EXHIBIT E

PATENT APPLICATION
ATTORNEY DOCKET NO. 11009/32695

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:

Fu-Kuen Lin

Serial No: 08/487,774

Filed: June 7, 1995

For: PRODUCTION OF ERYTHROPOIETIN

Group Art Unit: 1815

Examiner: Martinell

"EXPRESS MAIL" mailing label No. EG 473 138 519 US

Date of Deposit: December 20, 1995

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Mark Bonadonna

SECOND PRELIMINARY AMENDMENT AND REMARKS

Assistant Commissioner for Patents
Washington, DC 20231

irs:

This is a second preliminary amendment of the claims in the above-identified application, made following an October 18, 1995 interview kindly granted to the undersigned by Examiner Martinell. As noted in the Examiner Interview Summary Record, agreement on patentability of the subject matter claimed was not reached, but the Examiner agreed to consider certain amendments and arguments concerning the rejections propounded in the Office Action dated May 17, 1995 in parent U.S. patent application Serial No. 08/202,874 (abandoned in favor of the present Rule 62 application).

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AMENDMENT

In the Claims:

Please cancel pending claims 87-90, 93-96, 98 and 99 without prejudice.

Please enter new claims 100-110.

--100. A non-naturally occurring erythropoietin glycoprotein product having the *in vivo* biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and having glycosylation which differs from that of human urinary erythropoietin.

101. The non-naturally occurring EPO glycoprotein product according to claim 100 wherein said product has a higher molecular weight than human urinary EPO as measured by SDS-PAGE.

102. A non-naturally occurring glycoprotein product of the expression in a 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 bone marrow cells to increase production of reticulocytes and red blood cells.

103. A non-naturally occurring human erythropoietin glycoprotein possessing the *in vivo* biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells which is the product of the process comprising the steps of:

(a) growing, under suitable nutrient conditions, mammalian host cells transformed or transfected with an isolated DNA sequence

encoding the human erythropoietin amino acid sequence set out in FIG 6 or a fragment thereof; and

(b) isolating a glycosylated erythropoietin polypeptide therefrom.

~~104~~. A non-naturally occurring human erythropoietin glycoprotein possessing the *in vivo* biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells which is the product of the process comprising the steps of:

(a) growing, under suitable nutrient conditions, mammalian host cells transformed or transfected with an isolated DNA sequence comprising a sequence encoding the leader sequence of human erythropoietin set out in FIG 6; and

(b) isolating a glycosylated erythropoietin polypeptide therefrom.

~~105~~. A non-naturally occurring glycoprotein product of the expression in a non-human eucaryotic host of an exogenous DNA sequence ~~consisting essentially of~~ 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 and having an average carbohydrate composition which differs from that of naturally occurring erythropoietin.

~~106~~. The glycoprotein product according to claim ~~102~~, ~~103~~, ~~104~~, ~~105~~ ~~or 106~~ wherein the host cell is a non-human mammalian cell.

~~107~~. The glycoprotein product according to claim ~~107~~ wherein the non-human mammalian cell is a CHO cell.

~~108~~ 9. A pharmaceutical composition comprising an effective amount of a glycoprotein product effective for erythropoietin therapy according to claim 100, ~~101~~ 2, ~~102~~ 3, ~~103~~ 4, ~~104~~ 5 or ~~105~~ 6 and a pharmaceutically acceptable diluent, adjuvant or carrier.

~~109~~ 10. A method for providing erythropoietin therapy to a mammal comprising administering an effective amount of a pharmaceutical composition of claim ~~108~~ 9.

~~110~~ 11. A method for treating a kidney dialysis patient which comprises administering a pharmaceutical composition of claim ~~108~~ 9 in an amount effective to increase the hematocrit level of said patient.--

REMARKS

A. The Pending Claims

Upon entry of the above-requested amendments, claims 100-110 will be under examination. The general correspondence of claims 100-110 to prior claims 87, 88, 89, 90, 93, 94, 95, 96, 98 and 99 is as noted in the following Table.

TABLE

PRIOR CLAIM	NEW CLAIM
87 (Independent)	100
88 (Independent)	102
89 (Independent)	103
90 (Independent)	104
93 (Dependent)	106
94 (Dependent)	107
95 (Dependent)	108
96 (Dependent)	109
98 (Dependent)	110
99 (Independent)	105

New product claim 101 is dependent on claim 100 (prior claim 87 as amended) and further characterizes the claim 100 subject matter in terms of apparent molecular weight on SDS-PAGE *vis-a-vis* human urinary EPO. This dependent claim recitation finds written descriptive support in the specification at page 64, line 20 through page 65, line 3 wherein glycosylated COS and CHO cell products were noted to have higher SDS-PAGE molecular weights than the human urinary isolate--the molecular weights of the deglycosylated products being the same.

B. The Rejections of Previously Pending Claims

In the Office Action of May 17, 1995 in parent U.S. Serial No. 08/202,874, none of pending claims 87-90, 93-96 and 98 was allowed. The specification was objected to and all claims were variously rejected under 35 U.S.C. §112, first and second paragraphs and under 35 U.S.C. §102(b) or, in the alternative 35 U.S.C. §103 in view of the disclosures of Sugimoto *et al.*, (U.S. 4,377,512), Chiba *et al.* (U.S. 4,465,624), Miyake *et al.*, *J. Biol. Chem.*, *252*:5558-5564 (1977), Espada *et al.*, *Federation Proceedings*, *41*:1159 (1982), or Papayannopoulou *et al.*, *J. Clin. Invest.*, *51*:1179-1185 (1972).

C. Response and Remarks Supporting Patentability

1. Section 112 Issues

(a) The Examiner's objection to the inappropriate reference "to mammal" in prior claim 96 is mooted by its cancellation. The error does not occur in new claim 109.

(b) The objection to the specification text at page 9, line 20 was the subject of discussion at the above-noted interview wherein it was explained that "Citations omitted" referred to the fact that literature citation cross references in the passage quoted had not been included in the text of the quote.

(c) Applicant would appreciate the Examiner's assistance in Correction by Examiner's Amendment of the word "how" to "show" in the amendment referring to Figure 5 requested February 22, 1995.

(d) At the above-noted interview, counsel explained that Figure 6 provided no new matter in view of the fact that it merely replaced prior Table 6.

(e) Likewise, counsel explained that Figure 14 involved no new matter because it merely replaced prior Table XII.

(f) Applicant solicits the Examiner's assistance in correction of the description of Figure 17 in the amendment of February 22, 1995 to replace "SPCEPO" with --SCEPO-- by Examiner's amendment.

(g) At the above-noted interview, the Examiner agreed that reference to "fragment" in prior claim 89 (corresponding to claim 103) was definite and supported by the specification.

(h) At the interview it was agreed that the negative limitation, "non-naturally occurring" would, when combined with the notation of glycosylation differences in prior claims 87 and 99 (corresponding to new claims 100 and 105) meet Section 112 specificity requirements.. All of independent claims 100-105 are similarly limited.

(i) As agreed at the above-noted interview, reference to the EPO gene "signal" sequence has been replaced by reference to the "leader" sequence in claim 104 (corresponding to prior claim 90).

2. Prior Art Issues

Consistent with the discussions at the above-noted interview, Applicants incorporation of "non-naturally occurring" in all independent claims operates to distinguish the subject matter claimed from all prior art reference relating to erythropoietin isolates (Chiba *et al.*, Miyake *et al.*, Espada *et al.* and Papayannopoulou *et al.*), leaving only the Sugimoto *et al.* reference available for consideration on Section 102(b)/Section 103 issues.

Applicant reiterates its prior position that 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 reference.

In further support of the above position, Applicant notes that it has contacted the named proprietors of the Sugimoto *et al.* reference in an attempt to secure materials relevant to determining precisely what "erythropoietin" product was described in the document. Attached as Exhibit A hereto is a copy of correspondence sent by Applicant's assignee. Exhibit B hereto is a copy of the recently-received response wherein the proprietor has refused to provide either cells described in the reference or the "erythropoietin" assertedly produced by those cells. Applicant thus maintains that the erythropoietin product mentioned in the Sugimoto *et al.* reference is

not a available material susceptible to analysis and correspondingly respectfully submits that no rejection based on the indefinite disclosures of the Sugimoto *et al.* reference may properly be propounded.

CONCLUSION

The foregoing amendments and remarks are believed to establish that claims 100-110 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,

MARSHALL, O'TOOLE, GERSTEIN,
MURRAY & BORUN

BY: 

Michael F. Borun
Registration No. 25,447
6300 Sears Tower
233 S. Wacker Drive
Chicago, IL 60606-6402
(312) 474-6300

Chicago, Illinois
December 20, 1995