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Short Communication

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TECHNICAL IMPROVEMENTS IN PROTEIN MICROSEQUENCING

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Summary. Improved techniques for preparing samples and sequencing reagents have been developed to achieve highly sensitive protein sequencing. These improvements include a new sequencing buffer system which gives extremely low chromatographic background, a method for preparing Polybrene, a key chemical in gas-phase protein microsequencing, and techniques for preparing protein samples suitable for microsequencing.

Protein microsequencing is important in protein characterization for production of recombinant DNA-derived protein products. In the past few years, the sensitivity of protein sequencing has been remarkably increased by improvements in sequencer design, methods of determining phenylthiohydantoin amino acids (PTH amino acids) and sample preparation. The most significant improvement in sequencer design has been the gas-phase sequencer which uses polybrene, a polymeric quaternary ammonium salt, for the physical immobilization of a protein sample in the reaction chamber and aqueous trimethylamine (TMA) and anhydrous trifluoroacetic acid (TFA) in coupling and cleavage steps, respectively [1]. Both reagents are delivered as gases. Both the polybrene and TMA can cause problems. Commercially available polybrene contains impurities which interfere with Edman degradation. Polybrene can be purified by running Edman degradation cycles in the presence of a dipeptide prior to sample application [1, 2]. The precycling of polybrene takes 8—12 h for each analysis which significantly reduces the time available for actual analysis.

In the case of TMA, water vapor is delivered with TMA vapor causing the partial degradation of phenylisothiocyanate. Secondly, dimethylamine can be formed from TMA during storage in the sequencer; it reacts with phenylisothiocyanate to form phenylthiocarbamyldimethylamine which interferes with PTH-amino acid analysis [3].

To improve the overall performance of protein sequence analysis, several approaches were made to improve sequencer usage, to eliminate interference caused by degraded sequencing reagents, and to remove contaminating salts in the protein sample by liquid—liquid extraction.

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DEFENDANT'S DEPOSITION EXHIBIT
LDX-45
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TABLE 1

Comparison of reagents/solvents used in the published and modified procedures

Reagent/ solvent	Published procedure [1][a]	Modified procedure	Improvement
Immobilizing carrier	polybrene + dipeptide	prepurified polybrene	50% more analysis
R1	10% PITC[b] in n-heptane	same	>50% reduction in cost
R2	25% TMA in water	25% TMA in 2-propanol + 2 g ninhydrin 0.2 g hydrindantin	20-fold reduction in levels of DPTU and PTCDMA; no distillation required; 15-fold reduction in cost; more sensitive analysis less overlap
S4	methanol/0.001% dithiothreitol	10% acetonitrile in methanol/0.001% dithiothreitol	

[a]No changes were made to R3 (TFA), R4 (1 M HCl/methanol), S2 (ethyl acetate) or S3 (n-butyl chloride). [b]Phenylisothiocyanate.

reported evaluation of a gas-phase sequencer (i.e., 110 analyses per year [2]), the gas-phase sequencer using prepurified polybrene can be used for 50% more analyses. The use of prepurified polybrene also significantly improved the cost efficiency. The cost of precycling is reduced by at least 50% compared to the cost for precycling commercial polybrene. It is also possible to do two sequence analyses with one sequencer in a day. This is particularly important for testing the purity of peptide or protein samples before an extended sequence analysis is conducted.

The improved R2 can achieve the same coupling efficiency as the original one (Table 1), yet it uses no purification apparatus and greatly reduces the formation of two major gas-phase sequencing artifacts, i.e., diphenylthiourea and phenylthiocarbamyldimethylamine (PTCDMA), as shown in Fig. 1. 2-Propanol, which replaces water in the original R2, decreases the formation of diphenylthiourea, the hydrolysis product of phenylisothiocyanate. Ninhydrin is added to react with contaminating primary and secondary amines such as dimethylamine and prevents them from being delivered to the reaction chamber. As shown in Fig. 1, the levels of diphenylthiourea and PTCDMA observed with the improved R2 are only about 5% of those obtained with the original R2. The diphenylthiourea interferes with the identification of PTH—methionine and PTH—proline, while PTCDMA coelutes with PTH—glutamine when the system described by Hunkapiller and Hood [3] is used. Although the h.p.l.c. gradient system can be modified to separate PTCDMA from PTH—glutamine and diphenylthiourea slightly from PTH—methionine, it loses some resolution between certain pairs of PTH amino acids, such as PTH—tyrosine and PTH—valine, and PTH—leucine and PTH—phenylalanine. The ability to determine PTH—glutamine and

TABLE 2

Polypeptides studied with the gas-phase sequencer using improved procedures

Sample	Residues identified/ total residues	Amount (pmol)
Yeast-secreted β-endorphin peptides [5][a]		
Peptide I	12/12	880
Peptide II	19/19	140
Peptide IIIa	18/18	150
Tryptic peptides derived from human erythropoietin		
T13	4/4	85
T25	6/6	80
T35	7/7	80
T28	15/15	45
T38	21/21	60
E. coli Colicin Ib [6]	28/625	1800
rDNA-derived chicken growth hormone [7][b]	68/191	15000

[a] β-Endorphin peptides I: ÑAIIKNAYKKGĒ; II: ŶGGFLTSEKSQTPLLVTLFK and III: ĒAEAŶGGFLTSEK. [b] rDNA-derived chicken growth hormone: M̄FPAMFLSNLFANAVLRAQHLHLLAAETYKEFERTYIPEDQRYTNKNSQAAFXY(S)ETIXAPT(G)KXXAXQKXXM.

techniques is clearly illustrated in Table 2 and was particulary important in the structural determination of human erythropoietin and rDNA-derived β-endorphin peptides. Sequence information obtained from a tryptic peptide derived from human erythropoietin has been used to synthesize DNA probes and finally has led to the successful cloning and expression of this protein [8]. Using the improved microsequencing techniques, it was also possible to identify and determine the β-endorphin peptides secreted and proteolytically processed by genetically engineered yeast [5]. Sequencing of 15 nmol of intact rDNA-derived chicken growth hormone yielded the structure of the amino terminal 68 residues, which is 36% of the entire protein molecule [7].

Reproducible and highly sensitive protein sequencing with high resolution
al for productive recombinant DNA research. Although its most
ant role is in the determination of the sequence of minute amounts
logically important proteins, protein microsequencing has many other applications. It is required to identify the amino terminus of secreted protein and in the determination of the coding regions of genomic sequences containing introns. It can be used to identify post-translational modifications of proteins and to confirm DNA sequence analysis [9–13]. In addition, it is required in elucidating the structure of proteins produced by recombinant DNA techniques.

EXHIBIT B

[13] Scripps charges that Genentech's recombinantly-produced Factor VIII:C infringes the product-by-process claims, either literally or by application of the doctrine of equivalents. The district court remarked that the product-by-process claims would not be infringed unless the same process were practiced. Scripps correctly points out that this statement appears to diverge from our precedent, recognizing that this precedent arose in the context of patent prosecution, not patent infringement. *E.g.*, *In re Thorpe*, 777 F.2d 695, 227 USPQ 964 (Fed. Cir. 1985) (holding that prior art pertinent only to product is proper ground for rejecting product-by-process claims); *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972) (in product-by-process claims the patentability of the product must be established independent of the process); *In re Bridgeford*, 357 F.2d 679, 682 n.5, 149 USPQ 55, 58 n.5 (CCPA 1966) (recognizing that some courts in infringement litigation have construed product-by-process claims as limited to the particular process, but holding that patentability is determined independent of the process). In determining patentability we construe the product as not limited by the process stated in the claims. Since claims must be construed the same way for validity and for infringement, the correct reading of product-by-process claims is that they are not limited to product prepared by the process set forth in the claims. Thus, these claims are subject to an infringement analysis similar to that described in Part V, *ante*. Infringement of the product-by-process claims may be considered at trial.

IX

Attorney Fees

The district court held that this was an exceptional case under 35 U.S.C. §285, apparently due to the court's rulings on inequitable conduct and failure to comply with the best mode. Holdings under §285 are reviewed for abuse of the trial court's discretionary authority, considering the court's findings and conclusions and any other appropriate factors. *See Reactive Metals & Alloys Corp. v. ESM, Inc.*, 769 F.2d 1578, 1583, 226 USPQ 821, 824 (Fed. Cir. 1985). In view of our reversal of the grants of summary judgment on the issues of best mode and inequitable conduct, the award of attorney fees flowing therefrom must be vacated. *See State Indus., Inc. v. A.O. Smith Corp.*, 751 F.2d 1226, 1238, 224 USPQ 418, [...] holding case exceptional and accompanying award of attorney fees).

X

Other Issues

We have not repeated all the arguments and issues raised by both sides, including charges of frivolity, misstatement, and worse. Encumbered by the summary nature of the proceedings, neither scientific nor evidentiary truth has risen easily to the surface. However, we *DENY* Scripps' motion for sanctions against Genentech for filing a frivolous cross-appeal, for some of the issues raised were not clearly hopeless in law and fact. We also *DENY* each side's motions to strike various materials filed and to dismiss issues raised by the other.

Costs

Each party shall bear its costs.

AFFIRMED IN PART, REVERSED IN PART, VACATED IN PART, AND REMANDED

Court of Appeals, Federal Circuit

Amgen Inc. v. Chugai Pharmaceutical Co Ltd.

Nos. 90-1273, -1275

Decided March 5, 1991

PATENTS

1. Patentability/Validity — Date of invention — Conception (§115.0403)

Conception of chemical compound requires that inventor be able to define compound so as to distinguish it from other materials, and to describe how to obtain it, rather than simply defining it solely by its principal biological property; thus, when inventor of gene, which is chemical compound albeit complex one, is unable to envision detailed constitution of gene so as to distinguish it from other materials, as well as method for obtaining it, conception is not achieved until reduction to practice has occurred, and until after gene has been isolated.

2. Patentability/Validity — Date of invention — Conception (§115.0403)

Conception of generalized approach for screening DNA library that might be used to

identify and clone erythropoietin gene of then-unknown constitution is not conception of "purified and isolated DNA sequence" encoding human EPA since it is not "definite and permanent idea of the complete and operative invention."

3. Patentability/Validity — Obviousness — Relevant prior art — Particular inventions (§115.0903.03)

Federal district court did not err in holding non-obvious claims for purified and isolated DNA sequence encoding human hormone erythropoietin, in view of evidence showing that procedures may have been obvious to try, but also showing that there was no reasonable expectation of success.

4. Patentability/Validity — Specification — Best mode (§115.1107)

Determination of whether best mode requirement is satisfied is question of fact and thus is reviewed under clearly erroneous standard.

5. Patentability/Validity — Specification — Best mode (§115.1107)

Biological deposit is required to satisfy best mode requirement, for patents involving novel, genetically-engineered biological subject matter, if invention is incapable of being practiced without access to that organism, but if organism is created by insertion of genetic material into cell obtained from generally available sources, then cell deposit itself is not necessary and all that is required is description of best mode and adequate description of means of carrying out invention, if cells can be prepared without undue experimentation from known materials, based on description in patent specification, deposit is not required.

6. Patentability/Validity — Specification — Best mode (§115.1107)

Evidence showing that scientists were unable to duplicate inventor's genetically-heterogeneous best mode cell strain does not demonstrate that best mode requirement is not satisfied, since issue is whether disclosure is "adequate," and exact duplication is not necessary.

7. Patentability/Validity — Specification — Enablement (§115.1105)

Issue of whether claimed invention is enabled under 35 USC 112 is question of law that is reviewed de novo.

8. Patentability/Validity — Specification — Enablement (§115.1105)

Patent applicant is entitled to claim invention generically, if invention is described sufficiently to meet requirements of 35 USC 112; however, applicant, in claims for DNA sequences encoding erythropoietin, who has claimed every possible analog of gene containing about 4,000 nucleotides, but which has provided details for preparing only few EPO analog genes has not provided sufficient disclosure to support its claims since, in view of structural complexity of EPO gene, manifold possibilities for change in its structure, and uncertainty as to what utility will be possessed by these analogs, additional disclosure is needed as to identifying various analogs within scope of claim, methods for making them, and structural requirements for producing compounds with EPO-like activity.

9. Infringement — Defenses — Fraud or unclean hands (§120.1111)

Ultimate conclusion of inequitable conduct is reviewed under abuse of discretion standard, but underlying factual findings are reviewed under clearly erroneous standard.

10. Patentability/Validity — Specification — Enablement (§115.1105)

Federal district court erred by concluding that patent for method for purification of erythropoietin sufficiently enabled person of ordinary skill in art to obtain homogeneous EPO from natural sources having mean in vivo specific activity of at least 160,000, since court erred in accepting in vitro data as support for claims containing in vivo limitation.

11. Patentability/Validity — Specification — Claim adequacy (§115.1109)

Patent construction — Claims — Defining terms (§125.1305)

Claim whose meaning is in doubt is properly declared invalid, especially when there is close prior art; thus, federal district court did not err in holding that claim for homogeneous erythropoietin which has specific activity limitation of "at least about" 160,000 was indefinite, although such holding does not preclude any and all uses of term "about" in patent claims, since such term may be acceptable in appropriate fact situations.

Particular patents — Chemical — Erythropoietin

4,677,195, Hewick and Seehre, method for the purification of erythropoietin and erythropoietin compositions, claims 1, 3, 4 and 6 invalid.

4,703,008, Lin, DNA sequences encoding erythropoietin, claims 2, 4, and 6 valid and infringed; claims 7, 8, 23-27, and 29 invalid.

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patent because of Amgen's alleged inequitable conduct before the PTO. GI also counterclaimed, alleging that Amgen infringed the '195 patent, asserting unfair competition, and seeking a declaratory judgment that the '008 patent was invalid and not infringed.

GI and Chugai then filed a joint motion for a partial summary judgment that Amgen infringed the claims of the '195 patent. Chugai also filed its own motion for summary judgment. On February 24, 1988, the district court granted GI's and Chugai's motion for partial summary judgment and, on January 31, 1989, the court granted Chugai's motion for partial summary judgment only to the extent of ruling that the '008 patent does not contain a process claim, an issue that is not now before us.

In response to Amgen's motion for a preliminary injunction, the district court, on February 7, 1989, issued an order finding that "Amgen had shown a reasonable likelihood of success on the merits of the validity of its patent; that it would suffer irreparable injury due to the needs of an incipient market and the attendant burdens on a new company, . . ." and that, as to the public interest, "recombinant EPO is an extraordinarily valuable medicine that promises marked relief from renal failure." Because of this public interest finding, the court determined that it would not enter an order to delay or prevent production or shipping of EPO, but would require the defendant GI to place with the court all profits from the sale of EPO.

In order to expedite trial, the parties consented to trial before a magistrate. The judge entered judgment upon findings of fact and conclusions of law set forth by the magistrate. With respect to Amgen's '008 patent, the court held that claims 2, 4, and 6 are valid, enforceable and have been infringed by GI; that infringement was not willful; that claims 7, 8, 23-27, and 29 are invalid for lack of enablement under 35 U.S.C. §112 but, if valid, were infringed by GI; that the '008 patent does not contain a process claim; and that Chugai has not infringed, contributorily infringed, or induced infringement of any claim of the '008 patent. The court also dismissed Amgen's complaint against Chugai.

With respect to GI's '195 patent, the court concluded that claims 1 and 3 are valid, enforceable, and have been infringed by Amgen; that Amgen has not infringed claims 2 and 5; that Amgen's infringement was not willful; and that claims 4 and 6 are invalid for indefiniteness under 35 U.S.C. §112, but, if valid, were infringed by Amgen. The court also concluded that Amgen did not misuse the '008 patent and that this was not an "exceptional" case under 35 U.S.C. §285.

DISCUSSION

I. AMGEN'S '008 PATENT (Lin)

A. *Alleged prior invention under 35 U.S.C. §102(g)*

The first issue we review is whether the district court erred in finding that the claims directed to a purified and isolated DNA sequence encoding human EPO were not invalidated by the work of GI's Dr. Fritsch. Section 102(g) provides in relevant part that:

> A person is entitled to a patent unless—
> (g) before the applicant's invention thereof the invention was made . . . by another who had not abandoned, suppressed, or concealed it. 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.

Defendants assert error in the district court's legal conclusion that in this case Lin's conception occurred simultaneously with reduction to practice. *See e.g. Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1376, 231 USPQ 81, 87 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). They claim that Fritsch was first to conceive a probing strategy of using two sets of fully-degenerate cDNA probes of two different regions of the EPO gene to screen a gDNA library, which was the strategy which the district court found eventually resulted in the successful identification and isolation of the EPO gene. Defendants further claim that Fritsch conceived this strategy in 1981, was diligent until he reduced the invention to practice in May of 1984, and thus should be held to be a 102(g) prior inventor over Lin, who reduced the invention to practice in September of 1983.

Conception is the "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*, 802 F.2d at 1376, 231 USPQ at 87 (citing 1 *Robinson on Patents* 532 (1890)); *Coleman v. Dines*, 754 F.2d 353, 359, 224 USPQ 857, 862 (Fed. Cir. 1985) (citing *Gunter v. Stream*, 573 F.2d 77, 80, 197 USPQ 482, 484 (CCPA 1978)). Conception requires both the idea of the invention's structure and possession of an operative method of making it. *Oka v. Youssefyeh*, 849 F.2d 581, 583, 7 USPQ2d 1169, 1171 (Fed. Cir. 1988).

In some instances, an inventor is unable to establish a conception until he has reduced the invention to practice through a successful experiment. This situation results in a simultaneous conception and reduction to practice. *See* 1 D. Chisum, *Patents* §10.04[5] (1990). We agree with the district court that that is what occurred in this case.

The invention recited in claim 2 is a "purified and isolated DNA sequence" encoding human EPO. The structure of this DNA sequence was unknown until 1983, when the gene was cloned by Lin. Fritsch was unaware of it until 1984. As Dr. Sadler, an expert for GI, testified in his deposition: "You have to clone it first to get the sequence." In order to design a set of degenerate probes, one of which will hybridize with a particular gene, the amino acid sequence, or a portion thereof, of the protein of interest must be known. Prior to 1983, the amino acid sequence for EPO was uncertain, and in some positions the sequence envisioned was incorrect. Thus, until Fritsch had a complete mental conception of a purified and isolated DNA sequence encoding EPO and a method for its preparation, in which the precise identity of the sequence is envisioned, or in terms of other characteristics sufficient to distinguish it from other genes, all he had was an objective to make an invention which he could not then adequately describe or define.

[1] A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. *See Oka*, 849 F.2d at 583, 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, *i.e.*, until Fritsch had a goal of obtaining the isolated EPO gene, whatever its identity, and even had an idea of a possible method of obtaining it, but he did not conceive a purified and isolated DNA sequence encoding EPO and a viable method for obtaining it until after Lin. It is important to recognize that neither Fritsch nor Lin invented EPO or the EPO gene. The subject matter of claim 2 was the novel *purified and isolated* sequence which codes for EPO, and neither Fritsch nor Lin knew the structure or physical characteristics of it and had a viable method of obtaining that subject matter until it was actually obtained and characterized.

[2] Defendants further argue that because the trial court found that the probing and screening method employed by Lin was distinguished the invention of the '008 patent over the prior art, Fritsch's strategy in 1981 had priority over Lin's use of that strategy. We disagree. The trial court found that Fritsch's alleged conception in 1981 of an approach that might result in cloning the gene was mere speculation. Conception of a generalized approach for screening a DNA library that might be used to identify and clone the EPO gene of then unknown composition is not conception of a "purified and isolated DNA sequence" encoding human EPO. It is not "a definite and permanent idea of the complete and operative invention." Fritsch's conception of a process had to be sufficiently specific that one skilled in the relevant art would succeed in cloning the EPO gene. *See Coleman*, 754 F.2d at 359, 224 USPQ at 862. Clearly, he did not have that conception because he did not know the structure of EPO or the EPO gene.

The record indicates that several corporations, as well as Amgen and GI, were unsuccessful using Fritsch's approach. As the trial court correctly summarized:

> Given the utter lack of experience in probing genomic libraries with fully degenerate probes and the crudeness of the techniques available in 1981, it would have been mere speculation or at most a probable deduction from facts then known by Dr. Fritsch that his generalized approach would result in cloning the EPO gene.

13 USPQ2d at 1760. As expert testimony from both sides indicated, success in cloning the EPO gene was not assured until the gene was in fact isolated and its sequence known. Based on the uncertainties of the method and lack of information concerning the amino acid sequence of the EPO protein, the trial court was correct in concluding that neither had an adequate conception of the DNA sequence until reduction to practice

had been achieved; Lin was first to accomplish that goal.

Defendants also argue that the court failed to consider that 1983, just prior to Lin's conception, was the relevant time for determining the completeness of Fritsch's conception, not 1981. However, the record shows that the court did consider what occurred in 1983. Moreover, Fritsch had no more of a conception in 1983 than he did in 1981, because he did not then know the sequence of the gene encoding EPO.

B. *Alleged obviousness of the inventions of claims 2, 4, and 6*

Claim 2, as noted above, recites a purified and isolated DNA sequence, and claims 4 and 6 are directed to host cells transformed with such a DNA sequence. The district court determined that claims 2, 4, and 6 are not invalid under 35 U.S.C. §103, concluding that the unique probing and screening method employed by Lin in isolating the EPO gene and the extensive effort required to employ that method made the invention nonobvious over the prior art.[3]

Obviousness under Section 103 is a question of law. *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568, 1 USPQ2d 1593, 1597 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987). The district court stated that one must inquire whether the prior art would have suggested to one of ordinary skill in the art that Lin's probing and screening method should be carried out and would have a reasonable expectation of success, viewed in light of the prior art. *See In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). "Both the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure." *Id.*

[3] 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."[4] 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

[3] We note that both the district court and the parties have focused on the obviousness of a process for making the EPO gene, despite the fact that it is products (genes and host cells) that are claimed in the patent, not processes. We have directed our attention accordingly, and do not consider independently whether the products would have been obvious aside from the alleged

[4] At this point, some explanation of the involved technology may be useful, consistent with that expressed in the district court opinion. DNA consists of two complimentary strands of nucleotides, which include the four basic compounds adenine(A), guanine(G), cytosine(C), and thymine(T), oriented so that bases from one strand weakly bond to the bases of the opposite strand. A bonds with T, and G bonds with C to form complementary base pairs. This bonding process is called hybridization and results in the formation of a stable duplex molecule. The structure also includes 5-carbon sugar moieties with phosphate groups.

The genetic code for a particular protein depends upon sequential groupings of three nucleotides, called codons. Each codon codes for a particular amino acid. Since there are four nucleotide bases and three bases per codon, there are 64 (4x4x4) possible codons. Because there are only 20 natural amino acids, most amino acids are specified by more than one codon. This is referred to as a "redundancy" or "degeneracy" in the genetic code, a fact that complicates and renders more difficult the techniques of recombinant DNA.

In order to prepare a protein using recombinant DNA technology, the gene for the protein must first be isolated from a cell's total DNA by screening a library of that cell's DNA. The DNA library is screened by use of a probe, a synthetic radiolabelled nucleic acid sequence which can be used to detect and isolate complementary base sequences by hybridization. To design a probe when the gene has not yet been isolated, a scientist must know the amino acid sequence, or a portion thereof, of the protein of interest. Because some amino acids have several possible codons and the researcher cannot know which of the possible codons will actually code for an amino acid, he or she may decide to design a set of probes that covers all possible codons for each amino acid comprising the protein, known as a "fully-degenerate" set of probes. A library to be screened can be a genomic library (gDNA), which contains a set of all the DNA sequences found in an organism's cells or a complementary DNA (cDNA) library, which is much smaller and less complex than a gDNA library, and is used frequently when the tissue source for a given

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.

Defendants assert that whether or not it would have been obvious to isolate the human EPO gene from a gDNA library with fully-degenerate probes is immaterial because it was obvious to use the already known monkey EPO gene as a probe. Defendants point out that, in the early 1980s, Biogen did significant work with an EPO cDNA obtained from a baboon, and that they used it as a probe to hybridize with the corresponding gene in a human gDNA library. However, this technique did not succeed until after Lin isolated the EPO gene with his fully-degenerate set of probes.

To support its obviousness assertion, defendants rely upon the testimony of their expert, Dr. Flavell, who testified that the overall homology of baboon DNA and human DNA was "roughly 90 percent." While this testimony indicates that it might have been feasible, perhaps obvious to try, to successfully probe a human gDNA library with a monkey cDNA probe, it does not indicate that the gene could have been identified and isolated with a reasonable likelihood of success. Neither the DNA nucleotide sequence of the human EPO gene nor its exact degree of homology with the monkey EPO gene was known at the time.

Indeed, the district court found that Lin was unsuccessful at probing a human gDNA library with monkey cDNA until after he had isolated the EPO gene by using the fully degenerate probes. Based on the evidence in the record, the district court found there was no reasonable expectation of success in obtaining the EPO gene by the method that Lin eventually used. While the idea of using the [illegible] human gene may have been obvious to try, the realization of that idea would not have been obvious. There were many pitfalls. 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.

C. *Best Mode*

Defendants argue that the district c[ourt] erred in failing to hold the '008 patent inv[al]id 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 patent satisfied the best mode requirement as to the invention of the challenged claims[5] and that a deposit of the preferred CHO cells was not necessary.

[4] A determination whether the best mode requirement is satisfied is a question of fact. *DeGeorge v. Bernier*, 768 F.2d 1318, 1324, 226 USPQ 758, 763 (Fed. Cir. 1985), we

[5] 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, 21-27, 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 F.2d 931, 940, 15 USPQ2d 1321, [illegible] (Fed. Cir.), *cert. denied*, [illegible] U.S. [illegible], 111 S.Ct. [illegible]

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EXHIBIT C