EXHIBIT E

68. A glycoprotein product according to Claim 67 wherein the exogenous DNA sequence is a cDNA sequence.

69. A glycoprotein product according to Claim 67 wherein the exogenous DNA sequence is a genomic sequence.

70. A glycoprotein according to Claim 67, 68 or 69 wherein the host cell is a mammalian cell.

71. A glycoprotein product according to Claim 70 wherein the host cell is a COS cell.

72. A glycoprotein product according according to Claim 70 wherein the host cell is a CHO cell.

73. A pharmaceutical composition comprising an effective amount of a glycoprotein product according to Claim 67 and a pharmaceutically acceptable diluent, adjuvant or carrier.

74. A method for providing erythropoietin therapy to a mammal comprising administering an effective amount of a glycoprotein product to Claim 67.

75. A method according to Claim 74 wherein the therapy comprises enhancing hematocrit levels.--

1411a - 2 -

225

Remarks

Applicant wishes to express appreciation to Examiners Kushan and Schain for their time and thoughtful consideration of the issues during the interview of May 24, 1989, with Mr. Steven Odre and the undersigned. It is earnestly believed that the interview materially advanced prosecution of the subject application (a copy of the Interview Summary is attached).

Entry of this Amendment and reconsideration and allowance of the subject application are respectfully requested. The amendments proposed herein are believed to place the application in condition for allowance.

The art cited in the subject Official Action has been carefully considered by the Applicant together with the Examiner's comments relevant thereto and, in response, new independent Claim 67, which combines previously pending Claims 41 and 61, is presented in an effort to more particularly point out and distinctly claim the subject invention. New Claims 68-75 correspond to previously pending Claims 62-66 and 55-57.

Claims 41, 55-57, and 61-66 were rejected under 35 U.S.C. 112, first and second paragraphs. Reconsideration is requested in view of the above-noted new claims and the remarks which follow.

All product claims in the subject application are now product-by-process claims. Independent Claim 67, and thus all of the pending claims, specifically define the erythropoietin of the subject invention as a "glycoprotein product of the expression of

an exogenous DNA sequence in a eucaryotic host cell...." These product-by-process claims are presented in an effort to positively recite the physical properties of recombinant erythropoietin, and to further define the product of the subject invention since the recombinant erythropoietin claimed cannot be precisely defined except by the process by which it is produced. It is submitted that the claims now pending herein fully meet the requirements of 35 USC 112.

Claims 41 and 61-66 were rejected under 35 USC 103 as being unpatentable over Miyaki et al., Chiba et al., Takezawa et al. (D or E) or Sugimoto et al. Reconsideration is requested in view of the above-noted new claims and the remarks which follow.

All of the references cited by the Examiner in this rejection relate to naturally occurring erythropoietin. The claims of the subject invention relate to erythropoietin which is produced through recombinant DNA techniques. Recombinant erythropoietin is different from naturally occurring erythropoietin (for a description of the differences, see the response filed December 5, 1988). Moreover, naturally occurring human erythropoietin is not a viable human therapeutic product; human recombinant erythropoietin, on the other hand, has been proven to be clinically effective, and is the first therapeutic product which can be used to effectively treat the hundreds of thousands of patients who suffer from anemia and other disorders involving low red blood cell counts.

In determining whether the subject claims are obvious under 35 USC 103, all evidence bearing on the subject must be considered. The proof of unobviousness of a claimed product can be through evidence that the product solves a long felt need, through evidence of the failure of others, or through evidence of its commercial success. Evidence of these Graham v. John Deere "secondary considerations" must always be taken into account in connection with the determination of obviousness (see Hybritech Inc. v. Monoclonal Antibodies, Inc. 231 USPQ 81 (Fed. Cir. 1986)).

The International Trade Commission recently applied the Graham v. John Deere "secondary considerations" in ITC Investigation No. 337-TA-281, involving commonly owned U.S. Patent 4,703,008, covering erythropoietin DNA, vectors and host cells (which resulted from the parent application to the subject application). The ITC upheld the validity of the '008 patent. Judge Harris, in his Initial Determination, used the Graham v. John Deere "secondary considerations" and found that these indicia supported a finding of unobviousness. The Initial Determination is attached for the Examiner's convenience.

In the subject invention, the Graham v. John Deere "secondary considerations" establish the unobviousness of recombinant erythropoietin. As to the "long felt need", Judge Learned Hand viewed "the length of time the art, though needing the invention, went without it" as the best nontechnical guidepost for inferring nonobviousness (see Safety Car Heating and Light Co. v. General Electric Co. 69 USPQ 401 (2nd Cir. 1946)). Indisputably, prior to the subject invention, there

was a long felt need for a compound which could be used for treating patients suffering from anemia. The "long felt need" was solved by recombinant erythropoietin, which can and is being used in the treatment of patients (see also pgs. 50-52 of the ITC Initial Determination). Judge Harris states at page 52 of the Initial Determination:

> Thus it is evident that since at least the early 1960's the medical community felt a need for a supply of exogenous EPO as an alternative treatment of the anemia suffered by patients with advanced renal disease. In 1983, it had not been possible to meet this need by isolating natural EPO or by recombinant methods...

In contrast to recombinant erythropoietin, naturally occurring human erythropoietin is not used to treat patients. In the past, efforts were made to obtain purified erythropoietin from natural sources such as the urine of patients with aplastic anemia. The results of these efforts however yielded only a small amount of material which was far too little for clinical research. Similarly, a program to purify natural erythropoietin from non-anemic persons failed because of impurities in the urine, and the resulting product made patients sick (see pgs. 51-52 of the ITC Initial Determination). In a statement (copy attached) announcing the FDA approval of recombinant erythropoietin, Commissioner Frank Young noted:

> Although there is not enough naturally occurring erythropoietin produced to collect it from healthy persons for use in treatment, gene splicing techniques have permitted its production.

Other "failure of others" were the efforts made by others to produce recombinant erythropoietin (see pgs. 52-54 and 153-160 of the ITC Initial Determination). In summary, there was a long felt need solved by recombinant erythropoietin and, prior to the subject invention, others failed in attempts to produce compounds, including recombinant erythropoietin, which could be used to treat patients.

Regarding commercial success, it is estimated that recombinant erythropoietin sales will be several hundred million dollars annually (see also pgs. 49-50 of the ITC Initial Determination). The product license application for recombinant erythropoietin was approved by the FDA on June 1, 1989. In contrast, no application has been filed at the FDA for naturally occurring human erythropoietin, and it is unlikely that one will ever be filed.

Applicant respectfully submits that none of the cited art of record, either taken alone or in combination, discloses, suggests or renders obvious the invention as claimed herein.

Claims 41, 55-57, and 61-66 were rejected under 35 USC 103 as being unpatentable over Miyaki et al., Chiba et al., Takezawa et al. (D or H) or Sugimoto et al. in view of Papayannopoulo et al. Reconsideration is requested.

This rejection includes the same references as the above noted prior art rejection with the addition of the Papayannopoulo et al. reference which relates to increasing the hematocrit of animals. The subject matter of the claims is unobvious in view of these references for the reasons noted above in response to the first prior art rejection.

Conclusions

In view of the above, Applicant respectfully submits that all claims now pending herein fully and patentable define the present invention over the applied art of record. As such, entry of the Amendment and early receipt of the Official Notice of Allowance is awaited.

Should any small matters remain outstanding, the Examiner is encouraged to telephone Applicant's undersigned attorney collect at (805) 499-5725 ext. 3161, so that same can be resolved without the necessity of an additional action and response thereto.

Respectfully submitted,

AMGEN INC.

Thomas E. Byrne
Reg. No. 32,205 6/2/89

TEB:jlm

Attachments

Amgen Inc.
1900 Oak Terrace Lane
Thousand Oaks, CA 91320