Exhibit L

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

LIN, Fu-Kuen — Group Art Unit: 1804

Serial No.: 08/100,197 — Examiner: Stanton, B.

Filing Date: August 2, 1993

For: PRODUCTION OF ERYTHROPOIETIN

REQUEST FOR RECONSIDERATION

Honorable Commissioner
of Patent and Trademarks
Washington, D.C. 20231

Sir:

This is in response to the Official Action of June 1, 1994 in the above-identified application, the period for response having been extended up to and including December 1, 1994 by submission of the required petition and fee concurrently herewith. Reconsideration of this application is respectfully requested.

The 35 USC §112 Rejections

Claims 62 and 63 were rejected under §112 second paragraph for being vague and indefinite in the use of the term "effective" and "recombinant" respectively. Applicant submits that in view of the extensive disclosure of the specification these terms are well-defined and understood by a person of skill in the art. Consequently, Applicant requests the Examiner to withdraw these rejections.

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The specification indicates several potential therapeutic uses for the claimed invention. More particularly, the specification at pages 86-87 recites the following:

> *Similarly, to the extent that polypeptide products of the invention share the in vivo activity of natural EPO isolates they are conspicuously suitable for use in erythropoietin therapy procedures practices on mammals, including humans, to develop any or all of the effects herefore attributed in vivo to EPO, e.g., stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis (see, Eschbach, et al., supra) and as indicated in Example 10, increasing hematocrit levels in mammals. Included within the class of humans treatable with products of the invention are patients generally requiring blood transfusions and including trauma victims, surgical patients, renal disease patients including dialysis patients, and patients with a variety of blood composition affecting disorders, such as hemophilia, sickle cell disease, physiologic anemias and the like.*

It is believed that these sentences from the specification and others provide a clear and definite description of the uses for which the claimed erythropoietin compositions would be therapeutically effective. A person of skill in the art would understand that the amount of erythropoietin necessary to achieve these defined therapeutic results would vary for each use. However, clinicians can readily determine the "therapeutically effective" amounts for each condition, and indeed for each patient. Applicant submits that the claim language

"therapeutically effective amount" is commonly used in this type of case where the product is useable to treat various conditions. Accordingly, the term is defined and meaningful to one of skill in the art, and the Examiner is requested to withdraw this rejection.

As for the term "recombinant" in claim 63, the Examiner's rejection is not understood. Certainly, the term "recombinant erythropoietin" is clear and definite in view of the disclosure of the specification which provides a detailed description of the pioneering invention of Dr. Lin in cloning the genes encoding human and monkey erythropoietin and using the cloned DNA to produce recombinant erythropoietin.

The Examiner's explanation of the rejection of claim 63 seems to indicate that the Examiner believes the claim to be redundant with claim 61 and not that the term "recombinant" is vague and indefinite. It should be clear, however, that claim 61 includes pharmaceutical compositions containing erythropoietin from various sources, e.g. urinary, recombinant, etc. Consequently, the term "recombinant" does serve as a further limitation to claim 61 as required for a dependent claim. It is widely accepted that recombinant erythropoietin is different, at least in the carbohydrate, from erythropoietin isolated from urinary sources as purified by the prior art processes. As noted by the Examiner, the specification indicates that recombinant

erythropoietin expressed in eukaryotic cells, e.g., CHO cells, may be fully glycosylated, but the carbohydrate chains are different in terms of composition, structure and the overall distribution of various glycoforms from those isolated from urinary erythropoietin. See, e.g., Takeuchi et al., Journal of Chemistry 262, 3657-63(1988), and Storring et al., Journal of Endocrinology, 134, 459-484(1992), copies of which are enclosed. Various reasons can be given for these differences including degradation of the erythropoietin in the urine, different cell mechanisms and materials for glycosylation between the natural kidney cells and other cells, etc. As a result, "recombinant" is a clear and meaningful limitation in dependent claim 63, and the Examiner is requested to withdraw this rejection.

The 35 USC §103 Rejections:

The Examiner has cited three prior references showing various levels of purification of erythropoietin from urinary sources and combined those with Bock and/or the present specification. First, it should be noted that none of these cited references (except the present specification) disclose or even suggest the claimed compositions. Bock relates to a totally different protein. The Examiner has in hindsight combined references disclosing urinary erythropoietin with references which suggest the use of HSA in general in pharmaceutical

compositions. This is improper. From the disclosure of Miyake and the two Takezawa patents, there is no indication that a diluent such as human serum albumin would be required to prepare a pharmaceutical composition with erythropoietin.

Second, the Patent Office has already determined that the claimed compositions are patentable in issuing not one but two patents encompassing the same subject matter as presently claimed. Both of these issued patents have priority dates well after the priority dates of the present invention. One of these issued patents, U.S. Patent No. 4,879,272 has already been disclaimed in view of an interference with the present application and the clear priority to the invention described and claimed in the present application. A second interference must now be declared with U.S. Patent No. 4,806,524. Applicant respectfully submits that the claimed invention is not obvious for the very same reasons that led to the issuance of '272 and '524 patents. For the Examiner to take a different position now with respect to the present invention which enjoys a much earlier filing date is simply not sustainable.

Applicant therefor requests that the rejections be withdrawn and an interference be entered between this application and U.S. Patent No. 4,806,524.

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Request for Interview:

Upon receipt of this response, it is respectfully requested that the Examiner contact the undersigned attorney for the purpose of an interview in order to resolve the formal and prior art rejections should the Examiner not be favorably persuaded by the foregoing.

For the reasons set forth hereinabove, it is believed that this application warrants the favorable reconsideration of the Examiner and such action is respectfully solicited.

Respectfully submitted,

KECK, MAHIN & CATE

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