning of the EPO gene took place in September or early October, 1983" (relying on the testimony and laboratory notebooks of Lin). The Toole et al patent, on the other hand is based on an application filed October 28, 1983, and has an effective date for purposes of 35 U.S.C. 102(e) after Lin's reduction to practice of the EPO gene. Hence, the Toole

et al patent is not citable as prior art.[41] Fritsch et al's references to the alleged September, 1983, dates of cloning work at GI are not relevant to obviousness of Lin's invention because the secret work on Factor VIII is not prior art to Lin.

(e) Lin is the True Inventor of the Process At Issue

Lin is the true inventor of the process defined by the count and his claims corresponding to the count. Fritsch admits as much when he states in his brief (FB 24) that "as in the '096 interference, priority turns upon the first conception of the purified and isolated EPO gene". Clearly, priority and inventorship go hand-in-hand. Thus, if Lin is the first to conceive the purified and isolated gene, as the Federal Circuit has affirmed, priority and inventorship of the count of this interference, and the invention represented thereby go to Lin.

Fritsch et al argue that Lin is not the inventor of the process involving expression of recombinant EPO because Lin did not presently carry out any of the process steps (culturing and isolating). However, this argument clearly has no merit. It is not essential for the inventor himself to carry out the steps involved. Furthermore, by the acknowledgement of Fritsch et al, the isolated DNA sequence is the novel feature of the process claims and Lin's inventorship with regard to the sequence has not been challenged.

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[41] The Examiner-in-Chief visualized this possibility in his decision on motions (Paper No. 35) and the reference back to motion A in Interference No. 102,096 in the discussions regarding Fritsch et al motion H.

The Lin record shows that the expression of EPO in mammalian cells (293 cells, COS cells and CHO cells) using the DNA sequence isolated by Dr. Lin was carried out by Dr. Jeff Browne at Dr. Lin's request (LR 3, 10, 41). Clearly, the whole purpose of isolating the DNA sequence was to use the sequence in expression to obtain in vivo biologically active recombinant EPO. Dr. Lin provided the DNA sequence which he had isolated to Dr. Browne for such expression (LR 3) and the recombinant EPO obtained by Dr. Browne was determined by Dr. Egrie to have in vivo biological activity (LR 4, 10, 67, 68). The production process is not obvious but the process is properly attributable to Lin as the one who succeeded in isolating the DNA sequence and requested its use in expression to give recombinant human EPO. The expression and isolation of the recombinant EPO did not involve separate inventive input by anyone other than Lin. Clearly, Lin is the true inventor since he obtained the sequence to use in the production of recombinant human EPO.

As for the isolating step, there is clearly nothing separately inventive in this. Fritsch et al again try to equate isolation with purification but, as noted earlier, these two are not the same, as Fritsch et al obviously recognized when they referred to their own disclosure for support for their claims corresponding to the count.

(f) The Fritsch et al Motion to Correct Inventorship Should be Denied

With regard to the Fritsch argument that he is the sole inventor (FB 32-34), Lin submits that Fritsch should not be permitted to correct the inventorship of the Fritsch

et al application and the Fritsch et al preliminary statement for the reasons noted in the Lin opposition to the Fritsch et al motion to correct (Paper Nos. 63, 64), the Lin opposition being incorporated herein by reference. In brief, Fritsch et al have not shown that the alleged misjoinder of the latecomers Hewick and Jacobs occurred through error and without deceptive intent. They also have not shown how the error occurred nor have they adequately demonstrated when the error was discovered or that they proceeded diligently when the error was discovered.

The Lin opposition to the Fritsch et al motion, to correct inventorship points out in detail how, prior to the Fritsch et al motion, Fritsch et al attested that they were joint inventors of the subject matter disclosed and claimed in the Fritsch et al '258 and '688[12] applications at least ten times. Many of these attestations overlapped in time with arguments which were being advanced by his assignee's trial counsel in the District Court litigation to the effect that Edward F. Fritsch alone ("Fritsch sole") was the inventor of this subject matter. Inventorship was discussed with trial counsel in a context from which it is clear that at least Dr. Fritsch considered himself the sole inventor. See, FR 2787-2794, especially at 2790 and 2793. However, Fritsch et al took no action herein to correct inventorship until 10 months after the District Court decision. No newly discovered facts have been presented as forming the basis of this determination. No

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[12] The '258 application (Serial No. 693,258) is the subject of the motions to correct inventorship filed by Fritsch et al in Interference Nos. 102,096 and 102,097. The '688 application (Serial No. 824,688) is involved in motion to correct filed in Interference No. 102,334.

light is shed on how, in view of repeated analysis of the same facts by the originally named inventors and their counsel, there could have been so many "erroneous" declarations of joint inventorship. Instead, statements are now made to the effect that, until the motion to correct was filed, no lawyer or scientist possessed a sufficient understanding of the technology or the standards of inventorship to properly determine who "invented" the subject matter of the counts at issue here and in the related interferences. Under such circumstances, correction of inventorship designations in the Fritsch et al applications should not be permitted, particularly when the proposed correction is based on the erroneous assumption that there could be conception of the isolated EPO gene separate from its reduction to practice.

As for when the error was discovered, it is manifest that the "error" could have been, and should have been, discovered when at least one of the Fritsch et al. applications was filed or at the latest when the Rule 608(b) showing was filed. The Fritsch testimony on discussions with counsel concerning the work of his co-inventors for purposes of the 608(b) showing reveals that nothing new factually was provided to counsel for purposes of the motions for correction. Compare FR 2716-2721 with 2714-2715 and 2753-2759.

The Fritsch et al attorney must have been aware of the late arrival of Jacobs on the scene (1983) when he prepared the Rule 608(b) showing. This did not require any knowledge as to biotechnology. At least as of the date when the Rule 608(b) showing was prepared, the attorney had to know, or should have known, that the Fritsch et al. inventorship was wrong if the Fritsch et al. allegations as to dates of invention in the

Rule 608(b) were considered reasonably based. Moreover, when the Fritsch et al attorney prepared the preliminary statement herein and in the other two interferences, he also prepared preliminary motions addressing complex issues of biotechnology and inventorship. Clearly, the attorney must have considered the Fritsch et al., "inventive contribution" evidence said to be the basis for the present motion when the preliminary statements and motions were prepared and he also had to be familiar with the litigation proceedings and the issues there involved[7]. All of this knowledge on the attorney's part clearly negates the required diligence to correct inventorship at this stage.

For all of the above reasons, it is submitted that the Fritsch et al motion to correct inventorship and the related motion to correct their preliminary statement, should be denied.

(g) **Lin Is Entitled to Priority on the Basis of His Earlier Filing Dates**

At least two of Lin's applications Serial No. 561,024, filed December 13, 1983 and Serial No. 582,185, filed February 21, 1984 are prior to any possible date

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[7] Rule 11 of the Federal Rules of Civil Procedure mandates inter alia that:

> "...The signature of an attorney or party constitutes a certificate by the signer that the signer has read the pleading, motion, or other paper; that to the best of the signer's knowledge, information, and belief formed after reasonable inquiry it is well grounded in fact and is warranted by existing law or a good faith argument for the extension, modification, or reversal of existing law, and that it is not interposed for any improper purpose, such as to harass or to cause unnecessary delay or needless increase in the cost of litigation..." (emphasis supplied)

Fritsch may rely on taking into account the Federal Circuit position regarding simultaneous conception and reduction to practice. Fritsch et al have not challenged the adequacy of these earlier applications at final hearing. Since Lin has satisfied best mode requirements, Lin is entitled to priority on the basis of his earlier applications on constructive reduction to practice.

IV. CONCLUSION

The Lin motion for judgment should be granted and all Fritsch et al claims should be found unpatenteable under 35 USC 102(g) in view of the Federal Circuit ruling as to Lin's prior work. Priority should be awarded to Lin for the reasons indicated herein with a holding that Lin is entitled to his claims corresponding to the count and that Fritsch et al are not entitled to their claims corresponding to the count.

The Fritsch et al motion to correct inventorship should be denied.

Respectfully submitted,

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