Exhibit 7

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/113,179	10/23/87	LIN	F D-8272

EXAMINER
HODGES, R

18N2/0901

MARSHALL, O'TOOLE ET AL.
TWO FIRST NATIONAL PLAZA, SUITE 2100
CHICAGO, IL 60603

ART UNIT	PAPER NUMBER
1805	29

DATE MAILED: 09/01/93

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 65-69 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 65-69 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 re Patent Drawing, 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 on _____ has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under 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

A 4063

'S ACTION

A protest against issuance of a patent based upon this application filed under 37 C.F.R. § 1.291(a), filed on 7/23/93, has been considered and a copy has been served on applicant. Any comments or response applicant desires to file in connection with the protest must be filed with applicant's response to this Office Action

Response to Protest filed by Lai

Protestor asserts that he made a critical contribution to the instantly claimed invention. Specifically, Protestor asserts five contributions (not all independent) which indicate that he is in fact a co-inventor of the instantly claimed subject matter (page 1). All five alleged contributions are offered in support of Protestor's assertion that 1) the amino acid sequence of EPO fragments T-35 and T-38 were critical to obtaining the instant invention, 2) that Protestor, independently of Lin, the inventor, obtained the amino acid sequences, and 3) that obtaining the amino acid sequences of EPO fragments T-35 and T-38 required non-obvious methods. It is considered by the examiner that all three of these assertions must be sustained before Protestor's contribution can be considered inventive

In regard to point 1 above, the examiner asserts that the Federal Circuit in Amgen Inc. v. Chugai Pharmaceutical Co., Ltd (18 USPQ2d 1016, 1021-22 (CAFC 1991)) has decided that the amino acid sequence of EPO fragments T-35 and T-38 were critical to obtaining the instant invention (see Exhibit B).

In regard to point 2 and 3, the examiner notes that there is a presumption that the inventorship of the instant application is correct and that Protestor is burdened with overcoming this presumption by showing clear and convincing evidence to the contrary. The evidence presented by Protestor is analyzed below.

Protestor asserts (Protest, page 2, bottom) that the amino acid sequencing was done under his supervision. Protestor also asserts (Protest, page 4, middle) that he was not Dr. Lin's assistant, and was not under Dr. Lin's direction, and that Dr. Vapnek was the EPO project leader. Protestor has provided evidence that Protestor was not an assistant of Dr. Lin (Exhibit J) and that Dr. Vapnek was supervising both Protestor and Dr. Lin in the EPO project (Exhibit L). Such evidence is not convincing. It is entirely possible that Protestor, while under the official or direct supervision of Dr. Vapnek, was indirectly under Dr. Lin's supervision (through Dr. Vapnek, for example, who apparently supervised both Dr. Lin and Protestor). Protestor also asserts (Protest, page 3, bottom) that Dr. Vapnek's memo (Exhibit D) and Dr. Wang's notebook (Exhibit E) provides evidence that Dr. Lin was not involved in the acquisition of EPO fragments from Dr. Goldwasser. It is noted that the memo mentions numerous researchers working on various aspects of the EPO project. In fact, Dr. Lin is mentioned in the first paragraph as communicating the sequencing results of Protestor to Dr. Goldwasser. This statement contradicts Protestors assertion that Dr. Lin was not involved in Protestor's part of the EPO project. Dr. Wang's notebook provides only evidence that the EPO fragments were sent to Protestor, not that Protestor was working independently.

After considering Protestor's evidence that Protestor provided amino acid sequences independently of Dr. Lin, the examiner finds no clear and convincing evidence that Protestor was not under the direction of Dr. Lin or that the amino acid sequencing was not done at his behest. While it may be that Dr. Lin was not a direct supervisor of Protestor, this mere fact is not evidence that the sequencing work performed by Protestor was not at the behest or suggestion of Dr. Lin. The evidence on this point presented by Protestor is entirely consistent with the current

inventorship. An inventor need not perform the actual manipulations required to make an invention if such manipulations do not require an inventive contribution (i.e. if such manipulation are routine; see infra).

Protestor asserts (Protest, page 1, (a) and (b)) that non-routine peptide sequencing techniques were used by Protestor to obtain the critical amino acid sequences. Protestor has submitted several documents (Exhibit A) purporting to evidence the non-routine nature of Protestor's sequencing methods. Firstly, the notebook pages and laboratory documents presented in Exhibit A, while describing peptide fragment sequencing, do not provide motivations, reasoning or specific details that would indicate that the particular method used was critical to obtaining the amino acid sequence. Secondly, even granting, arguendo, that the microsequencing paper by Protestor included in Exhibit A indicates that Protestor developed such techniques, it fails to establish that such techniques were critical to obtaining the amino acid sequences of EPO fragments. Protestor also asserts (Protest, page 5, middle) that statements in the Amgen 1984 Annual Report (Exhibit M) are evidence of Protestor's inventive contribution. Firstly, the Annual Report does not indicate whether Protestor developed such techniques. Secondly, due to the promotional nature of summary statements in Annual Reports in general, these statements must be given little weight. There is no clear and convincing evidence that the sequencing technique used by Protestor was critical to obtaining the instant invention.

Protestor asserts (Protest, page 2, (c) and (d)) that Exhibit A provides evidence that Protestor selected the critical T-35 and T-38 fragment sequences for probe design. However, Protestor has presented no clear and convincing evidence that the choice of fragments T-35 and T-38 was 1) critical to obtaining the invention and 2) based on other than random selection or

well known principles (i.e. selecting a fragment because its encoding probe would be less degenerate). In fact, Protestor indicates (Exhibit O, Explanation of Item 10) that fragments T-35 and T-38 were merely the first fragments chosen (at random?) for sequencing. In addition, Protestor indicates (Exhibit O, Explanation of Item 13) that fragment T-38, like T-35, was chosen for the presence of tryptophan. Choosing such an amino acid sequence for the derivation of degenerate cloning probes on this basis was well known at the time (see Suggs et al., page 6614, first paragraph of Results).

Protestor's history of his dispute with Amgen over inventorship (Protest, page 5, bottom) and the correspondence from Protestor's representative to Amgen is not evidence of Protestor's alleged co-inventorship but merely evidence of a dispute.

The examiner finds that all of the submitted evidence remains consistent with the inventorship as originally presented by Dr. Lin. Accordingly, Protestor has failed to provide clear and convincing evidence that Dr. Lin did not himself invent the instantly claimed subject matter.

New Grounds of Rejection

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 therefore, subject to the conditions and requirements of this title".

Claims 65-69 are rejected under 35 U.S.C. § 101 because the claimed invention is inoperable and therefore lacks patentable utility.

Claim 65 recites "a process for the preparation of... [a] biologically active glycosylated polypeptide" but then limits the transformed gene to one encoding human EPO. It is not seen how a process involving only DNA encoding human EPO can lead to the preparation of any

desired polypeptide. Accordingly, the instantly claimed process is inoperable and therefore lacks patentable utility. It is noted that the instant rejection could be overcome by amending the claim to recite "a process for the preparation of biologically active glycosylated human erythropoietin."

Claims 65-69 are directed to an invention not patentably distinct from claim 9 of commonly assigned Patent No. 4,667,016 (Lai et al.).

Claim 9 of Lai et al. recites a process of preparing EPO from a cell culture fluid. The claimed process implicitly involves the basic steps of 1) production of EPO containing cell culture fluid and 2) isolation of EPO from the fluid. While claim 9 of Lai et al. recites details of step 2 and the instant claims recite details of step 1, both claim 9 and the instant claims read on both steps. In this regard it should be noted that Lai et al. refers (paragraph bridging columns 2 and 3 and column 4, lines 34-48) explicitly to the instantly claimed method of producing recombinant EPO containing fluid. The referenced applications are ancestors of the instant application and Example 10 therein describes the exact subject matter of the instant claims.

Commonly assigned Patent No. 4,667,016, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. § 103 if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 C.F.R. § 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application. A showing that the inventions were commonly owned at the time the invention in this application was made will

preclude a rejection under 35 U.S.C. § 103 based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g).

Claims 65-69 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 9 of U.S. Patent No. 4,667,016 (Lai et al.).

Claim 9 of Lai et al. recites a process of preparing EPO from a cell culture fluid. The claimed process implicitly involves the basic steps of 1) production of EPO containing cell culture fluid and 2) isolation of EPO from the fluid. While claim 9 of Lai et al. recites details of step 2 and the instant claims recite details of step 1, both claim 9 and the instant claims read on both steps. Lai et al. teaches (paragraph bridging columns 2 and 3 and column 4, lines 34-48) production of recombinant EPO containing fluid by the same method as instantly claimed. Accordingly, it would have been obvious to one of ordinary skill in the art to produce human EPO by the method of Patent No. 4,667,016, including production of cell culture fluid containing recombinant EPO. One would have been motivated to do so by the clear reference to preparation of EPO containing cell culture fluid by Lai et al.

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term 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 C.F.R. § 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 C.F.R. § 1.78(d).

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 failing to provide an adequate written description of the claimed invention and as failing to provide an enabling disclosure

Applicant claims a method of preparing EPO, in part, by growing a host "capable of effecting post-translational glycosylation of polypeptides expressed therein." Applicant has provided no guidance for, and no working examples of, any test or procedure for determining which host cells have such capability and which do not. Without such a procedure, one of ordinary skill in the art could would have had no way to determine operable from inoperable embodiments of the claimed invention It is further noted that the instantly claimed host capability would be especially difficult to determine because it is not clear if such a host must be capable of glycolsylating all polypeptides expressed therein, heterologous polypeptides expressed therein, or a subset of polypeptides Accordingly, it would require undue experimentation by one of ordinary skill in the art to practice the invention as claimed.

It is also noted that the claimed host limitation does not appear in the specification as filed. Accordingly, the recitation of such a limitation in the claims lacks basis in the specification. It is noted that the instant objection may be overcome by deleting the recitation of the host's capability.

Applicant also claims specific expression steps (i), (ii) and (iii) reciting transcription, translation and glycosylation The detailed recitation of these steps has no basis in the specification. It is also not clear what limitation applicant intends to claim with these steps which are inherent to the production of a glycosylated polypeptide. It is noted that this objection may be overcome by deleting steps (i), (ii) and (iii) from claim 65.

Applicant also claims "glycosylation in a pattern directed by the amino acid sequence of said...polypeptide and sufficiently duplicative of the pattern of glycosylation of naturally occurring human erythropoietin." Firstly, there is no basis in the specification for glycosylation directed by the amino acid sequence of the expressed polypeptide. It is also not clear what limitation applicant is claiming with the recitation "glycosylation...in a pattern directed by the amino acid sequence of said polypeptide."

Secondly, applicant has provided no guidance for, and no working examples of, "sufficiently duplicative" glycosylation. Applicant has not described what constitutes sufficiency. Applicant has provided no guidance for or means of determining the similarity of any glycosylation pattern. The evidence applicant has provided that the glycosylation pattern between recombinant EPO and urinary EPO are different indicates that EPO made by the instantly claimed method is not "duplicative" of natural glycosylation. It is noted that this objection may be overcome by deleting the recitations of "glycosylation...in a pattern directed by the amino acid sequence of said...polypeptide" and "sufficiently duplicative of the pattern of glycosylation of naturally occurring human erythropoietin."

Claims 65-69 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 65-69 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to preparation of human EPO. See M.P.E.P. §§ 706.03(n) and 706.03(z).

Applicant claims a process for the preparation of a biologically active glycosylated polypeptide. However, the specification provides guidance for and a working example of only

the production of EPO. Considering the primitive state of the art of heterologous gene expression at the time the invention was made, it is questioned whether the instantly claimed method could have been practiced by one of ordinary skill in the art to produce any other biologically active glycosylated polypeptide. For example, at the time the invention was made, it was highly unpredictable that a heterologous protein would be produced in a biologically active glycosylated form. In addition, at the time the invention was made, most of the genes encoding the instantly claimed polypeptides were unknown. The instantly claimed invention is critically dependent on an isolated clone encoding a polypeptide of interest. At the time the invention was made, it would have required extensive and unpredictable experimentation to obtain such a clone for most of the myriad claimed polypeptides because gene isolation methods at the time depended on unavailable and unpredictable sequence information. Accordingly, it would have required undue experimentation by one of ordinary skill in the art to practice the instantly claimed invention to produce most of the claimed polypeptides. It is noted that the instant rejection may be overcome by amending the claim to recite "a process for the preparation of biologically active glycosylated human erythropoietin."

It is noted that enablement of the above mentioned scope is provisional pending the resolution of the objection to the specification presented supra.

Claims 65-69 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.

Claim 65 is vague and indefinite because it claims a process for the production of any polypeptide but recites only DNA encoding human EPO. It is not clear if applicant intends to

claim a process of preparing any polypeptide or a process of preparing human EPO. It is noted that the instant ground of rejection could be overcome by amending the claim to recite "a process for the preparation of biologically active glycosylated human erythropoietin."

Claim 65 is vague and indefinite in the recitation "a host cell capable of effecting post-translational glycosylation of polypeptides." It is not clear what relationship applicant intends between the glycosylation of polypeptides and the recited cell. A cell capable of effecting post-translational glycosylation of polypeptides is not necessarily effecting post-translational glycosylation and so it is not clear if applicants intend to claim said a cell which is in fact effecting post-translational glycosylation, said cell which is not effecting post-translational glycosylation or both. It has been held that the recitation that an element is "capable of" performing a function is not a positive limitation but only requires the ability to so perform. It does not constitute a limitation in any patentable sense. *In re Hutchison*, 69 USPQ 138. It is noted that the instant ground of rejection may be overcome by deleting the recitation of the hosts capability.

This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Hodges whose telephone number is (703) 308-4229.

A 4073

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) 308-0196.

Robert Hodges
September 1, 1993

RICHARD A. SCHWARTZ
SUPERVISORY PATENT EXAMINER
ART UNIT 185

A 4074