EXHIBIT 13

PATENT APPLICATION
ATTORNEY DOCKET NO. 11009/31956

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:

Fu-kuen Lin

Serial No: 08/202,874

Filed: February 28, 1994

For: PRODUCTION OF ERYTHROPOIETIN

Group Art Unit: 1805

Examiner: J. Martinell

I hereby certify that this paper is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope addressed to:

Commissioner of Patents and Trademarks, Washington, DC 20231, on this date:

Dated: February 16, 1995

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APPLICANT'S AMENDMENT AND REQUEST FOR RECONSIDERATION UNDER 37 C.F.R. §§1.111 AND 1.115

Hon. Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

This is in response to the Office Action dated August 16, 1994 in the above-identified application wherein, of pending claims 87-97, all but claims 88, 93 and 94 were rejected under 35 U.S.C. §112, first or second paragraph, and all claims were variously rejected under 35 U.S.C. §102(b) and/or 103. Reconsideration and allowance is respectfully requested in view of the foregoing amendments and remarks.

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AMENDMENTS

In the Specification

As page 1, delete lines 2 through 6 and also delete the amendment requested upon filing of the present application on February 28, 1994 and insert the following in place thereof.

--This is a continuation of U.S. patent application Serial No. 07/113,178 filed October 23, 1987, and now abandoned, which was a continuation of U.S. patent application Serial No. 675,298 filed November 30, 1984, and issued October 27, 1987 as U.S. Letters Patent No. 4,703,008, which was a continuation-in-part of U.S. patent application Serial No. 655,841 filed September 28, 1984, and now abandoned, which was a continuation-in-part of U.S. patent application Serial No. 582,185 filed February 21, 1984, and now abandoned, which was a continuation-in-part of U.S. patent application Serial No. 561,024 filed December 13, 1983, and now abandoned.--

At page 64, line 30, please correct the spelling of "recombinant.

On page 25, after line 3 of the text inserted by the amendment filed 10/23/87 (i.e. after "products of the invention,"), delete "FIGURES 2 through 4 illustrate vector construction according to the invention, and, FIGURES 5 through 21 are DNA and polypeptide sequences according to the invention" and insert therefor the following:

--Figure 2 shows vector pDSVL-MkE.

Figure 3 shows vector pSVgHuEPO.

Figure 4 shows vector pDSVL-gHuEPO.

Figure 5A, 5B and 5C (collectively referred to as Figure 5) how the sequence of monkey EPO cDNA and the encoded EPO.

Figures 6A, 6B, 6C, 6D and 6E (collectively referred to as Figure 6) show the sequence of human genomic EPO DNA and the encoded EPO.

Figure 7 shows the sequence of the ECEPO gene.

Figure 8 shows the sequence of the SCEPO gene.

Figure 9 shows a comparison of the human and monkey EPO polypeptides.

Figure 10 shows the ECEPO section 1 oligonucleotides.

Figure 11 shows section 1 of the ECEPO gene.

Figure 12 shows the ECEPO section 2 oligonucleotides.

Figure 13 shows section 2 of the ECEPO gene.

Figure 14 shows the ECEPO section 3 oligonucleotides.

Figure 15 shows section 3 of the ECEPO gene.

Figure 16 shows the SCEPO section 1 oligonucleotides.

Figure 17 shows section 1 of the SCEPO gene.

Figure 18 shows the SCEPO section 2 oligonucleotides.

Figure 19 shows section 2 of the SCEPO gene.

Figure 20 shows the SCEPO section 3 oligonucleotides.

Figure 21 shows the section 3 of the SCEPO gene.--

In the Claims

Please cancel claims 91, 92 and 97 without prejudice.

Please amend claims 87, 88, 93, 94 and 95 as follows.

87. (Amended) A[n] human erythropoietin glycoprotein product having the *in vivo* biological activity of causing human bone marrow cells to increase production of reticulocytes and red blood cells and having glycosylation which differs from that of human urinary erythropoietin.

88. (Amended) A glycoprotein product of the expression in a [eucaryotic] non-human mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin said product possessing the *in vivo* biological property of causing human bone marrow cells to increase production of reticulocytes and red blood cells.

93. (Amended) A glycoprotein product according to claim [89, 90, 91 or 92] 89 or 90 wherein the host cell is a non-human mammalian cell.

94. (Amended) A glycoprotein product according to claim 88 or claim 93 wherein the non-human mammalian cell is a CHO cell.

95. (Amended) A pharmaceutical composition comprising an effective amount of a glycoprotein product effective for erythropoietin therapy according to claim 87, 88, 89 or 90 and a pharmaceutically acceptable diluent, adjuvant or carrier.

Please enter new claim 98.

--98. A method for treating a kidney dialysis patient which comprises administering a pharmaceutical composition of claim 95 in an amount effective to increase the hematocrit level of said patient.--

REMARKS

Upon entry of the above-requested amendments, claims 87-90, 93-96 and 98 will be pending in the application.

Applicant acknowledges with thanks the interview kindly granted by Examiner Martinell on September 7, 1994 to the undersigned and counsel for Applicant's assignee. As noted in the Interview Summary Record (Paper No. 39) agreement was not reached on allowability of the claims.

I. Comments Concerning the Requested Amendments To the Specification and Claims

The above-requested amendments to the specification and claims are intended to be responsive to the Examiner's requests and to certain of the objections to the specification and rejections of claims advanced in the Office Action of August 16, 1994.

More particularly, the amendments to pages 1, 25 and 64 are as requested by the Examiner to provide a description of the status of related applications, provide more detailed information concerning the drawings and correct a typographical error. The amended information concerning the drawings is exactly as suggested by Examiner Hodges in related U.S. Application Serial No. 07/113,179, which was recently allowed by Examiner Martinell.

The amendments to the claims do not introduce any new matter. Applicant notes in particular that support for terminology of claim 98 reference to erythropoietin therapy of kidney dialysis patients is found at specification at page 86, lines 32-35.

To facilitate the Examiner's reconsideration, Exhibit A hereto sets out the text of pending claims 87-90, 93-96 and 98 including the above-requested amendments.

II. The Outstanding Rejections

Claim 89 was rejected under 35 U.S.C. §112, first paragraph, upon the assertion that the claim's recitation of a "fragment" of EPO glycoprotein constitutes new matter.

Claim 87 was rejected under the second paragraph of Section 112 upon the assertion that reference to the "*in vivo* biological activity" of erythropoietin was vague and indefinite.

Claim 87 was rejected under the second paragraph of Section 112 upon the assertion that reference to "having glycosylation which differs form hat of human urinary erythropoietin" was vague and indefinite.

Claim 89 was rejected under the second paragraph of Section 112 upon the assertion that the reference to a "fragment" of EPO glycoprotein was indefinite.

Claim 90 was rejected under the second paragraph of Section 112, as lacking antecedent basis for "the signal sequence of human erythropoietin set out in FIG. 6."

Claims 95 and 96 were rejected under the second paragraph of Section 112 as vague, indefinite and incomplete in reciting "effective amount" because the "effect" of the *in vivo* biological activity of erythropoietin is allegedly not mentioned.

Claim 97 was rejected under the second paragraph of Section 112 upon the assertion that the term "enhancing" as applied to hematocrit levels was vague and indefinite.

Claims 89, 91 and 92 were rejected, apparently under the second paragraph of Section 112 as duplicative. The same rejection was entered with respect to claims 96 and 97.

Claims 87 and 95-97 were rejected under 35 U.S.C. §112, first paragraph, upon the assertion that the claims are somehow not limited to "EPOs shown in the instant application."

Claims 87 and 95-97 were rejected as assertedly anticipated under 35 U.S.C. §102(b) by the disclosures of sheep EPO preparations in Esbach et al., *Clin. Res., 29(2):*518A (1981).

Claims 87 through 94 were rejected as assertedly anticipated under 35 U.S.C. §102(b) or rendered obvious under 35 U.S.C. §103 by the disclosures of either Sugimoto, U.S. 4,377,513 or Chiba, *Biochem., Biophys. Res. Comm., 47:*1372 (1972).

Claims 89 through 94 were rejected as assertedly anticipated under 35 U.S.C. §102(b) or rendered obvious under 35 U.S.C. §103 by the disclosures of the abstract of Espada et al., *Fed. Proc., 41:*1159 (1982) or Miyake et al., *J. Biol. Chem., 252:*5558 (1977).

Claim 95 was rejected as assertedly rendered obvious under 35 U.S.C. §103 by the disclosures of either the Sugimoto or the Chiba publication cited above. Claims 96 and 97 were rejected on the same grounds as lodged against claim 95.

Claim 95 was rejected as assertedly rendered obvious under 35 U.S.C. §103 by the disclosures of either the Espada et al. or the Miyake et al. publications cited above, and further in view of the disclosures of Papayannopoulou et al. which assertedly teaches increasing hematocrits in animals. Claims 96 and 97 were also rejected on the same grounds as lodged against claim 95.

III. Patentability Arguments

A. The Outstanding Rejections Under 35 U.S.C. §112 May Properly Be Withdrawn

Applicant respectfully submits that, for the following reasons, all outstanding objections to the specification and/or rejections of the claims under Section 112 may properly be withdrawn.

1. Reference to a "fragment" in claim 89 of EPO glycoprotein is not new matter as asserted by the Examiner and the rejection thereof should be withdrawn. The specification and original claims of the application as filed contain multiple references to EPO polypeptide fragments having part of the disclosed polypeptide sequence and to the recombinant production thereof through use of fragments of the EPO DNA disclosed. See, *e.g.*, the discussion of "EPO products" commencing at page 91, line 5 and continuing through page 92, line 22. See also, original claims 1 *et seq.* directed polypeptides with "part or all" of the EPO amino acid sequence, original glycoprotein claims 40 and 41, original synthetic peptide claims 47 through 49, and original DNA and polypeptide expression product claims 58 and 59 specifically referring to "fragments."

2. Applicant disagrees that reference in claim 87 to the "*in vivo* biological activity" of erythropoietin is in any sense vague or indefinite. The issue is mooted, however, by the amendment of claim 87.

3. Applicant disagrees that reference to glycosylation differences vis-a-vis human urinary erythropoietin renders the claim vague and indefinite. The isoelectric focussing results of the Strickland Declaration cited by the Examiner simply show that there is charge microheterogeneity in any sample of uEPO. The glycoprotein products made available according to the present invention also will display charge heterogeneity. This does not mean that the uEPO glycosylation cannot be compared to that of recombinant EPO. As confirmed by Takeuchi article cited by the Examiner, the

glycosylation of recombinant EPO products is different from that of urinary EPO. The fact that recombinant EPO is inevitably different in its glycosylation from urinary EPO is manifest from the attached copy of the January, 1994 expert statement of Dr. Richard Cummings (Exhibit B hereto) as submitted in proceedings before the European Patent Office in counterpart European Patent EP 0 148 605. The expert statement can be re-iterated in the form of a Declaration under 37 C.F.R. §1.132 if the Examiner believes it to be appropriate. Applicant thus submits that the terminology employed in claim 87 is entirely in keeping with the requirements of 35 U.S.C. §112, second paragraph, and the outstanding rejection of the claim should be withdrawn.

4. The rejection of claim 89 under Section 112, first paragraph, based its use of the term "fragment" should also be withdrawn. As pointed out previously, the reference to *in vivo* biologically active EPO fragments is not new matter. The scope of this term is readily determined by reference to the continuous sequence of 166 amino acids of mature human EPO and to the known and readily performed assays for *in vivo* biological activity.

5. The rejection of claim 90 under 35 U.S.C. §112, second paragraph should be withdrawn because FIG. 6 does indeed include reference to polypeptide residues -27 to -1 and this sequence is identified at specification page 49 as the polypeptide "leader" sequence. "Leader" and "signal" are appositive terms in the context of the present invention.

6. The amendment of claim 95 to refer to "erythropoietin therapy" provides a statement of "effect" within the claim and moots the outstanding rejection of claims 95 and 96 based on alleged indefinite recitation of an "effective amount."

7. The cancellation of claim 97 moots the outstanding rejection of the claim. The term "increasing" is employed in new claim 98.

8. The cancellation of claims 91 and 92 moots the rejection of claims 89, 91 and 92 as duplicative. Applicant agrees with the Examiner's position that both

genomic DNA and cDNA are within the recitation of claim 89. Likewise the cancellation of claim 97 moots the rejection of claims 96 and 97 as duplicative.

9. The amendment of claim 87 to specify human erythropoietin is believed to moot the Section 112, first paragraph, rejection of claims 87 and 95, 96 and 98 which refer to claim 87.

B. The Outstanding Section 102(b), Section 102(b)/103 and Section 103 Rejections May Properly be Withdrawn

1. The rejection of claim 87 (and claims 95-97) under 35 U.S.C. §102(b) as anticipated by the disclosures of sheep EPO in the Esbach et al. reference is mooted by amendment of claim 87 to recite human erythropoietin.

2. The rejection of claims 87 through 94 under 35 U.S.C. §102(b)/103 based on the disclosures of Sugimoto et al. and Chiba et al. is respectfully traversed. Chiba et al. addresses only isolation of human urinary EPO, while Sugimoto et al. addresses formation of human hybridoma cells assertedly producing a product with EPO biological activity. First of all neither Chiba et al. nor Sugimoto et al. provide any disclosure of any means for the recombinant production of erythropoietin as recited in claims 88, 89 and 90. No isolated human EPO DNA (as called for by claims 89 and 90) is disclosed or enabled in Sugimoto et al. or Chiba et al. No non-human mammalian host cells (as called for by claim 88 and claims 93 and 94) are disclosed or enabled by Sugimoto et al. or Chiba et al. Indeed, no isolated protein having biological activity is described or characterized by Sugimoto et al. Biological activity is attributed to ascites fluids and only a prospective notation is made that highly purified products can easily be obtained if desired. In view of the lack of any disclosure in Sugimoto et al. of: (1) any repeatable means for producing the hybridomas which allegedly generate a product with erythropoietin activity (the human tumor cells assertedly employed in hybridoma formation are nowhere identified, characterized, deposited or otherwise enabled); or (2)

isolation of any actual protein product to which the activity can be attributed, there is simply no factual basis whatever for maintaining that the presently claimed human erythropoietin glycoproteins, pharmaceutical compositions and treatment methods are rendered obvious by, much less anticipated by, the cited references.

3. The rejection of claims 89-94 under 35 U.S.C. §102(b) and/or §103 based on the disclosures of human urinary EPO in Espada et al. and Miyake et al. should also be withdrawn inasmuch as it is based on the assumption that the recombinant erythropoietin glycoprotein products recited therein are the same as human urinary EPO. This assumption, of course, is directly contradicted by the publications made of record as attachments to the Exhibit B expert opinion of Dr. Cummings. These publications establish that it is in fact "evident that the process of production defines the product" as alluded to by the Examiner at page 9 of the Office Action.

Most simply put, no human urinary EPO product as describe in Miyake et al. or Espada et al. is embraced by the claims, nor does any such human urinary EPO product render the claimed glycoproteins, pharmaceutical compositions and methods of claims 89 through 94 obvious.

4. Because the "primary" references of record (Sugimoto et al., Chiba et al., Espada et al. and Miyake et al.) fail to disclose or suggest the products of claims 87, 88, 89 and 90, no basis exists for maintaining that the claim 95 pharmaceutical compositions incorporating these products are rendered obvious by these references, standing alone, or in combination with Papayannopoulou et al. The same is true of the therapeutic methods of claims 96 and 98 involving use of the claim 95 pharmaceutical compositions.

CONCLUSION

The foregoing and amendments and remarks are believed to establish that claims 87-90, 93-96 and 98 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,

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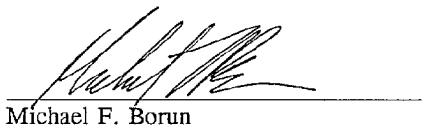
By: 

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