EXHIBIT H

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IN THE

UNITED STATES PATENT and TRADEMARK OFFICE

Before the Board of Patent Appeals and Interferences

Interference No. 102,097

FRITSCH

v.

LIN

Examiner-in-Chief Marc L. Caroff

BRIEF FOR THE PARTY FRITSCH

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degenerate. It also teaches how to screen the genomic DNA library under conditions to achieve probe hybridization to the desired library DNA sequence. Findings III-14, III-15. The cloning of the Factor VIII DNA from a genomic DNA library, as reported in the Toole et al. patent, took place at GI on September 20, 1983, Finding II-102, before Lin commenced the screening of the genomic DNA library which ultimately resulted in his cloning of the EPO gene.

ARGUMENT

I. DR. FRITSCH IS THE PRIOR INVENTOR OF THE SUBJECT MATTER INVOLVED IN THIS INTERFERENCE

A. The Legal Standard

Under 35 U.S.C. § 102(g), a person is entitled to a patent unless "before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it." Section 102(g) further provides that in

> determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

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Thus, an inventor is considered the first inventor if he or she was the first to conceive of the invention and exercised reasonable diligence in reducing it to practice, even if the second inventor reduced to practice first. 3 D. Chisum, Patents, §10.03(1) at 10-20 (1988). See also Marconi Wireless Tel. Co. v. United States, 320 U.S. 1, 34-35, 63 S.Ct. 1393, 1409 (1943) ("It is well established that as between two inventors, priority of invention will be awarded to the one who by satisfying proof can show that he first conceived the invention").

In interferences, the Board applies a preponderance of the evidence standard in determining which party is the prior inventor. Morgan v. Hirsch, 728 F.2d 1449, 1451, 221 U.S.P.Q. 193, 194 (Fed. Cir. 1984); Fisher v. Gardner, 215 U.S.P.Q. 620, 632 (Bd. Pat. App. & Int. 1981). The presumption of validity of 35 U.S.C. § 282 is inapplicable. Lamont v. Berguer, 7 U.S.P.Q.2d 1580, 1582 (Bd. Pat. App. & Int. 1988).

Conception requires "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1376, 231 U.S.P.Q. 81, 87 (Fed. Cir. 1986) (quoting 1 Robinson on Patents 532 (1890)), cert. denied, 480 U.S. 497 (1987); Coleman v. Dines, 754 F.2d 353, 359, 224 U.S.P.Q. 857, 862 (Fed. Cir. 1985). To be complete, a conception need not include every detail of how

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to reduce the invention to practice. In re Tansel, 253 F.2d 241, 243, 117 U.S.P.Q. 188, 189 (C.C.P.A. 1958); see Lazo v. Tso, 480 F.2d 908, 178 U.S.P.Q. 361 (C.C.P.A. 1973) (research plan and trip report sufficient to show conception); Vanderkooi v. Hoeschele, 7 U.S.P.Q.2d 1253, 1255 (Bd. Pat. App. & Int. 1987) (mere determination of suitable range of values for suggested result is prima facie within the realm of ordinary skill). Rather, a conception is complete if it would enable one skilled in the art to reduce the invention to practice. Kardulas v. Florida Mach. Products Co., 438 F.2d 1118, 1121, 168 U.S.P.Q. 673, 675 (5th Cir. 1971).

Conception of a chemical compound, such as a gene, requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1206, 18 U.S.P.Q.2d 1016, 1021 (Fed. Cir. 1991). The inventor can define the compound by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it from other materials. Id.

Conception of a purified and isolated gene may occur when the inventor has sufficient information to envision the detailed constitution of the gene so as to distinguish it from other materials, as well as a method for obtaining it. Amgen Inc. v. Chugai Pharmaceutical Co. 927 F.2d 1200, 1206, 18 U.S.P.Q.2d 1016,

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1021 (Fed. Cir. 1991). Similarly, conception may occur when the inventor conceives of a process for identifying the gene with sufficient specificity that one skilled in the relevant art would succeed in cloning the gene. 927 F.2d at 1207, 18 U.S.P.Q.2d at 1021.

In the context of the count involved in this interference, a complete conception would comprise (1) conception of a purified and isolated EPO gene, together with (2) a method for using the gene to express in vivo active EPO. Only the first of these two components can be argued to have required more than ordinary skill. The use of transfected mammalian host cells to express proteins was well known by 1981. FR 1396-98 (Fritsch). And as the examiner of Lin's involved '179 application recognized, the prior art also taught that mammalian host cells could be used for the expression of in vivo active glycosylated proteins. '179 Application, Examiner's Rejection, paper 9, p. 2. Moreover, the record shows that Fritsch conceived of using such mammalian expression systems for the expression of EPO by 1981. PX 38; see also FX 113 (Fritsch Summary of Cloning Strategy, August 1982, at pp. 9599, 9606); FR 1575 (Fritsch); FR 3486-87 (Shoemaker).

Accordingly, as in the '096 interference, priority turns upon the first conception of the purified and isolated EPO gene. The record here establishes that Dr. Fritsch, not Dr. Lin, was the first to make such a conception of the isolated EPO gene and

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thereafter exercised reasonable diligence in reducing it to practice. Thereafter, he and his staff were also diligent in expressing the EPO gene in mammalian host cells to obtain in vivo active EPO. And such in vivo active recombinant human EPO was in fact expressed. Accordingly, Fritsch is the prior inventor.

B. Dr. Fritsch First Conceived Of The Invention

Precision in dating Dr. Fritsch's conception is, to some degree, unnecessary given Amgen's failure to show a conception date prior to September 1983. Since the record clearly shows that Dr. Fritsch had conceived of an operative probing technique by December 1981, the corroborated evidence of Dr. Fritsch's conception makes his invention prior to Dr. Lin's whether conception is dated in early 1982, when Dr. Fritsch first obtained the Hewick N-terminal sequence data; or in August 1982, when his description of the invention was sent to Toyobo; or in September/October 1982, when his probing technique was first used; or in June 1983, when he designed, ordered, and received the first of a set of oligonucleotide probes that would have succeeded in isolating the EPO gene. Findings II-8, II-16 - II-18, II-21, II-41, II-42, II-54 - II-59, II-63, II-98 - II-101. Any one of these dates is sufficient to make Dr. Fritsch the first inventor.

Moreover, the record establishes that Fritsch's conception was complete. Dr. Fritsch did not engage in the sort of

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trial and error which is the hallmark of "those unusual cases" where conception cannot occur prior to reduction to practice. See Alpert v. Slatin, 305 F.2d 891, 894, 134 U.S.P.Q. 296, 299 (C.C.P.A. 1962). Rather, he formulated his conception, predicted its success using a mathematical formula and then consistently applied the very same conception until the invention was successfully reduced to practice. The results of Dr. Fritsch's initial screenings consistently demonstrated beyond doubt that he had mastered the hybridization technology embodied in his concept. A similar concept was successful in isolating the Factor VIII gene prior to Dr. Lin's isolation of the EPO gene. And, most significantly, Dr. Fritsch, like Dr. Lin, was immediately successful in implementing this cloning approach upon obtaining accurate sequence information.[3]

To establish a conception date prior to the application for the '008 patent, Lin was required to offer independent and

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[3] Correct sequence information and designing probes based on the best region for screening is part of the art which one of ordinary skill would have had available in using Dr. Fritsch's conception. Finding III-33, Conclusion of Law III-22. Lack of this additional correct sequence information and the probes based upon it does not preclude a finding of conception. Vanderkooi v. Hoeschele, 7 U.S.P.Q.2d at 1255 ("the law does not require that every limitation in the counts must be exactly foreseen before a conception can be said to be complete"); Philco Corp. v. Radio Corp. of America, 276 F. Supp. 24, 41, 155 U.S.P.Q. 372, 378-80 (D. Del. 1967) (means to effect an integral function of the invention were known to those skilled in the art and the inventor's conception by implication embodied the necessary means).

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corroborated evidence.[4] Kardulas, 438 F.2d at 1121, 168 U.S.P.Q. at 676; Chisum, supra, §3.08[3] at 160-61. The earliest date satisfying this evidentiary standard is September 25, 1983, the date Dr. Lin began screening a genomic library with two sets of fully degenerate probes.

Moreover, prior to September 1983, there is no evidence, corroborated or otherwise, that Dr. Lin ever designed or used two sets of fully degenerate probes from two different regions to probe a genomic library. Finding II-312. This was the "method for obtaining" the gene required for a valid conception. Amgen, 927 F.2d at 1206, 18 U.S.P.Q.2d at 1021. Under a "rule of reason" for determining whether the corroboration requirement has been met, Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d at 1376-

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[4] Lin's record contains testimony concerning a 1981 conversation between Dr. Lin and Martin Cline, a member of Amgen's scientific advisory board, and certain handwritten notes allegedly taken by Dr. Cline during that conversation. This testimony, however, fails to corroborate a conception by Lin prior to September 1983. Findings II-304 - II-312. Indeed, Dr. Cline's testimony does not mention any conversations with Dr. Lin at all. Nor is there competent testimony in the record that Dr. Cline's notes were based on conversations with Dr. Lin. Neither the notes nor Dr. Cline's testimony, alone or in combination, describes in full an operative method for obtaining the EPO gene. Nor do they show that Lin possessed sufficient information regarding the EPO gene "to distinguish it from other materials." Amgen, 927 F.2d at 1206, 18 U.S.P.Q.2d at 1021. In short, the only evidence of a conception by Dr. Lin in 1981 is his own testimony. This is insufficient to satisfy the corroboration requirement. Ganguly v. Sunagawa, 5 U.S.P.Q.2d 1970, 1973 (Bd. Pat. App. & Int. 1987).

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77, 231 U.S.P.Q. at 87-88, this absence of record support for an earlier use of the method for obtaining the gene is fatal to Lin's attempt to establish a date of conception prior to September 1983. Dr. Lin's failure to use the method for obtaining the gene until two years after the Cline conversation also precludes a finding that Dr. Lin's purported conversation with Dr. Cline represented in Dr. Lin's mind "a definite and permanent idea of the complete and operative invention." Id.

C. Dr. Fritsch Is The Prior Inventor

Lin cannot seriously dispute that Dr. Fritsch worked diligently to reduce his conception to practice. With the exception of honoring pre-existing commitments to teach cloning techniques, Dr. Fritsch's professional work was continuously devoted to GI's EPO project from the time he first conceived of the invention until its reduction to practice. Findings II-1 - II-15, II-27 - II-147. The record also contains ample evidence of diligence on the part of the GI employees working under Dr. Fritsch's direction. These included at least 36 scientists, six of whom were Ph.D.'s. These 36 scientist were diligent both in working toward the cloning of the EPO gene and in expressing the protein thereafter. Findings II-154 - II-301. This diligence is sufficient to establish Dr. Fritsch as the prior inventor pursuant to 35 U.S.C. §102(g).

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Between the dates of September 1982 and March 1983, Dr. Fritsch and the scientists working under his direction carried out three full screenings of genomic libraries using his method. In these screenings, designated at the E, G, and H screens, Dr. Fritsch was assisted by his laboratory technicians Elizabeth Orr, Marilee Shaffer and Suzanne Neill. Ms. Shaffer and Ms. Neill performed work on the screens, while Ms. Orr characterized the isolated probable "positive" clones by sequencing the isolated DNA sequences on sequencing gels. Findings II-63 - II-81. And in May 1983, Dr. Fritsch conducted a fourth screen, designated the A screen. Ms. Shaffer assisted Dr. Fritsch in the A screen, and Ms. Orr sequenced the isolated DNA of one of the putative positive clones. Findings II-82 - II-85.

By the spring of 1983 the cause of failure to isolate the EPO gene by these screens was correctly diagnosed by Dr. Fritsch: the available amino acid sequence of the EPO protein upon which he was relying was erroneous. Findings II-21, II-86. Accordingly, immediate steps were taken to obtain additional EPO for sequencing. Initially, a promising kidney carcinoma cell line was obtained as a potential source of EPO mRNA and of EPO protein. In addition, a small quantity of low purity EPO was located, but the quantity was insufficient to be upgraded for sequencing. These activities took place from the summer of 1983 to February 1984. Findings II-87 - II-96.

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In the meantime, while the search for additional EPO protein was ongoing, and commencing in mid 1983 and continuing until March 1984, Dr. Jacobs and Ms. Neill, acting pursuant to Dr. Fritsch's directions, performed four additional screens, designated the Jacobs A, U, V and T screens, using a new set of probes based on regions of the amino acid sequence which were correct.[5] Findings II-97 to II-99.

Early in 1984, GI opened new discussions with Dr. Miyake (a former colleague of Dr. Goldwasser) concerning obtaining additional EPO of suitable purity for sequencing. An agreement was quickly reached with Dr. Miyake to supply purified EPO and the first EPO shipment arrived in April 1984. Dr. Hewick further purified this sample, prepared tryptic fragments and sequenced the sample, then supplied the sequence information to Dr. Fritsch. Findings II-103 - II-106.

Upon receiving the new amino acid sequence information, Dr. Fritsch designed and ordered new fully degenerate probes, and on May 30, 1984 the K screen was commenced by plating the library used to isolate the EPO gene and then hybridizing it with two sets of fully degenerate probes from different regions of the amino acid sequence. The technique was similar to the technique used in the

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[5] As indicated in the statement of facts, the new set of probes was divided into two subsets because of the high degeneracy of one of the regions (position 15 to 19). The second subset contained the exact sequence but was not used because a new EPO sample for sequencing was soon to arrive. Finding II-100.

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E, G, H, and A screens and was at once successful. The EPO gene was among the clones isolated from the K screen. Finding II-113. Dr. Fritsch was assisted in the K screen by his laboratory technician Ms. Neill and Dr. Jacobs. Dr. Shoemaker performed work in characterizing the isolated DNA sequences of the positive clones.

Ms. Neill's extensive activities on the EPO project between the dates of March 18, 1983 and July 20, 1984 are documented in Findings II-236 - II-239. Dr. Jacobs' involvement in the EPO project included plating and screening genomic libraries (screens A, U, T and V) with oligonucleotide probes and optimizing the hybridization thereof. His work on the project between the dates of July 12, 1983 and June 29, 1984 is documented in Findings II-201 - II-203. Ms. Orr's work in sequencing the DNA of potential EPO clones and other DNA in the period December 7, 1982 to October 19, 1984 is documented in Findings II-240 - II-243. Moreover, the record contains extensive evidence of further expression, purification, and characterization work by various GI scientists under Dr. Fritsch's direction through January 1985. Findings II-123 - II-141, II-154 - II-301.

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5. That Lin's claims corresponding to the count are unpatentable to Lin under 35 U.S.C. § 102(f).

Respectfully submitted,

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Dated: July 8, 1991

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