Exhibit 2, Part 1

PATENT

IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

Application of:	)	"Production of
	)	
FU-KUEN LIN	)	Erythropoietin"
	)	
Serial No: 675,298	)	Group Art Unit 127
	)	
Filed: November 30, 1984	)	Examiner - A. Tanenholtz

APPLICANT'S AMENDMENT AND REPLY
UNDER 37 C.F.R. §1.111 AND §1.115

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

Sir:

This is in response to the Office Action dated February 5, 1987 in the above-identified application wherein substantially all prior rejections of pending claims 14, 15, 17-36, 58 and 61-72 were withdrawn, but wherein new grounds for rejection were advanced under 35 U.S.C. §§102, 103 and 112, and wherein all claims were "provisionally" rejected under 35 U.S.C. §101. Reconsideration and allowance of all claims is respectfully requested in view of the following amendments and remarks.

AMENDMENT

IN THE CLAIMS

Please cancel claims 14, 15, 17-36, 58 and 61-72 without prejudice and enter the following new claims 73-103.

--73. A purified and isolated DNA sequence for use in securing expression in a procaryotic or eucaryotic

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host cell of a polypeptide product having at least a part of the primary structural conformation and having a therapeutic activity of naturally-occurring erythropoietin, said DNA sequence selected from the group consisting of:

(a) the DNA sequences set out in Figures 5 and 6 or their complementary strands;

(b) DNA sequences which hybridize under stringent conditions to the DNA sequences defined in (a); and

(c) DNA sequences which, but for the degeneracy of the genetic code, would hybridize under stringent conditions to the DNA sequences defined in (a) and (b).

74. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 73 in a manner allowing the host cell to express said polypeptide product.

75. A biologically functional circular plasmid or viral DNA vector including a DNA sequence according to claim 73.

76. A procaryotic or eucaryotic host cell stably transformed or transfected with a DNA vector according to claim 75.

77. A purified and isolated DNA sequence coding for procaryotic or eucaryotic host expression of a polypeptide having part or all of the primary structural conformation and having a therapeutic activity of erythropoietin.

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78. A cDNA sequence according to claim 77.

79. A monkey species erythropoietin coding DNA sequence according to claim 78.

80. A DNA sequence according to claim 79 and including the protein coding region set forth in Figure 5.

81. A genomic DNA sequence according to claim 77.

82. A human species erythropoietin coding DNA sequence according to claim 81.

83. A DNA sequence according to claim 82 and including the protein coding region set forth in Figure 6.

84. A manufactured DNA sequence according to claim 77.

85. A manufactured DNA sequence according to claim 84 and including one or more codons preferred for expression in E.coli cells.

86. A manufactured DNA sequence according to claim 85, coding for expression of human species erythropoietin.

87. A manufactured DNA sequence according to claim 86 including the protein coding region set forth in Figure 7.

88. A manufactured DNA sequence according to claim 84 and including one or more codons preferred for expression in yeast cells.

89. A manufactured DNA sequence according to claim 88, coding for expression of human species erythropoietin..

90. A manufactured DNA sequence according to claim 89 including the protein coding region set forth in Figure 8.

91. A DNA sequence according to claim 77 covalently associated with a detectable label substance.

92. A DNA sequence according to claim 91 wherein the detectable label is a radiolabel.

93. A single-strand DNA sequence according to claim 91.

94. A biologically functional circular plasmid or viral DNA vector including a DNA sequence according to claim 77.

95. A procaryotic or eucaryotic host cell stably transformed or transfected with a DNA vector according to claim 94.

96. A purified and isolated DNA sequence coding for a polypeptide fragment or polypeptide analog of

naturally-occurring erythropoietin having a therapeutic activity of erythropoietin.

97. A biologically functional circular plasmid or viral DNA vector including a DNA sequence according to claim 96.

98. A procaryotic or eucaryotic host cell stably transformed or transfected with a DNA vector according to claim 97.

99. A DNA sequence according to claim 96 which is a manufactured sequence.

100. A DNA sequence coding for [Phe^{15}]hEPO, [Phe^{49}]hEPO, [Phe^{145}]hEPO, [His^{7}]hEPO, [Asn^{2} des-Pro^{2} through Ile^{6}]hEPO, [des-Thr^{163} through Arg^{166}]hEPO, or [Δ27-55]hEPO.

101. A biologically functional circular plasmid or viral DNA vector including a DNA sequence according to claim 100.

102. A procaryotic or eucaryotic host cell stably transformed or transfected with a DNA vector according to claim 101.

103. A purified and isolated DNA sequence as set out in Figures 5 or 6 or the complementary strand of such a sequence.--

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REMARKS

Applicant acknowledges with thanks the interview kindly granted to his counsel, Mr. Borun and Mr. Odre, on March 4, 1987.

Upon entry of the above-requested amendments to the claims, claims 73 through 103 will remain in the application and will be correlated to prior claims 14, 15, 17-36, 58 and 61-72 in the manner indicated in the following Table.

Prior Claim	New Claim	Prior Claim	New Claim
14	73	30	90
15	74	31	91
61	75	32	92
62	76	33	93
69	--	63	94
17	77	64	95
18	78	70	--
19	79	34	96
20	80	65	97
21	81	66	98
22	82	71	--
23	83	36	99
24	84	35	100
25	85	67	101
26	86	68	102
27	87	72	--
28	88	58	103
29	89		

Applicant notes that none of the claims whose entry is sought correspond to prior claims 69-72. Applicant specifically reserves his right to pursue claims of the same or similar scope in a duly filed continuing application.

A. The Claimed Subject Matter

As related in Applicant's communication dated October 3, 1986, the claims remaining in this application relate to DNA sequences, DNA vectors, transformed and transfected host cells useful in the preparation of erythropoietin products including, e.g., polypeptide analogs of erythropoietin.

Independent claim 73 is thus directed to purified and isolated DNA sequences generally defined by reference to the DNA sequences revealed in Figures 5 and 6 (previously Tables V and VI). Dependent claims 74-76 respectively relate to host cells transformed or transfected with DNA of claim 73, vectors including the DNA of claim 73, and hosts transformed with such vectors.

Independent claim 77 is directed generally to DNA sequences which code for procaryotic or eucaryotic host polypeptides having erythropoietin amino acid sequences and having one or more of erythropoietin's biological activities. Dependent claims 78-95 are directed to presently preferred forms of DNA sequences, vectors, and transformed or transfected hosts based on the claim 77 DNA sequences.

Independent claim 96 is generally directed to DNA sequences of the invention which encode polypeptide fragments and analogs of erythropoietin and dependent claims 97-99 are likewise directed to preferred forms of sequences, vectors, and transformed and transfected hosts. Independent claim 100 and dependent claims 101 and 102 relate to specific erythropoietin analog DNA sequences.

Finally, independent claim 103 is directed to the specific human and monkey erythropoietin-encoding purified and isolated DNA sequences as revealed in Figures 5 and 6.

B. The Outstanding Office Action, The Rejections of the Claims and Applicant's Responses Thereto

In a communication dated October 3, 1986 responding to the Action of July 3, 1986, Applicant submitted the full text of the Chirgwin et al. reference (Ref. C8) to complete the Information Disclosure Statement filed on April 24, 1986 and also submitted a Supplemental Information Disclosure Statement directing the Patent Office's attention to references B15, B16, C135 and C136. Applicant respectfully solicits the Examiner's acknowledgement of receipt and consideration of the same and notation of such consideration on the previously submitted Forms PTO-1449.

Applicant understands that the amendments and remarks set out in his communication dated October 3, 1986 have resulted in the reconsideration and withdrawal of the following rejections propounded under Sections 101, 102, 103 and 112 in the Action dated July 3, 1986:

1. The Section 112 (first paragraph) rejection of claims 14, 15, 17-36, 58 and 61-72 on grounds relating to permanence of A.T.C.C. Budapest Treaty deposits;

2. The Section 112 (second paragraph) rejection of claims 14, 15, 17-36, 58 and 61-72 based on,

(a) alleged indefiniteness of the term "procaryotic or eucaryotic",

(b) alleged indefiniteness based on failure to specify a "fragment" size,

(c) alleged indefiniteness of the term "biological properties",

(d) an instance of improper Markush group language, and,

(e) an instance of improper characterization of dependence for one of the claims;

3. The Section 101 rejection of claims 14, 24, 34 and 36 as being drawn to naturally-occurring subject matter;

4. The Section 102(b) and/or 103 rejection of claims 14, 24, 34 and 36 based on the Sugimoto et al. reference;

5. The Section 102(b) and/or 103 rejection of claims 14, 15, 17, 18, 20, 24-27, 33, 34, 61-66, 69, 70 and 71 based on the Lee-Huang (P.N.A.S.) reference;

6. The Section 102(a) and/or 103 rejection of claims 14, 15, 17-20, 24, 33, 34, 36, 58, 61-66, 69-70 and 71 based on Applicant's publication [J.Cell.Bioch., Suppl. 8B, p. 45 (1984)]; and,

7. The Section 103 rejection of all claims based variously on the Sugimoto et al., Cohen et al., Paddock, Farber et al., Bennetzen et al. Gouy et al., and Lewin references.

Due to the number and variety of new objections and rejections set forth in the recently received Action dated February 5, 1987, Applicant once again submits that the issues raised therein are best treated by means of responses which "track" the order of their appearance in the Action.

1. The Objection to the Disclosure Based On Figures 5-8 May Properly Be Withdrawn

The Examiner asserts that new drawing Figures 5-8 did not accompany Applicant's communication of October 3, 1986. Applicant attaches hereto as Exhibit No. 1 an envelope containing another set of Figures 5-8 and requests