EXHIBIT 18

PATENT APPLICATION
ATTORNEY DOCKET NO. 11009/8272

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:

Fu-Kuen Lin

Serial No.: 07/113,179

Filed: October 23, 1987

For: PRODUCTION OF ERYTHROPOIETIN

Group Art Unit: 1805

Examiner: James Martinell, Ph.D.

APPLICANT'S AMENDMENT AND REMARKS
UNDER 37 C.F.R. §§1.111 AND 1.115

Hon. Commissioner of Patents
and Trademarks
Washington, DC 20231

Dear Sir:

This is in response to the Office Action dated August 11, 1994, in the above-identified application wherein the Notice of Allowance was withdrawn. Previously allowed claims 70 and 72-75 were rejected under 35 U.S.C. §112, second paragraph, and under the judicially created doctrine of obviousness-type double patenting. Reconsideration is respectfully requested in view of the following amendments and remarks.

437

AMENDMENT

In the Claims

Please amend claim 70 as follows:

70. (Amended) A process for the production of [an *in vivo* biologically active] a glycosylated erythropoietin polypeptide having the *in vivo* biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:

(a) growing, under suitable nutrient conditions, mammalian host cells transformed or transfected with an isolated DNA sequence encoding human erythropoietin; and

(b) isolating said glycosylated erythropoietin polypeptide therefrom.

REMARKS

Previously allowed claim 70, now amended, and previously allowed claims 72-75 are pending in the present application. To facilitate reconsideration, a copy of the pending claims (including amended claim 70) is attached as Appendix A hereto.

Applicant acknowledges with thanks the interview kindly granted on September 7, 1994 to the undersigned counsel and Messrs. Steven Odre and Stuart Watt, counsel for Applicant's assignee. At the interview, counsel advised the Examiner that Applicant intended to amend independent claim 70 as suggested in the Action dated August 1, 1994. Counsel further outlined the Applicant's position that no proper basis existed for rejection on obviousness-type double patenting.

I. THE CLAIMED SUBJECT MATTER

The present application addresses, and independent claim 70 recites, novel processes for the recombinant production of *in vivo* biologically active glycosylated erythropoietin polypeptides by means of the steps of growing mammalian host cells

transformed or transfected with an isolated DNA sequence encoding human erythropoietin and isolating the desired biologically active glycoprotein therefrom. Dependent claims 72 and 73 address presently preferred mammalian host cells employed in the claim 70 process and dependent claims 74 and 75 address presently preferred DNA forms for practice of the process.

II. THE OUTSTANDING REJECTIONS

Claim 70 and the claims dependent thereon were rejected under 35 U.S.C. §112, second paragraph, upon the allegation that the recitation "*in vivo* biologically active erythropoietin polypeptide" was indefinite. The Examiner suggested that amendment of the claim to recite causing bone marrow cells to increase production of reticulocytes and red blood cells as the *in vivo* biological activity would obviate the rejection.

Claims 70 and 72-75 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-6 of parent U.S. Letters Patent No. 4,703,008 in view of the disclosures of U.S. Letters Patent No. 4,695,542 to Yokota *et al.* It was the Examiner's position that Yokota *et al.* taught methods of producing glycosylated GM-CSF protein using DNA encoding mammalian GM-CSF. It was alleged that it would have been obvious to practice the claimed preparative process by "substituting the instant erythropoietin DNA for the [Yokota *et al.*] DNA encoding GM-CSF."

III. PATENTABILITY ARGUMENTS

A. The Section 112 Rejection May Properly Be Withdrawn

Applicant respectfully submits that the rejection of claim 70 under 35 U.S.C. §112, second paragraph, was in error in that it is clear from the present specification what *in vivo* biological activity is referred to in the claims. To expedite prosecution, however, Applicant has requested amendment of claim 70 in the manner

suggested by the Examiner. Applicant submits that the requested amendment does not involve new matter and renders moot the outstanding rejection.

B. The Double Patenting Rejection May Properly Be Withdrawn

Applicant respectfully submits that no proper basis exists for application of the judicially created doctrine of obviousness-type double patenting to foreclose issuance of claims 70 and 72-75 in the absence of a terminal disclaimer keyed to the expiration of the term of claims 1-6 of parent U.S. Patent No. 4,703,008.

1. Decisional Authorities

An appropriate starting point for consideration of the obviousness-type double patenting issue is the recent Federal Circuit decisional authority of *In re Braat*, 937 F.2d 589 (Fed. Cir. 1991) and *General Foods Corp. v. Studiengesellschaft Kohle GmbH*, 972 F.2d 1272 (Fed. Cir. 1992). At pages 592-593 of the *Braat* decision, Judge Rich set out the general basis for the judicially created doctrine, noting that the obviousness/non-obviousness determination is based on analysis of the claims, rather than the disclosures of the specification supporting those claims.

> Obviousness-type double patenting is a judicially created doctrine intended to prevent *improper* timewise extension of the patent right by prohibiting the issuance of claims in a second patent which are not "patentably distinct" from the claims of a first patent. *See in re Longi*, 759 F.2d 887, 892, 225 USPQ 645, 648 (Fed.Cir. 1985). The doctrine has also been phrased as prohibiting claims in the second patent which define "merely an obvious variation" of an invention claimed in the first patent. *In re Vogel*, 422 F.2d 438, 441, 164 USPQ 619, 622 (CCPA 1970). We note at the outset the difficulty which arises in all obviousness-type double patenting cases of determining when a claim is or is not an obvious variation of another *claim*. As this court's predecessor, the CCPA, noted in *Vogel*, 422 F.2d at 441-42, 164 USPQ at 622, a claim often does not describe any particular thing but instead defines the boundary of patent protection, and it is difficult to try to determine what is a mere obvious variation of a legal boundary. However, this court has endorsed an

> obviousness determination similar to, but not necessarily the same as, that undertaken under 35 USC § 103 in determining the propriety of a rejection for double patenting. *See Longi*, 759 F.2d at 892 n. 4, 225 USPQ at 648 n. 4.

As part of its holding in *Braat*, the Federal Circuit noted at pages 594-595 that only an "unjustified" timewise extension of patent protection would support an obviousness-type double patenting rejection.

The Federal Circuit decision in *General Foods* addressed the issue of double patenting in the context of a first patent's claims directed to a process for decaffeination of coffee through water-moist CO_2 treatment to remove caffein and a second patent's claims to caffein purification involving multiple steps applied to the water-moist CO_2 fraction containing caffein such as developed during the decaffeination process of the first patent. In the Federal Circuit's analysis supporting reversal of the District Court holding of double patenting, the court held at pages 1278-1279 that:

> Double patenting is altogether a matter of what is claimed. Claim interpretation is a question of law which we review de novo. *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 228 USPQ 90 (Fed.Cir. 1985). As we construe the claims here involved, claims 1 and 4 of the patent in suit, '639, define a process of decaffeinating raw coffee with supercritical water-moist carbon dioxide and recovering the decaffeinated coffee. They say nothing about what happens to the caffeine. Claim 1 of the '619 patent, relied on to show double patenting, defines a *9-step process* of "obtaining caffein from green coffee." Anything less than a process with all 9 steps is not what is claimed, and is, therefore, not patented. Claims must be read as a whole in analyzing a claim of double patenting. *Carman Indus., Inc. v. Wahl*, 724 F.2d 932, 940, 220 USPQ 481, 487 (Fed.Cir. 1983) ("we wish to clarify that double patenting is determined by analysis of the claims as a whole.") These two inventions, decaffeination of coffee and recovery of caffeine, are separate, *patentably distinct* invention between which there cannot be double patenting. Clearly the two patents do not claim the *same* invention, and this is not argued. Under an obviousness-type double patenting analysis, neither *claimed* process is a mere obvious variation of the other. No other kind of "double patenting" is recognized, so there is no double patenting. That concludes the case so far as this appeal is concerned.

In the discussion of legal authorities supporting its decision in *General Foods*, the Federal Circuit addressed the decisions of the Court of Customs and Patent Appeals in *In re Vogel*, 422 F.2d 438 (C.C.P.A. 1970) and *In re Borah*, 354 F.2d 1009 (C.C.P.A. 1966). First addressing *Vogel*, the Court reiterated the decision's restatement of the law of double patenting at page 1278 as follows:

> To summarize it, the opinion says that the first question is: Is the same invention being claimed twice? If the answer to that is no, a second question must be asked: Does any claim in the invention define merely an obvious variation of an invention claimed in the parent asserted as supporting double patenting? If the answer to that question is no, there is no double patenting.

At page 1278-1279 of the *General Foods* decision, the Court maintained that the *Borah* decision

> ...shows beyond question that the determining factor in deciding whether or not there is double patenting is the existence vel non of *patentable difference* between two sets of claims. The phrases actually used in the opinion include 'patentably distinguishable.' 'patentable distinctions,' and 'whether such differences would have been obvious to one of ordinary skill in the art. They are all equivalent.

2. The Subject Matter of the Present Claims Has Already Been Determined to be Patentably Distinct from Claims 1-6 of U.S. 4,703,008

As maintained by Applicant during the above-noted interview, the production process subject matter claimed herein has already been determined by the Patent and Trademark Office to be patentably distinct from the DNA-related (*i.e.*, DNA, vector, host cell) subject matter of U.S. 4,703,008. Moreover, there has already been a judicial determination confirming that the process subject matter of the present claims is not "covered" by the DNA-related claims of U.S. 4,703,008 so that issuance of process claims herein could not constitute a timewise extension of rights in claims 1-6 of the issued patent.

In proceedings before the Board of Patent Appeals and Interferences, separate interferences were drawn for the DNA-related subject matter of U.S. 4,703,008 and the production process subject matter claimed herein. Interference No. 102,096 was drawn with its sole Count identical to claim 2 of the '008 patent and all patent claims were designated as corresponding thereto. On the other hand, all pending claims of the present application were designated as corresponding to the Count in Interference No. 102,097 and the sole Count therein was identical to then-pending claim 65 of the application. It has thus been the position of the Patent and Trademark Office that the production process subject matter claimed herein was patentably distinct from the DNA-related subject matter claimed in U.S. 4,703,008. As a result, Applicant was placed at risk of loss of priority (and hence loss of patent rights) separately for each of the claimed subject matters. No rationale has been advanced in the present application for departing from the position already maintained by the Patent Office in the Interference Nos. 102,096 and 102,097 on the issue of separate patentability. A copy of the Board decisions in these two interferences is attached hereto as Appendix B.

In proceedings before the International Trade Commission and the subsequent appeal to the Court of Appeals for the Federal Circuit, it was judicially determined that the claims of U.S. Patent No. 4,703,008 did not "cover" recombinant production processes within the meaning of 19 U.S.C. §337. (See the CAFC decision attached hereto as Appendix C.) There has thus been a judicial determination that rights in the subject matter of '008 patent claims do not extend to the subject matter of the process claims herein and it correspondingly cannot be argued that issuance of claims herein would operate to "extend" rights already granted in U.S. Patent No. 4,703,008.

3. Factual Support for Patentable Distinctiveness of the Process Claims Has Already Been Made of Record

At the interview of September 7, 1994, Applicant maintained that it had already been established in the record of prosecution herein that the claimed production of a recombinant glycoprotein having the *in vivo* biological activity of erythropoietin was unexpected and non-obvious to those skilled in the art at the time of the invention. Evidence of non-obviousness was provided in the Applicant's Preliminary Amendment dated May 24, 1988 (Paper No. 8) and in Applicant's Reply dated September 26, 1988 (Paper No. 11).

Briefly summarized, it was noted that human erythropoietin had been established to be an "obligate" glycoprotein which required glycosylation for *in vivo*, but not *in vitro*, biological activity. An array of scientific publications was provided representing the state of the art in production of recombinant glycoproteins as of late 1983,[1] and it was established that the production of an *in vivo* biologically active erythropoietin product as described in the present specification constituted what appeared to be the first instance of recombinant production of a human obligate glycoprotein in *in vivo* biologically active form. It was further noted that no report of the production of *in vivo* biologically active human tissue plasminogen activator glycoprotein (tPA) had appeared until the 1984 publication of Collen *et al.* (Reference C35). It was also maintained that, even if the Collen *et al.* publication had preceded Applicant's work, a single disclosure of the recombinant production of an obligate human glycoprotein would not have provided a reasonable expectation of success at recombinant production of a glycoprotein product having the *in vivo* biological activity of human erythropoietin.

[1]The then-cited publications correspond to references B4, B7, B8, C35, C89, C94, C234 and C280 of the Information Disclosure Statement considered by Examiner Hodges on February 9, 1994 and to references X-1 through X-38 of the Information Disclosure Statement considered by Examiner Tanenholtz on November 29, 1988.

Attached as Appendix D is a copy of the summary analysis of references X-1 through X-38 which accompanied Applicant's submission of September 26, 1988.

The above point was also substantiated during recent proceedings before the European Patent Office Board of Appeal wherein the non-obviousness of recombinant product and production process claims of Applicant's corresponding European Patent 0 148 605 was placed in issue. At the hearing of September 20-24, 1994, it was argued by the appellants (opponents) that the combined teachings of eighteen documents relating to glycoproteins established a cumulative basis for maintaining that production of an *in vivo* biologically active recombinant erythropoietin product could reasonably have been expected by the notional skilled worker as of the December 13, 1983 priority date of EP 0 148 605. Attached hereto as Appendix E is the August 18, 1994 Declaration of Dr. Arthur Sytkowski presenting the eighteen references. Attached hereto as Appendix F is Applicant's graphic tabular presentation to the European Board of Appeal which addressed the eighteen documents in terms of whether any provided a disclosure of *in vivo* biological activity for a recombinant human glycoprotein which required glycosylation for *in vivo* biological activity.[2] None of the documents provided such a disclosure. The published German patent applications relating to recombinant tPA are believed to correspond to reference B4 and to provide no data concerning *in vivo* biological activity for any mammalian host cell expression product. It thus again appears that the Collen *et al.* publication after Applicant's priority date was the first disclosure of *in vivo* biological activity for a recombinant form of human obligate glycoprotein.

[2]In the copy of the table attached as Appendix F, cross-reference has been made to the document numbers employed by Applicant in the most recent Information Disclosure Statement. Those documents listed which have not previously been provided to the U.S. Patent Office are provided with a Supplemental Information Disclosure Statement submitted herewith.

4. The Yokota *et al.* Reference Is Not Relevant to Obviousness-type Double Patenting

Applicant respectfully submits that the Yokota *et al.* reference is not relevant to obviousness-type double patenting which, as noted in the decisional authorities, must be determined through consideration of the *claims* of the pending application and issued patent -- and not with reference to the prior art. To the extent that Yokota *et al.* might have been cited as prior art under 35 U.S.C. §102(e)/103 on the issue of obviousness of the claimed subject matter, it is also irrelevant because human M-CSF[3] is not an obligate human glycoprotein. This was clearly established at pages 3-5 of Applicant's submission of September 26, 1988, responding to the Examiner's citation of Yokota *et al.* and particularly by reference to Exhibits B and C attached thereto. As established by those exhibits, recombinant M-CSF can be prepared in non-glycosylated form in E. coli and retains *in vivo* biological activity.

5. Summary of Double Patenting

Applicant thus respectfully submits that the subject matter claimed herein was unobvious *vis-a-vis* the subject matter of claims 1-6 of U.S. 4,703,008 and that no proper basis exists for application of the judicially created doctrine of obviousness-type double patenting.

[3]The subject matter of the reference is M-CSF and not GM-CSF as indicated by Examiner Hodges.

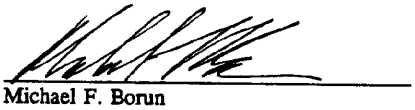
IV. CONCLUSION

The foregoing amendments and remarks are believed to establish that claims 70 and 72-75 are in condition for allowance and an early notice thereof is solicited.

Because the present application was withdrawn from issue after payment of the base issue fee, Applicant solicits the Examiner's assistance in providing for expedited issuance of Letters Patent thereon.

Respectfully submitted,

MARSHALL, O'TOOLE, GERSTEIN,
MURRAY & BORUN

BY: 

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