EXHIBIT M-1

UNITED STATES DEPARTMENT OF COMMERCE
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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
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EXAMINER	
KUSHAN, J	
ART UNIT	**PAPER NUMBER**
186	13

DATE MAILED: 06/20/89

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 6/5/89 ☐ 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 67-75 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 1-66 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 67-75 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

15. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

16. Claims 67 to 75 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the prior invention as set forth in claim 1 to 11 of of U.S. Patent No. 4,667,016. Although the conflicting claims are not identical, they are not patentably distinct from each other because the process claims of commonly owned U.S. Patent No. 4,667,016 teach a procedure for purification of the recombinant EPO claimed in the instant application. The ordinary worker, in view of the cited disclosure, would be able to produce the EPO instantly claimed using the claimed process in said patent. Furthermore, the commonly owned patent teaches as the preferred embodiment use of the recombinantly produced EPO as taught by Lin et al. As a result, the instantly claimed recombinantly produced, biologically active in vivo erythropoeitin is obvious in view of the cited claims of the commonly owned patent.

16. The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of monopoly by prohibiting claims in a second patent not patentably distinct from claims in a first patent. In re Vogel, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is

shown to be commonly owned with this application. See 37 CFR 1.78(d).

17. Claims 67 to 75 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 claims as presented remain deficient under 35 USC 112 first and second paragraphs. The following modifications are suggested to overcome this rejection.

1 In claim 67, line 3, the phrase "a primary structural conformation" should be changed to "a primary structure and conformation...". This modification makes it clear that the recombinant protein possess the primary structure (e.g. the amino acid sequence of naturally occurring human EPO) and the tertiary or spatial conformation of human EPO to the extent that the recombinant EPO retains the biological activity of the human EPO in vivo.

2. The claim must be limited to recombinant human erythropoeitin. As presented, a non human analog which possesses enough similarity to native human erythropoeitin is encompassed by the claims. This breadth is not supported by the disclosure. Applicant may recite that the exogenous DNA sequence codes for human erythropoeitin.

3. At lines 5 to 7 of claim 67, applicant presents a general description of the biological activity of the recombinantly

produced EPO. A more accurate description of the biological effects of the protein which are observed upon administration in vivo is found at page 10, lines 28 to 33. Applicant should recite in the claims the following description of the biological effects observed upon administration of the recombinant EPO;

> ... sufficient for retention of the in vivo biological property of stimulation of the conversion of primitive precurser cells in the bone marrow into pro-erythroblasts which subsequently mature, synthesize hemoglobin, and are released into the circulation as red blood cells. .

This description of the observed biological in vivo response of EPO particularly points out and describes in accurate detail what the response will be, and with this description, the ordinary worker finds clear direction in ascertaining what species of EPO are encompassed by the claims presented. Note also that the phrase "sufficient for retention of" is also suggested for inclusion in the claims, as this phrase clarifies the relationship between the recombinant protein and the observed in vivo effect of the protein.

4. Applicant's claims encompass erythropoeitin produced recombinantly in any eucaryotic cell line which has an average carbohydrate composition which differs from naturally occurring human EPO, and which possess a particular in vivo activity when administered to humans. The breadth of this claim exceeds the scope of the disclosure, specifically because it encompasses EPO produced in non-mammalian, eucaryotic cell hosts. Applicant has not shown how to produce biologically active in vivo species of EPO produced by non-mammalian cell hosts. The basis for this point of the rejection arises from the lack of teaching in any disclosure of a non-mammalian eucaryotic host produced recombinant EPO which retains the recited biological in vivo

activity of native human EPO. Applicant is directed to the disclosure of Sasaki et al, page 12059, right hand column, second full paragraph. Sasaki et al state;

> "Interestingly, the erythropoietin produced in E.coli or yeast was inactive or very weakly active in vivo. On the other hand, the erythropoeitin produced in COS cells or Chinese hamster ovary cells was found to be fully active in vivo."

In view of the differences in the EPO produced by transfected mammalian cells, and the EPO produced by non-mammalian eucaryotic hosts such as yeast, the claims must be limited to recombinant EPO produced by mammalian cell lines.

18. Claims 67 to 73 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 teach production of human EPO from isolated lymphoblastic cell lines. The EPO produced by the teachings of this disclosure has been shown by Sugimoto et al, and also summarized by applicant, to possess erythropoeitic activity. The disclosed method of production of human EPO also appears to yield amounts of the protein sufficient for use in therapy.

Applicant has proven that human EPO isolated from urine is distinct from the EPO produced recombinantly according to the instant disclosure. It seems clear that the urinary derived EPO is inactive in vivo, and this results presumably from a number of factors, such as degradation of the EPO in the urine during

purification. Another possible source of the difference between the recombinant and urinary EPO may lie in the source from which the two species derive. Isolation of EPO from aplastic anemic patients may account for the lack of in vivo erythropoeitic activity of the urinary species.

In any case, the distinction which has been proven between the recombinant EPO and urine derived EPO cannot be relied upon to prove a distinction of the recombinant and lymphoblastoid derived human EPO. The procedure of Sugimoto et al does not expose the human EPO produced to the same sources of degradation or variance that the urinary species of EPO is exposed. It would seem more likely that the lymphoblastoid produced EPO would be active in vivo, and not identical to the urinary derived species. Applicant must provide for a distinction between the lymphoblastoid derived EPO and the instantly claimed recombinant species. Applicant is encouraged to file a declaration in the form of the previous declaration of Strickland, which provided evidence of a distinction between the urinary and recombinant species. In the alternative, applicant can submit other evidence which characterizes the two species in a manner which can be relied upon to overcome this rejection.

20. Claims 67 to 75 are rejected under 35 U.S.C. 103 as being unpatentable over Sugimoto et al in view of Papayannopoulo et al.

Claims 75 and 75 are directed to a conventional use of EPO, namely administration to raise the hematocrit of a human host. The

prior art of Sugimoto et al suggest pharmaceutical applications of the isolated EPO produced by their methodology. Although this suggestion is a clear motivation to the ordinary worker to apply the EPO produced by this method to a pharmaceutical regimen, it does not disclose the particular details of administration. The disclosure of Papayannopoulo et al, however, do provide for general procedures for administration of EPO in experimental animals. This disclosure would have enabled the ordinary worker to practice the instantly claimed method of EPO therapy in view of the teachings of Sugimoto et al.

21. The submissions and response to the last office action are sufficient to overcome the rejections of record over 35 USC 103 based on the disclosures of Miyake et al, Chiba et al, and Takezawa et al. As shown by applicant, urinary EPO lacks in vivo biological activity. Furhtermore, the evidence of secondary considerations presented as the findings of fact of the ITC decision submitted warrant removal of rejections over prior art which teach isolation of EPO from urine.

22. No claims are allowed.

23. This action includes rejections based upon new grounds, and as such, the finality of the previous Office action is withdrawn.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner

Kushan whose telephone number is (703) 557-7627. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 557-0664.

5

jpk
June 14, 1989.

MM
MARGARET MOSKOWITZ
SUPERVISORY
PATENT EXAMINER
ART UNIT 186