EXHIBIT F

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EXAMINER [illegible]

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MARSHALL, O'TOOLE, GERSTEIN
MURRAY & BORUN
6300 SEARS TOWER
233 SOUTH WACKER DRIVE
CHICAGO, IL 60606-6357

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 04/08/94 + 06/13/94 ☐ 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 of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☒ Copy of p. 62- Methods in Yeast Genetics

Part II SUMMARY OF ACTION

1. ☒ Claims 87-97 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 1-83 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☐ Claims _____ 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 under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ 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).
12. ☐ Acknowledgement 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 Claims 84-86 (filed 03/16/90) were not entered.

445

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

The amendment filed March 16, 1990 and adding claims 84-86 has not been entered. The amendment filed June 13, 1994 has been entered. Applicant should note that the numbering of claims 84-94 submitted in the amendment filed June 13, 1994 has been changed. Claims 84-94 have been renumbered as claims 87-97 and the claim dependencies have also been changed accordingly. Applicant's attention is directed to 37 CFR § 1.126.

The Information Disclosure Statement filed April 8, 1994 has been received. The following are noted in connection with the Information Disclosure Statement.

(a) Farber et al (reference C 71) was not considered because the submitted copy is illegible.

(b) A copy of reference C 217 was not found in the submitted references. However, this reference was readily available to the PTO and was considered. A copy is enclosed with this Office action for applicant's convenience.

(c) A copy of "Points to consider . . .", reference C 259 could not be found in the references submitted by applicant. This reference is not readily available to the PTO and has not been considered.

(d) The copy of Testa et al, reference C 313, is illegible and has not been considered.

The disclosure is objected to because of the following informalities.

(a) In claim 96, "to mammal" should be changed to "to a mammal".

(b) At page 64, line 30, "recombinent" is a typographical error.

(c) At page 9, line 20, "(Citations omitted)" is not understood.

(d) The status of each of the parent applications should be updated.

(e) The specification needs a section entitled "Brief Description of the Drawings". The description of the drawings included in the amendment filed October 23, 1987 is inadequate because it does not describe each of the figures. Any amendment to correct this deficiency should point to basis in the application as filed for the amendment.

Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as is now claimed. The recitation of "fragment thereof" in claim 89 is new matter.

Claims 89-91 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 87 and 89-97 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and

distinctly claim the subject matter which applicant regards as the invention. The claims are vague, indefinite, and incomplete.

(a) Claim 87 is vague and indefinite for reciting "in vivo biological activity". It is not clear whether the claimed material has all or only some of the properties of EPO.

(b) The recitation of "having glycosylation which differs from that of human urinary erythropoietin" (claim 87) is vague and indefinite because there is no glycosylated standard for human urinary EPO. The record has evidence in it which indicates that the amount of glycosylation of EPO is variable. For example:

(1) The Strickland declaration (filed 12/5/88) at page 10, lane (4) of the isoelectric focusing gel shows several faint bands for u-EPO. If u-EPO were a single species, it would show as only one band. Likewise, at page 14 of the same declaration, in lane 3 the u-EPO digested with sialidase results in several bands.

(2) Takeuchi et al (J. Biol. Chem. 263(8), 3657 (1988)) at page 3660 indicates that variation of glycosylation depends on the level of glycotransferases in the cells. This paper also shows levels of glycosylation of EPO vary. Even though the publication date is later than the effective filing date of the application, the information can be used to support the § 112 rejection and reasoning supporting the rejection.

448

(3) Chiba et al (Biochem. Biophys. Res. Comm. 47: 1372 (1972)) discloses variations in glycosylation of u-EPO depending on the degree of degradation of the glycoprotein that occurs during collection, extraction, purification, and storage of the u-EPO. Thus, the amount of glycosylation of EPO is variable and no standard exists in the art to disclose what the glycosylation composition of EPO is. Neither does the instant application fill this void. Therefore, one of skill in the art would not know whether a given sample of EPO infringed the claims. Hence, the claims are vague and indefinite.

(c) The recitation of "fragment thereof" (claim 89) is vague and indefinite because no lower limit of fragment size is mentioned.

(d) Claim 90 is vague, indefinite, and incomplete because there is no antecedent basis for "the signal sequence of human erythropoietin set out in FIG 6". There is no signal sequence identified as such in FIG 6.

(e) Claims 95 and 96 are vague, indefinite, and incomplete in reciting "effective amount" because the "effect" is not mentioned.

(f) Claim 97 is vague and indefinite in reciting "enhancing". Substituting "increasing" for "enhancing" would be sufficient to overcome this part of this rejection.

Claims 89, 91, and 92 are each rejected over either one of the remaining two as being duplicate claims. The protein product is the same whether the exogenous DNA in the host cell is cDNA or genomic DNA.

449

Claims 87 and 95-97 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to those EPOs shown in the instant application. See M.P.E.P. §§ 706.03(n) and 706.03(z). The instant application does not teach the extraction and purification of EPO from any and all sources. Additionally, the instant application does not give guidance as to which "fragments" of EPO may have any activity. Accordingly, the claims are broader than the enabling disclosure.

Claims 96 and 97 are each rejected over the other as duplicate claims. The intended outcome of the therapy (claim 97) does not change the method of administration (claim 96).

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 --
>
> (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.

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) or (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 the same person.

450

Claims 87 and 95-97 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Eschbach et al (Clin. Res. 29(2), 518A (1981)). The reference teaches the administration of a preparation of sheep EPO to nephrectomized sheep to increase hematocrit levels. The claims embrace the EPO preparation of the reference as well as the methods of the reference.

Claims 87-94 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 either one of Sugimoto et al (U.S. 4,377,513) or Chiba et al. Sugimoto et al fused human kidney tumor cells that produce EPO with human leukemic lymphoblastoid cells (cancer cells) to get hybridoma cells that produce EPO. The idea here was to produce an immortal cell line capable of producing EPO much like one would produce monoclonal antibody producing hybridoma cell lines. After screening the hybridomas for EPO producing clones and isolating an EPO producing clone, Sugimoto et al grew up large amounts of the hybridomas as ascites tumors (in the peritoneal cavity of nude mice) and recovered preparations of human EPO (h-EPO). There's a good chance that h-EPO is not the same as u-EPO because as Chiba et al reports, degradation (via de-glycosylation) of u-EPO is a problem. Thus, one would reasonably expect the EPO circulating in the blood to be more glycosylated than u-EPO. Additionally, the h-EPO of Sugimoto et al is not "naturally-occurring" in the sense that some EPO producing cells were excised from the body, cultured to produce EPO, and then the EPO collected. Sugimoto et al made a hybridoma. As Takeuchi et al disclose, the glycosylation can vary depending on the enzymes present in the producing cell. Absent evidence to the contrary, the hybridoma-produced EPO is considered to have a different glycosylation pattern than the original kidney-cell-produced EPO. Thus, the

claimed EPOs read on the EPO of Sugimoto et al. Applicant asserts (paper no. 15, filed July 12, 1999) that there was no reason to believe that the EPOs were different. This assertion is not convincing. On page 5 of the response, applicant states, "Applicant submits that there is no evidence or reason to believe that erythropoietin produced by a human lymphoblastoid cell line is identical to the glycosylation product produce by a non-human transformed or transfected cell line." This misrepresents the issue. The claims embrace all EPOs that have an average carbohydrate composition that differs from the carbohydrate composition of "naturally-occurring" EPO (whatever that is, see the rejections under § 112 above). For purposes of this rejection, the average carbohydrate composition of naturally-occurring EPO is taken as that for u-EPO because that is what was measured by applicant (see page 65 of the specification). Thus, the EPO produced by the hybridoma of Sugimoto et al does not have to be identical to the EPO produced by any of the specific transformed cells disclosed in the instant application (although it may indeed be, no evidence or reasons are in the record to indicate otherwise). The EPO of Sugimoto et al has merely to have a different average carbohydrate composition than naturally-occurring EPO (i.e. u-EPO) in order to meet the claims. The same can be said for the various EPOs of Chiba et al. Additionally, the burden is on the applicant to provide evidence. If the EPOs differ, then at least one of the EPOs reads on the claimed EPO. Note that the EPOs at issue are the various intermediately degraded u-EPOs which are isolated from urine (Chiba et al) and h-EPO (human EPO) which is produced in the hybridoma cells of Sugimoto et al. Applicant has not carried his burden to show a difference between what exists in the prior art and what is claimed

(In re Brown, 173 USPQ 685, CCPA 1972). Finally, the term "exogenous" in claim 84 means only that the gene has an origin outside of the host cell. It does not mean that the host cell has to be non-human in this claim. Thus, the claim reads on human EPO produced in human cells.

Claims 95-97 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 Sugimoto et al. Sugimoto et al discloses pharmaceutical preparations of EPO for the administration of EPO to animals. These preparations are embraced by the claims. The discussion in the previous rejection is incorporated here.

Claims 89-94 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 either one of Espada et al (Fed. Proc. 41: 1159 (1982)) or Miyake et al (J. Biol. Chem. 252: 5558 (1977)). Each of the references discloses the purification of human EPO. Absent evidence to the contrary, the EPO of the references is the same or essentially the same as the EPO of the claims. It is not evident that the process of production defines the product. Since the PTO has no laboratories, the burden is on applicant to show a difference between a claimed product and a product of the prior art (see In re Brown, 173 USPQ 685, CCPA 1972).

Claim 95 is rejected under 35 U.S.C. § 103 as being unpatentable over either one of Sugimoto et al or Chiba et al as applied to claims 87-94 above, and further in view of applicant's admitted state of the prior art (page 87, line 29 through page 88, line 28). Applicant acknowledges pharmaceutically acceptable carriers, adjuvants, and diluents to be standard. It would be obvious for one of ordinary skill in the art to prepare a pharmaceutically acceptable composition containing the EPO of either one of the primary

references in order to administer the EPO to an animal or human to effect a higher hematocrit.

Claim 95 is rejected under 35 U.S.C. § 103 as being unpatentable over either one of Espada et al (Fed. Proc. 41: 1159 (1982)) or Miyake et al (J. Biol. Chem. 252: 5558 (1977)) as applied to claims 89-94 above, and further in view of applicant's admitted state of the prior art (page 87, line 29 through page 88, line 28). Applicant acknowledges pharmaceutically acceptable carriers, adjuvants, and diluents to be standard. It would be obvious for one of ordinary skill in the art to prepare a pharmaceutically acceptable composition containing the EPO of either one of the primary references in order to administer the EPO to an animal or human to effect a higher hematocrit.

Claims 96 and 97 are rejected under 35 U.S.C. § 103 as being unpatentable over either one of Sugimoto et al or Chiba et al as applied to claims 87-94 above, and further in view of Papayannopoulou et al. Papayannopoulou et al teaches the administration of compositions containing EPO to animals including mammals. The reference further discloses higher hematocrits in animals receiving EPO. It would be obvious for one of ordinary skill in the art to administer the compositions of either one of Sugimoto et al or Chiba et al to animals in the manner of Papayannopoulou et al in order to increase hematocrits in animals as disclosed by Papayannoupoulou et al.

Claims 96 and 97 are rejected under 35 U.S.C. § 103 as being unpatentable over either one of Espada et al (Fed. Proc. 41: 1159 (1982)) or Miyake et al (J. Biol. Chem. 252: 5558 (1977)) as applied to claims 89-94 above, and further in view of Papayannopoulou et al. Papayannopoulou et al

454

teaches the administration of compositions containing EPO to animals including mammals. The reference further discloses higher hematocrits in animals receiving EPO. It would be obvious for one of ordinary skill in the art to administer the compositions of either one of Espada et al or Miyake et al to animals in the manner of Papayannopoulou et al in order to increase hematocrits in animals as disclosed by Papayannoupoulou et al..

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1805.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 at (703) 305-3014. The faxing of such papers must conform with the rules published in the Official Gazette, 1156 OG 61 (November 16, 1993).

Any inquiry concerning this communication should be directed to J. Martinell at telephone number (703) 308-0296.

JAMES MARTINELL, PH.D.
SENIOR LEVEL EXAMINER
GROUP 1800

455