EXHIBIT D

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO
[illegible]	[illegible]	[illegible]	

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CHICAGO, IL 60603

PUSH-EXAMINER	
ART UNIT 253	PAPER NUMBER
	4

DATE MAILED: 06/04/88

This is a communication from the examiner in charge of your application.

COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☐ Claims 1-13, 16, 39-41, 47-49, 55-7 are pending in the application.

Of the above, claims _____ are withdrawn from consideration.

☐ Claims 14-15, 17-38, 42-6, 50-4, 58-60 have been cancelled.

☐ Claims _____ are allowed.

☒ Claims 1-13, 16, 39-41, 47-49, and 55-57 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☒ This application has been filed with informal drawings which are acceptable for examination purposes until such time as allowable subject matter is indicated.

8. ☐ Allowable subject matter having been indicated, formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. These drawings are ☐ acceptable; ☐ not acceptable (see explanation).

10. ☐ The ☐ proposed drawing correction and/or the ☐ proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved. ☐ disapproved (see explanation). However, the Patent and Trademark Office no longer makes drawing changes. It is now applicant's responsibility to ensure that the drawings are corrected. Corrections MUST be effected in accordance with the instructions set forth on the attached letter "INFORMATION ON HOW TO EFFECT DRAWING CHANGES", PTO-1474.

12. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

PTOL-326 (Rev. 7-82) EXAMINER'S ACTION

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The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless-
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-7, 9-13, 16, 40-41 and 47-49 provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-12 and 25-26 of copending application Serial No. 113178.

This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claims 1-13, 16, 39-41, 47-49 and 55-57 are rejected under 35 U.S.C. 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The use of alternate terms in the claim language renders the cited claims indefinite, and presents questions of enablement and scope. With respect to the actual physical properties, such as amino acid sequence and degree and locations of glycosylation, the actual physical characteristic in question should be presented. The terms "part or all of," "sufficiently duplicative

of," and "average carbohydrate composition which differs from," do not particularly nor adequately point out the distinctions from native erythropoietin (EPO). The actual physical properties which clearly define the protein claimed should be used in the claim language. For example, the "parts" of EPO which are contemplated and supported by the disclosure (in terms of amino acid sequence) and the sites and extent of glycosylation and how they "differ" from native EPO should be pointed out. Note that the glycosylation of EPO is an important aspect of its activity and not every form of EPO is biologically equivalent. With respect to the term having "one or more of the biological properties of naturally occurring" EPO, applicant must point out which biological properties are contemplated. As currently et forth, any protein or peptide showing any biological property of EPO (e.g. "self" recognition of the protein by host) is encompassed. Applicant cannot support this assertion with the current disclosure.

Claims directed toward methods of therapy using the recombinant protein are not enabled. No in vivo results supporting these claims is presented which show the recombinant varient working in an identical manner as the native protein. The slight difference in glycosylation presented in the specification is not sufficiently

discussed with respect to its effect on the in vivo activity of rEPO. For example, does the glycosylation render the human protein antigenic in humans? In vitro assays do not provide clearly relevant support without some type of convincing display to correlate the two. The particular mode of treatment which is contemplated should be set forth. Simply stating administration is not sufficient.

The claims must particularly point out the essential aspects of the disclosed invention. The broadest limitations must also be supported by the disclosure. As currently set forth, the claims are indefinite and to an extent, non-enabled. The particular biological activities and physical properties which can be used to define the rEPO should be reflected in the claim language to adequately define the invention. The particulars concerning the actual method(s) of treatment and support for the claimed effectiveness of said treatment(s) must be shown.

Claims to "synthetic polypeptides" are not enabled by this disclosure. "Synthetic," as opposed to "recombinant," is an art recognized term which indicates a chemically derived rather than genetically engineered protein. No support for chemical synthesis of EPO or EPO fragments is shown by this disclosure. These claims

are also confusing with respect to the intent of the term "synthetic."

Support for the data concerning the glycosylation of the recombinant EPO is found only in the parent application. Support for the contemplated therapy using rEPO is also only found in the parent application of this application.

Claims 1-11, 16, 39 and 47-49 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Chiba et al or Takezawa et al.

As currently set forth, the cited claims define any protein having at least one of the biological properties of EPO. The limitations of claims 7 and 8 do not further limit this definition. The cited disclosures each show production of human EPO in substantially purified form having EPO activity. This protein is inherently identical to the claimed EPO by virtue of the same amino acid sequence (or an allelic varient thereof) and the same type of biological activity. The recombinant protein has not been shown to behave in a distinct and unobvious manner with respect to the naturally occurring EPO, and in any case the claims clearly encompass the naturally produced EPO shown by the cited art. The burden of proving the claimed rEPO

distinct and unobvious over the cited prior art is shifted to the applicant.

Claims 1-11, 16, 39 and 47-49 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Sugimoto et al or Takezawa et al (H).

For the reasons presented in the immediately preceding art based rejection, the cited claims are rejected as defining a protein which is inherently identical to the naturally derived EPO disclosed by the cited art. The burden of proving the claimed rEPO distinct and unobvious is shifted to the applicant.

Claims 1-13, 16, 39 and 47-49 are rejected under 35 U.S.C. 102 b as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Roh et al.

As previously shown, the claims directed to rEPO as currently set forth are anticipated by a disclosure showing purified biologically active EPO from native sources. Roh et al disclose this, and also show ^{125}I-radiolabeled EPO. This disclosure anticipates the claimed radiolabeled rEPO of applicant as disclosing an inherently identical radiolabeled EPO composition. The burden of proving otherwise is shifted to the applicant.

Claims 1-13, 16, 39 and 47-49 are rejected under 35 U.S.C. 103 as being unpatentable over Chiba et al

Takezawa et al (D or H) or Sugimoto et al in view of Roh et al further in view of Hunter et al.

EPO produced by various means is known in the art and is explicitly shown by the cited primary references. The disclosure of Roh et al provide a utility for radio labeled EPO, and thus establishes motivation for one of ordinary skill in the art to produce radiolabeled EPO. Hunter et al describe a means of radiolabeling proteins which has been successfully used by Roh et al in producing radiolabeled EPO. In view of these references, the claimed radiolabeled rEPO is obvious.

Claims 1-13, 16, 39-41 and 47-49 are rejected under 35 U.S.C. 102 b as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Miyake et al.

The disclosure of Miyake et al shows isolation and purification of naturally derived human EPO. These authors show that two forms of glycosylated EPO exist, and further show production of asialo-EPO. Production of ^{125}I radiolabeled human EPO is also shown. This disclosure anticipates the recombinant EPO as set forth in the cited claims. The definitions set forth are met by the human EPO and derivatives therefrom, which are disclosed by Miyake. Note especially that the varients of human EPO with the amino acid sequence, biological activity

and difference in degree of carbohydrate composition as claimed by applicant are shown by Miyake et al. In view of applicant's failure to clearly define the precise physical nature of the recombinant EPO, examiner believes the native and recombinant forms of human EPO to be inherently identical. With respect to claim 8, the limitation of being an allelic variant of simian EPO is also met. The burden of proving otherwise is shifted to the applicant.

Claims 1-13, 16, 39-41, 47-49 and 55-57 are rejected under 35 U.S.C. 103 as being unpatentable over Miyake et al Takezawa et al (D or H) Chiba et al or Sugimoto et al in view of Papayannopoulo et al.

Each of the primary references cited above would enable one of ordinary skill in the art to prepare biologically active, homogeneous human EPO. Papayannopoulo et al describe in detail the effect of EPO in vivo in a murine model. Note especially the abstract and introduction of this latter reference which summarizes the content of the paper. The effect of EPO on the rate of hemoglobin synthesis is recognized to be one of the most significant contributors to the hematocrit of an animal. In view of the cited art one would find it obvious to use EPO in a treatment to restore hemoglobin concentration in vivo, as the in vivo

effects of EPO administration have been shown and explained. Note also that the primary references suggest use of EPO in therapy (Takezawa et al "Background" section).

The claimed method is also considered to be obvious because the recombinant and native derived EPO are biologically equivalent. In other words, both forms show the same in vitro and in vivo activities as asserted by applicant. Use of an agent from a different source which behaves in a manner identical to its known analog would suggest to one skilled in the art that similar results could be obtained using the biologically equivalent analog. The expected result would make obvious the use of the new analog as its activity and effects would be expected (note in re Durden, 226 USPQ 359). In the instant case, use of recombinant EPO, which has been asserted to show the same biological activity as native EPO, in the treatment of an animal to achieve the same known effect of EPO in said animal would be obvious to one skilled in the art.

The art not used above made of record indicates and expands on the nature and utility of EPO.

Any inquiry concerning this communication should be directed to Jeff Kushan at telephone number 703-557-0664.

HOWARD E. SCHAIN
PATENT EXAMINER
GROUP 180 - ART UNIT 183

Kushan:meb
5/18/88:Retype 5/23/88

TO SEPARATE, REMOVE TOP AND BOTTOM EDGES. SNAP-APART AND DISCARD CARBON

1812

FORM PTO-892 (REV. 3-78) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

NOTICE OF REFERENCES CITED

SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER
113178	~~183~~	4

APPLICANT(S): Lin

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A	4467016	5/19/87	Lai et al	530	380	6/20/85
	B	4556066	12/10/85	Egrie	530	380	2/4/83
	C	4556055	12/10/85	Goldwasser et al	530	380	9/13/82
	D	4303650	12/1/81	Takezawa et al	530	397	—
	E	4377513	3/22/83	Sugimoto et al	530	397	8/10/81
	F	4677195	6/30/87	Hewick et al	530	397	1/11/85
	G	4568648	2/4/86	Cee-Huang	424	99	1/14/84
	H	4397840	8/9/33	Takezawa et al	424	99	3/3/82
	I	3865801	2/11/75	Chiba et al	424	99	
	J	4703008	10/27/87	Lin	435	240.2	
	K						

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
	L								
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

R: Miyata et al, J. Biol Chem, 252(15), 5558-64, (1977)
Dordal et al, Endocrin, 116(6), 2293-9, (1985)

S: Wang et al, Endocrin, 116(6), 2256-92, (1985)
Sasaki et al, J. Biol. Chem., 262(25), 12059-76, (1987)

T: Rob et al, Fed. Proc, 29(2), 782, Abs 3030, (1970)
(Hunter et al, Biochem. J., 89, 114-23 (1963) ✓

U: Papayannopoulou et al, J. Clin. Invest, 51, 1179-85, (1972)
Weiss et al, PNAS (USA), 79, 5465-9, (Sept 1982).

EXAMINER	DATE
Kushan	5/~~8~~/87

* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)

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