EXHIBIT 10

IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

Application of:	)	"PRODUCTION OF
FU-KUEN LIN	)	ERYTHROPOIETIN"
Serial No: 675,298	)	Group No. 127
Filed: November 30, 1984	)	Examiners - J. M. Giesser T. G. Wiseman

Applicant's Amendment and Reply
Under 35 U.S.C. 551.111 and 1.115

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

Sir:

This is in response to the Office Action dated July 3, 1986 in the above-identified application wherein all provisionally elected claims (14, 15, 17-36, 58 and 61-72) were variously rejected under one or more of the provisions of 35 U.S.C. §§101, 112 (paragraphs 1 and 2), 102 and 103 and non-elected claims (1-13, 16, 37-57 and 59-60) were withdrawn from consideration.

Reconsideration and allowance of all pending claims is respectfully requested in view of the following amendments and remarks.

IN THE SPECIFICATION

Please enter into the application the attached new Figures 5 through 8 which duplicate original Tables V, VI, XIV and XXI.

At page 25, line 5, please insert the following sentences after the period.

--Reference is made to Figures 1 through 8, wherein: FIG. 1 is a graphic representation of a

radioimmunoassay analysis of products of the invention; FIGS 2 through 4 illustrate vector constructions according to the invention; and, FIGS. 5 through 8 are DNA sequences according to the invention.--

At page 37, line 6, after the term "Table V", please insert --, duplicated as FIGURE 5 comprising portions 5A, 5B and 5C--.

At page 42, lines 25, after the term "Table VI", please insert --, duplicated as FIGURE 6 comprising portions 6A, 6B, 6C, 6D and 6E--.

At page 73, line 33, after the designation "XIV", please insert --, duplicated as FIGURE 7--.

At page 75, line 28, after the designation "XXI", please insert --(the last-mentioned Table being duplicated as FIGURE 8).

IN THE CLAIMS

Please amend claim 14 as follows:

--14. (Amended) A purified and isolated DNA sequence for use in securing expression in a procaryotic or eucaryotic host cell of a polypeptide product having at least a part of the primary structural conformation and one or more of the biological [properties] activities of naturally-occurring erythropoietin, said DNA sequence selected from [among] the group consisting of:

(a) the DNA sequences set out in [Tables V and VI] Figures 5 and 6 or their complementary strands;

(b) DNA sequences which hybridize to the DNA sequences defined in (a) or fragments thereof; and

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

In claim 17, line 4, please delete "properties" and insert --activities-- in place thereof.

In claim 20, line 2, please delete "Table V" and insert --Figure 5-- in place thereof.

In claim 23, line 2, please delete "Table VI" and insert --Figure 6-- in place thereof.

In claim 24, line 2, please delete "14" and insert --17-- in place thereof.

In claim 27, line 3, please delete "Table XIV" and insert --Figure 7-- in place thereof.

In claim 30, line 3, please delete "Table XXI" and insert --Figure 8-- in place thereof.

In claim 34, line 1, please insert --purified and isolated-- before the term, "DNA".

In claim 58, line 2, please delete "Table V or VI" and insert --Figure 5 or 6-- in place thereof.

In claim 69, line 3, please delete "properties" and insert --activities-- in place thereof.

In claim 69, line 7, please insert --62-- after the word "claim".

In claim 70, line 3, please delete "properties" and insert --activities-- in place thereof.

In claim 71, line 3, please delete "properties" and insert --activities-- in place thereof.

In claim 72, line 3, please delete "properties" and insert --activities-- in place thereof.

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REMARKS

Upon entry of the above-requested amendments, claims 14 (Amended), 15, 16-36, 58 and 61-72 will remain in the application.

Applicant acknowledges with thanks the interview kindly granted by Examiners Wisemen and Giesser to Applicant's counsel, Mr. Borun and Mr. Odre, on July 30, 1986. Attached hereto as Exhibit No. 1 are copies of the documents referred to as Exhibits "A" and "B" in the Examiner Interview Summary Record prepared by Examiner Giesser.

A. The Claimed Subject Matter

The present invention reflects Applicant's discovery of DNA sequences encoding erythropoietin. This discovery, in turn, has allowed the first determination ever made of the entire primary structural conformation of erythropoietin. Significantly, this discovery has allowed recombinant methods to be brought to bear in the development of DNA vectors and transformed and transfected host cells useful to secure large scale production of polypeptide products sharing in the biological activities of erythropoietin.

The present claims are accordingly directed to DNA sequences, DNA vectors, transformed and transfected host cells and processes for the use of these materials in the preparation of erythropoietin products including, e.g., polypeptide fragments and polypeptide analogs of erythropoietin. Independent claim 14 is thus generally directed to purified and isolated DNA sequence defined by reference to the DNA sequences revealed in Figures 4 and 6. Dependent claims 15, 16, 62 and 69 respectively relate to host cells transformed or transfected with DNA of claim 14, vectors

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including the DNA of claim 14, hosts transformed with such vectors, and production processes employing such hosts. Independent claim 17 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 18-33, 63-64 and 70 are directed to presently preferred forms of DNA sequences, vectors, transformed or transfected hosts and production processes based on the claim 17 DNA sequences. Independent claim 34 is generally directed to DNA sequences of the invention which encode polypeptide fragments and analogs of erythropoietin and dependent claims 35, 36, 65-68, 71 and 72 are likewise directed to preferred forms of sequences, vectors, transformed and transfected hosts and production processes. Finally, independent claim 58 is directed to the specific human and monkey erythropoietin-encoding purified and isolated DNA sequences as revealed in Figures 5 and 6 (previously Tables V and VI).

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

In the Action dated July 3, 1986, the Examiner noted that the full text of the Chirgwin, et al. reference (Ref. C8) did not accompany Applicant's Information Disclosure Statement filed April 24, 1986. Attached hereto as Exhibit No. 2 is a full text copy. Applicant respectfully solicits the Examiner's consideration of the same, and notation of such consideration on the previously submitted Form PTO-1449.

Due to the number and variety of objections and rejections set forth in the Action dated July 3, 1986,

Applicant submits that the issues raised therein are best treated by responses which precisely "track" the order of their appearance in the Action.

1. The Rejection of Claims 14, 15, 17-36, 58 and 61-72 Under The First Paragraph of 35 U.S.C. §112 May Properly Be Withdrawn

At page 4 of the Action, the Examiner lodged a rejection of all claims under 35 U.S.C. §112 (first paragraph) based on a corresponding objection to the specification wherein the absence of an "assurance" of potential replacement of A.T.C.C. Budapest Treaty microorganism deposits was noted. While Applicant specifically disagrees with the Examiner's assertion to the effect that the "invention depends on certain specific plasmids/microorganisms", he has attached hereto as Exhibit No. 3 a Declaration by an officer of his Assignee, Kirin-Amgen, Inc., assuring replacement of deposited cultures if lost or destroyed during the 30-year Budapest Treaty deposit period. This Declaration is of the general form presented in Wiseman, T. "Biotechnology Patents", pp. 33-42 appearing in "Biotechnology Patent Conference Workbook" (American Type Culture Collection, Rockville, MD., 1986).

Applicant respectfully submits that all requirements of the first paragraph of Section 112 are met, that the objection to the specification should be withdrawn, and that the corresponding rejection of claims 14, 15 17-36, 58 and 61-72 may properly be withdrawn.

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2. The Rejection of Claims 14, 15, 17-36, 58 and 61-72 Under The Second Paragraph of 35 U.S.C. §112 May Properly Be Withdrawn

Bridging pages 4 and 5 of the Action, the Examiner lodged a rejection of all claims under 35 U.S.C. §112 (second paragraph) based on multiple assertions of indefiniteness of claim terminology. Each specific objection, designated (a) through (f), is discussed below.

(a) Applicant respectfully disagrees with the Examiner's assertion of indefiniteness for the term "procaryotic or eucaryotic" as employed to describe host cells in claims 14, 15 62, 64, 66, 68 and in claims dependent thereon. While Applicant agrees in general that unduly alternative language may not be in conformity with Section 112 requirements and that wholly non-equivalent terms ought not to be presented as equivalents in claims, it is respectfully submitted that the claim term "procaryotic or eucaryotic" quite accurately (i.e., "duly") specifies well known alternatives in selection of available host cell types for the application of recombinant DNA methods in polypeptide production. The Examiner's attention is directed to M.P.E.P. §706.03(d) wherein it is noted that:

> "Generally speaking, the inclusion of (1) negative limitations and (2) alternative expressions, provided that the alternatively expressed elements are basically equivalents for purposes of the invention, are permitted if there is no uncertainty or ambiguity with respect to the question of scope or breadth of claim is presented."

It is thus the case that the kind of invention claimed, together with the "purposes of the invention" are

both properly considered in determining the propriety of alternative language within any given claim.*

In this instance, support for the conclusion that "procaryotic or eucaryotic" is duly alternative and unambiguous may be found upon consideration of the nature of the "expression" process by which cells produce a polypeptide based on a DNA sequence as claimed, together with the context of the teachings of the present specification with regard to production of erythropoietin polypeptides. Whether a host cell is procaryotic or eucaryotic, the general cellular process by which any given (DNA) codon gives rise to the disposition of a given amino acid residue within a polypeptide is the same. The ATG codon, for example, codes, via mRNA and tRNA, for disposition of a methionine residue whether it is within a procaryotic or eucaryotic host, and no DNA codon directs a different amino acid residue simply depending on the procaryotic or eucaryotic nature of the host it is in. This concept is clearly reflected in the present specification wherein, at page 19, lines 6-11, it is noted that:

> "These polypeptides are also uniquely characterized by being the product of procaryotic or eucaryotic host expression (e.g., by bacterial, yeast and mammalian cells in culture) of exogenous DNA sequences obtained by genomic or cDNA cloning or by gene synthesis".

Specific examples within the specification describe the actual results of genomic, cDNA and synthetic DNA expression in mammalian, E.coli, and yeast systems. Thereafter, the

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* As an example, while "black or white" might appear unduly alternative or ambiguous, in vacuo, the term is quite properly employed when describing an invention related to squares of a chess board.

specification goes on to state, at page 92, line 33 through page 93, line 5:

> "Put another way, DNA sequences provided by the invention are useful in generating new and useful viral and circular plasmid DNA vectors, new and useful transformed and transfected microbial procaryotic and eucaryotic host cells (including bacterial and yeast cells and mammalian cells grown in culture), and new and useful methods for cultured growth of such microbial host cells capable of expression of EPO and EPO products".

Applicant respectfully submits that the term, "procaryotic or eucaryotic" is completely in keeping with the nature and purposes of the present invention as fully described in the specification and that the outstanding rejection of claims 14, 15, 62, 64, 66, 68 and claims dependent thereon may properly be withdrawn.

(b) The Examiner has alleged that claims 14, 17, 34, 58, 69-72 and claims dependent thereon are indefinite for failure to specify a "fragment" size and are thus "so vague as to read on single base pairs". Applicant respectfully disagrees. Whether the Examiner is referring to a DNA or polypeptide "fragment" is unclear, but it is clear from the context of the claims under consideration that a polypeptide is encoded (necessitating the presence of multiple 3-base pair codons) and that the polypeptide encoded must possess at least one of the biological properties of naturally-occurring erythropoietin. Within this context Applicant's claims certainly do not read on single base pairs (which "encode" nothing). Rather, they include specific and readily understood structural and functional limitations as to the length of the DNA sequences claimed which in turn allows for production of useful, biologically active mate-

rials. The outstanding rejection of claims 14, 17, 34, 58, 69-72 and claims dependent thereon may thus properly be withdrawn.

(c) The Examiner also objected to claims 14, 17, 69-72 and claims dependent thereon for their recitation of "biological properties". This term is alleged to be "so indefinite as to be meaningless". Applicant disagrees. While the "biological properties" of erythropoietin may be varied, they are not indefinite. The term, as used in reference to erythropoietin, is essentially defined at specification page 19, lines 3-5, by the recitation:

> "...one or more of the biological properties (e.g., immunological properties and in vivo and in vitro biological activity) of naturally-occurring erythropoietin...".

The presently known in vivo and in vitro activities of erythropoietin are well described in the prior art cited in the specification's "Background", beginning at page 9, line 33 and continuing through page 12, line 19. Moreover, at page 86, lines 21-32, certain of the major reported in vivo biological activities of erythropoietin are again recited:

> "...stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis...increasing hematocrit levels in mammals".

Applicant thus respectfully submits that the term "biological properties", as used in the specification, is definite and meaningful and that its use in the claims is fully in keeping with the requirements of Section 112. For purposes of advancing prosecution of this application, however, and without waiver of any right to pursue claims of