EXHIBIT F

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

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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
185	9

DATE MAILED: 02/10/89

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 12/5/88 ☒ 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 41, 55-57, 61-68 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 1-40, 42-54, 58-60 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 41, 55-57, 61-68 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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15. The text of those sections of Title 35, U.S. Code not included in this actions can be found in a prior Office action.

16. The double patenting rejection has been obviated in view of the abandonment of the co-pending application directed to the identical subject matter of the instant application.

17. Applicant's amendment to the claims is sufficient to obviate the rejection under 35 USC 112 regarding the use of the term biological activity.

18. Claims 41, 55-57, and 61-66 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.

Applicant's modification of existing claim 41 is not sufficient to overcome the rejection made in the first office action regarding the adequate definition of the claimed r-huEPO. The manner in which applicant has attempted to characterize the degree and extent of glycosylation of the r-huEPO does not particularly point out what the actual glycosylation comprises. Applicant, in the current claim structure, merely "carves out" what is known in the art (e.g. species of EPO which have the native glycosylation pattern) and claims all that do not possess this type of glycosylation, yet retain any degree of the reticulocyte and red blood cell producing biological activity of EPO. Applicant has not recited the actual pattern or

carbohydrate composition-he has attempted to define the recombinant species by reciting that the glycosylation is "different from the native species". This does not identify the difference, nor does it lead the person of skill in the art to the particular differences contemplated and shown in the declaration by Dr. Strickland.

Applicant should positively recite the physical properties related to carbohydrate composition and structure he asserts to be important, specifically, that feature of the glycosylation pattern (structure) which the native species does not possess. In addition, the claim modification reciting the biological property of the effect of EPO on bone marrow cells should recite the minimum degree of this biological activity that the claimed invention should possess (e.g. "...at least 90% of the biological activity of ... possessed by naturally occurring EPO...").

19. Claims 41 and 61 to 65 are rejected under 35 U.S.C. 103 as being unpatentable over Miyake et al, Chiba et al, Takezawa et al (D or H), or Sugimoto et al.

Rejections made in the first office action over the references cited above were based, in part, on the premise that naturally occurring EPO was inherently identical to the recombinant protein claimed by applicant. The parent claim (41) recites that the protein is to have the following physical properties;

1) a primary structural conformation substantially duplicative of naturally occurring human EPO,

2) glycosylation substantially duplicative of naturally occurring human EPO,

3) possession of the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells,

4) an average carbohydrate composition which differs from that of naturally occurring human EPO.

Each of the primary disclosures teaches isolation of human EPO from urine. Miyake et al present the most extensive analysis of their isolated EPO and applicant has used the EPO produced by this method to compare the disclosed and claimed recombinant hu-EPO.

Several issues were presented as the basis for rejections made in the first office action, including:

a) the difference in the average carbohydrate composition is not significant one when the product is considered as a whole;

b) applicant stated that the average composition of rHu-EPO differs from the naturally occurring species, but does not recite how it differs, making a determination of the actual physical state of the rHu-EPO impossible.

Applicant has shown through the declaration of Strickland

and via the disclosure of Takeuchi et al that there is a difference in the overall carbohydrate composition between the naturally occurring and recombinant species. Sasaki et al, cited in the first office action by the Examiner, also shows that certain differences exist in the overall carbohydrate composition between the recombinant and naturally occurring species of EPO. The proof of a distinction in the physical attributes of the naturally isolated and recombinant species is sufficient to overcome the rejections over 35 USC 102.

The differences shown by applicant, however, are not considered to be significant with respect to the activity and utility of EPO by people of ordinary skill in this field, and by the Examiner. For example, Takeuchi summarizes the differences as follows (page 3660):

> "Despite these dissimilarities, the most important evidence is that all the oligosaccharides found in rHuEPO were included in urinary HuEPO. The absence of unusual sugar chains in rHuEPO is favorable for the clinical applications of this hormone, since we do not need to take any account of antigenicity on its sugar moiety. [] Therefore, the fact that rHuEPO contained no neutral ologosaccharides might also be important for its clinical application."

This summary serves to show that while the differences can be shown, no significant changes in the carbohydrate composition

have occurred. Put another way, the differences in carbohydrate composition can be minimized with respect to the impact of these changes, since there were no unusual sugar chains introduced which would affect significantly the desired biological activity of the rHuEPO. Sasaki et al also conducted a thorough comparison of naturally occurring and recombinant human EPO (produced in CHO). In the paragraph bridging pages 12071 and 12072, these authors surmise that the key feature of the glycosylation patterns in human EPO is the presence (not degree) of (alpha)2-->3 linked sialic acid residues. At page 12072, these authors state:

> "This study demonstrated that the carbohydrate moiety of human erythropoietin isolated from human urine is indistinguishable from that of recombinant erythropoietin except for a difference in degree of sialylation. Urinary erythropoietin has a similar degree of sialylation as the highly sialylated batch of recombinant erythropoietin [].."

This reasoning is consistent with the assertions of the examiner that the difference in overall carbohydrate composition is not as significant feature of the recombinant species as applicant asserts. Both groups which authored the cited disclosures minimized the impact of the difference in the overall carbohydrate composition, preferring instead to emphasize the overall similarities as measured in terms of the structure and

activity. The actual overall differences in the glycosylation do not produce any unexpected changes in the activity, the stability, or the structure of EPO. As shown by Sasaki et al, the key to the importance in the glycosylation of EPO is the presence, rather than the degree of certain types of sialic acid residues. The compositional difference may be detectable and shown by evidence, but it certainly does not lead to a patentable distinction over the naturally occurring species.

The application of the principles of obviousness as measured by the Graham v. John Deere standard lead the person of ordinary skill to believe the recombinant species to be an obvious extrapolation from the naturally occuring species. That which is not taught in the prior art is considered to be an immaterial change in the physical properties of the recombinant EPO claimed.

The second basis of the original rejections over art was emphasized in the rejection using the disclosure of Miyake et al. It was shown that species meeting the requirements of the presented claim are shown by Miyake et al. Specifically, there are species of EPO found in nature which have slight or significant differences in the actual carbohydrate composition yet retain at least a small fraction of the original biological activity as recited in the amended claim. Current understanding of the effect of changing (or even complete removal) of the carbohydrate composition would suggest that the biological activity of EPO is not destroyed, rather it is the time of

retention in the host of EPO which diminishes the in vivo effect of the modified EPO. Thus, applicant's claims do not teach away from the naturally occurring species, but instead present an ineffective limitation when the intent of applicant is taken into account.

The newly added claims do not present limitations on the actual nature of the EPO product. The limitations are placed on steps used in the recombinant production process. As such, these new claims do not impart any physical features onto the rHuEPO defined by existing claim 41.

It is somewhat inconsistent for applicant to argue that a minute change in the glycosylation pattern can lead to a "novel and unobvious" species of EPO, then to claim all species of EPO which do not have the same pattern and degree of glycosylation as the naturally occurring species. Applicant's assertion that retention of the biological activity of EPO when produced recombinantly is an unexpected departure from the naturally occurring species is not convincing. Extension of this logic would make each and every recombinant species of protein a new and unobvious species if an applicant could show a slight distinction in the glycosylation pattern of the recombinant species and retention of the biological activity. This in turn would make a claim to a naturally occurring or recombinant species of protein essentially worthless, as the claim would protect only that species of protein which is produced according

to the applicant's disclosed process.

The overall composite of biological activity, physical properties and distinctions, and the effect of differences must be considered in the determination of obviousness. A distinction which the ordinary practioner would recognize as insignificant cannot be used to base an assertion of unobviousness.

20. Claims 41, 55-57, and 61-68 are rejected under 35 U.S.C. 103 as being unpatentable over Miyake et al, Chiba et al, Takezawa et al (D or H), or Sugimoto et al, in view of Papayannopoulo et al.

As stated in the first office action, the use of EPO for the stimulation of bone marrow cells to produce reticulocytes and red blood cells, and thus, to increase the hematocrit of animals is well known, and is demonstrated by Papayannopoulo et al. The primary disclosures each suggest in vivo applications of the EPO produced. The primary references, however, do not show rHuEPO being used in vivo. The ordinary practioner, having available a species of EPO (rHuEPO) which behaves in vivo in the identical fashion as the naturally occurring species, would find a method of erythropoietin therapy to be no more than a routine extrapolation (if any) from the teachings of the Papayannopoulo et al. The ordinary practioner would be concerned with the actual biological activity of the EPO used, not the source or particular, non-significant differences in the carbohydrate composition of said EPO. Similarly, the person of ordinary skill in the art would find no burden in formulating a composition of

biologically active EPO suitable for administration to a host in view of the art cited. The key consideration is the biological activity of the EPO used, not whether the source of the EPO is recombinant or natural. In view of the cited art, the ordinary practioner would find the therapy claims and the pharmaceutical composition claims to be obvious as of the time of applicant's filing of the instant application.

21. The declaration under 37 CFR 1.132 filed 12/9/88 is sufficient to overcome the rejection of claims 41, 55-57, and 61-66 based upon 35 USC 102/103 as set forth in the last Office Action.

23. 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 180, Art Unit 186.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeff 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) 557-0864.

jpk

January 24, 1989.

MARGARET MOSKOWITZ
SUPERVISORY PRIMARY EXAMINER
ART UNIT 186

TO SEPARATE, NO[illegible] TOP AND BOTTOM EDGES, SNAP-APART AND DISCARD CARBO[illegible]

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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	~~186~~	8

APPLICANT(S): Lin

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A	4667016	5/19/87	Lai et al	530	397	
	B						
	C						
	D						
	E						
	F						
	G						
	H						
	I						
	J						
	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 Chiba et al Biochem. Biophys. Res. Comm. 47(6), 1372-7, (1972)

S Miyake et al, J. Biol. Chem. 252(15), (1977)

T Takeuchi et al, J. Biol Chem. 263 (8), 365-7-63, (1988).

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EXAMINER [signature] DATE 1/27/89

* 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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