the same or similar scope ... a duly filed continuing application, claims 14, 17 and 69-72 have been amended to refer to biological activities of polypeptides encoded rather than biological properties. This term is widely employed in the literature of recombinant technologies and is fully supported in the present specification by, e.g., the above-cited disclosures of the biological activities of erythropoietin. Applicant thus respectfully submits that the outstanding objection to, and rejection of, claims 14, 17 and 69-72 is mooted and may properly be withdrawn.

(d) Claims 14, 20, 23, 27, 30, 58 and claims dependent thereon were rejected on grounds of reference to figures, with the assertion that the DNA sequences of the figures "can be adequately expressed in words". Applicant respectfully disagrees. Applicant first notes that while the DNA sequences set forth are alphabetical in nature, they are not "words" in the ordinary sense. Rather, they are "diagrams" reciting the relationship of many nucleic acids and the amino acids encoded thereby. It has always been the case that the requirements of Section 112 could be satisfied by a diagramatic, rather than verbal, presentation in the claims where, as here, prolixity is avoided and clarity of description is preserved. See, e.g., In re Faust, 86 U.S.P.Q. 114, 115 (1943) and Ex parte Squires, 133 U.S.P.Q. 598, 600 (Bd. App. 1961).* In issued U.S. Patents relating to inventions in biotechnology, it has been found appropriate to identify novel microorganisms and cell lines in the claims through reference to a deposit accession numbers. As an example, in recently issued U.S. Patent No.

* In the last-mentioned decision, the claim on appeal was "1. A font of numerals as shown in Fig. 1".

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4,530,901, specific DNA sequences encoding interferon polypeptides were also claimed by reference to unspecified (but presumably "knowable") DNA sequences present as plasmid inserts contained in deposited microorganisms.

Reference to figures of the drawing herein is in full conformity with the "particularity" and "distinctness" requirements of the second paragraph of Section 112 and such reference clearly avoids prolixity without introducing ambiguity. It is thus respectfully submitted that the outstanding rejection of claims 14, 20, 23, 27, 30, 58 and claims dependent thereon may properly be withdrawn.

(e) The above-requested amendment of the language of claim 14 (to specify selection "from the group consisting of") is believed to moot the outstanding rejection of the claim on grounds of "improper Markush language".

(f) The requested amendment of claim 69 to reflect dependence on claim 62 is believed to moot the outstanding rejection thereof.

3. The "Provisional" Rejections of Claims 14, 15, 17-36, 58 and 61-72 Under 35 U.S.C. §101 Based on Applicant's Co-pending Applications May Properly Be Withdrawn

Applicant acknowledges with thanks the Examiner's provisional notation of the possibility of "double patenting" grounds for rejection should the present claims issue and all original claims also issue in "parent" U.S. Patent Application Serial Nos. 561,024, 562,185 and 655,841. This notation will be kept in mind in any subsequent prosecution of said applications. Applicant submits, however, that the provisional notation does not provide a basis for present rejection of the claims or otherwise constitute a bar to allowance of the claims.

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4. The Rejection of Claims 14, 24, 34 and 36 Under 35 U.S.C. §101 May Properly Be Withdrawn

Amendment of claims 14 and 34 to include the recitation of "purified and isolated" with reference to the claimed DNA sequences is believed to moot the outstanding rejection of claims 14, 24, 34 and 26 wherein the Examiner suggested that non-statutory subject matter (non-isolated erythropoietin genes in cells naturally producing erythropoietin) might be embraced by the claims.

5. The Rejection of Claims 14, 24, 34 and 36 Under 35 U.S.C. §§102(b) or 103 Over the Sugimoto et al. Reference May Properly Be Withdrawn

Amendment of claims 14 and 34 to include the recitation of "purified and isolated" with reference to the claimed DNA sequences is believed to render moot the outstanding rejection of claims 14, 24, 34 and 36. Under no circumstance can the claims be urged to "read on" non-isolated DNA present in the erythropoietin-producing lymphoblastoid cells of the Sugimoto et al. reference.

6. The Rejection of Claims 14, 15, 17, 18, 20, 24-27, 33, 34, 61-66, 69, 70 and 71 Under 35 U.S.C. §§102(a)/103 Based on the Lee-Huang (PNAS) Reference May Properly Be Withdrawn

It was the Examiner's position that the DNA sequences described in claims 14, 15 17, 18, 20, 24-27, 33, 34, 61-66, 69, 70 and 71 "appear to be the same as those made by Lee-Huang et al." [referring to PTO Reference "R"; Applicant's Reference C-68; Lee-Huang, P.N.A.S., 81, 2708-12 (1984)] and that these claims should therefore be rejected as anticipated or obvious under 35 U.S.C. §§102(a)/103. Applicant respectfully disagrees.

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Applicant notes at the outset that the Lee-Huang article was published in May, 1984, a date which is well after the filing dates of "parent" U.S. Patent Application Serial Nos. 561,024 (December 12, 1983) and 582,185 (February 21, 1984).*

Applicant maintains that, irrespective of the publication date of the Lee-Huang P.N.A.S. article, it is not "legally" available as a reference under 35 U.S.C. §102(a) or (b). As set out in detail below, this is so because the publication's disclosure is conspicuously insufficient to allow a person ordinarily skilled in the art, armed with the publication and his own knowledge, to duplicate the alleged cloning and expression of a human erythropoietin gene.

(a) The Legal Requirements for a Publication to Qualify As a Reference Bar Under 35 U.S.C. §102

Applicant submits that no publication may serve as a bar to the patentability of a discovery under Section 102 if the reference does not itself substantially "enable" the duplication of the claimed discovery. For over a century the courts have maintained that for a publication to be such a bar, the account published must be of a complete and operable invention capable of being put into practical operation. See, Seymour v. Osborne, 78 U.S. 516, 555 (U.S. 1870). This position was uniformly adopted and applied by the former Court of Customs and Patent Appeals. The Court's decision in In re LeGrice, 301 F.2d 929 (CCPA, 1962) is directly in point.

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* Note, also, that the December 13, 1983 filing date of Serial No. 561,024 precedes the January 11, 1984 filing date of U.S. Serial No. 570,040, referred to on the face of Reference D-13, the Lee-Huang PCT published PCT Application.

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> "We think it is sound law, consistent with public policy underlying our patent law, that before any publication can amount to a statutory bar to the grant of a patent, its disclosure must be such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention" Id, at page 936.
>
> * * * * *
>
> "...the proper test of description in a bar to a patent as the clause is used in section 102(b) requires a determination of whether one skilled in the art to which the invention pertains could take the description of the invention in the printed publication and combine it with his own knowledge of the particular art and from this combination be put in possession of the invention on which the patent is sought." Id, at page 939.

See also, In re Sasse, 629 F.2d 675, 681 (CCPA, 1980).

This position concerning the "enablement" requirement of a reference has been carried forward by the Patent Office Board of Appeals with respect to a variety of technologies, including those involving microbiology. Thus, while the CCPA decision in In re Argoudelis et al., 434 F.2d 1390, (1970) is frequently cited for its holding concerning an applicant's "enablement" requirements, the Board of Appeals decision which gave rise to the CCPA decision clearly applied the ruling of In re LeGrice to eliminate from consideration under Section 102 two Japanese "prior art" references disclosing the same antibiotic as claimed, but disclosing the means for obtaining it in a manner which could not be duplicated by an ordinarily skilled worker. See, Ex parte Argoudelis et al., 157 U.S.P.Q. 437, 443-4 (Bd. App., 1967).

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(b) The Lee-Huang (P.N.A.S.) Reference Is Not Susceptible to Duplication By Exercise of Ordinary Skill

Applicant submits that it is manifest from the four corners of the Lee-Huang publication that a person of ordinary skill in the art could not duplicate its disclosures to obtain cDNA encoding human erythropoietin -- principally because the monoclonal antibody designated "7A7" which was used in the work reported was not publicly available at the time of the publication and could not have been obtained by an ordinarily skilled artisan at that time. Moreover, the highly purified immunogen used by Lee-Huang to generate the 7A7-producing hybridoma cell line could not be obtained by "non-inventive" means.

The work represented in the Lee-Huang publication can be fairly summarized by reference to page 2708 and the paragraph bridging its two columns, which states:

> "Recently, we have been engaged in the purification of human EP. Progress has been made in the development of effective techniques for improved Ep purification (10). This has enabled us to prepare sufficient quantities of purified materials for the production of monoclonal antibodies to human Ep. (11) These antibodies provide a specific means for identifying Ep mRNA and for screening recombinant plasmids containing Ep gene [DNA] sequences." (Emphasis supplied)

In the "Materials and Methods" section on page 2708 of the publication reveals that:

> "Monoclonal antibody to human Ep was prepared according to the hybridoma technique of Kohler and Milstein (17). Purified IgG was used for all experiments described in the present work. The particular antibody used in all these studies was designated monoclonal 7A7. It reacts specifically with our purified Ep. Our purified Ep gives a single polypeptide band of Mr 34,000 by silver stain on NaDodSO$_4$/polyacrylamide gel (see Fig. 2A, lane 3). It has a specific activity of 66,000 units/mg." (Emphasis supplied.)

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Commencing with the second full paragraph of the "Results" section on page 2709, it is stated that:

> "To determine whether the poly(A)+ RNA isolated from the Ep-rich human renal carcinomas indeed contained Ep message, in vitro translation was carried out. The labelled translation products were immunoprecipitated with monoclonal antibody to human Ep." (Emphasis supplied.)

In the description of isolation of messenger RNA from renal carcinoma cells* and of use of the messenger to generate cDNA, the publication states, at page 2710:

> "The majority of Ep mRNA was resolved in fraction 11 (Fig. 3, lane 11) as detected by immunoprecipitation with anti-Ep 7A7... This fraction was used to synthesize ^{32}P-labelled single-stranded cDNA..."

* * * * *

> "Positive recombinants from colony hybridization were picked and grown on gridded nitrocellulose filters in a registered fashion for immunological screening. This procedure relies on expression of the cDNA inserted in the pBR322 β-lactamase operon to produce a fused polypeptide containing the appropriate epitope for the anti-Ep recognition. From 1.4 x 10^5 screened transformants, three positive clones were identified that reacted consistently with 7A7. These were designated pEp1, -2, and -3." (Emphasis added.)

In the penultimate paragraph of the "Discussion on page 2712, it is stated that:

> "Several monoclonal antibodies to human Ep have been isolated; only one (7A7) was chosen for routine screening of the cDNA

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* There is at least a serious question concerning the public availability of the "Ep-rich human renal carcinomas" used by Lee-Huang. In the first paragraph of the "Results" section on page 2709, Lee-Huang describes an "extensive search" for such carcinomas. Only 2 of 36 renal carcinoma extracts tested qualified as "Ep-rich" sources for messenger RNA.

library, because it has the highest antigen binding affinity. Since these monoclonal antibodies do not complete with each other for Ep binding (unpublished results) and they most likely recognize different epitopes, a mixture of them may identify additional Ep cDNA clones as well as other Ep-related polypeptides. I have also not screened for the presence of additional Ep cDNA clones containing other inserts that would have remained undetected by the immunological screening." (Emphasis supplied.)

Based on the above-quoted portions of the Lee-Huang text, it is apparent that duplicatation of the erythropoietin cDNA isolation work described in the publication is not merely a formidable task, it is an impossible one.

Clearly, the key to Lee-Huang's initial mRNA isolation and subsequent cDNA isolation (resulting in 3 cDNA clones isolated from among 140,000 prepared) was the use of monoclonal antibody 7A7. Other monoclonals mentioned by Lee-Huang were described as having lower affinity and as reacting with different epitopes, not even alleged to be specific for erythropoietin. There is no notation in the P.N.A.S. article of public availability for antibody 7A7 or the hybridoma cells which produce it. If the skilled worker were to examine the "reference" (No. 11) cited by Lee-Huang as describing the monoclonal antibodies used in the published work, the worker would find only an abstract (previously submitted as Applicant's reference C-69) which describes three positive hybridoma cell lines, none of which are identified as producing antibody 7A7, and none of which are noted to be available from any public depository. Moreover, it is clear from the text that while the well-known Kohler and Milstein techniques may have been employed to generate 7A7 and the other monoclonal antibodies, the highly

pure immunogen used in the hybridoma development process was one which assertedly could only be "enabled" by practice of certain "improved" purification techniques. If the skilled worker were to examine the "reference" (No. 10) cited by Lee-Huang as relating to techniques for "improved Ep purification" which "enabled us to prepare sufficient quantities of purified material for the production of monoclonal antibodies to human Ep", the worker would find only a 1980 paper on hydrophobic interaction chromatography (HIC) (Applicant's Reference C-136). None of the erythropoietin preparations in the paper demonstrate the high specific activity of 66,000 units/mg which characterized the erythropoietin immunogen used to make the 7A7 antibody.

Without a public source for the 7A7 antibody, without a public description even of the purified immunogen used to raise the antibody, the skilled worker is simply without the wherewithal to take possession of the "discovery" related in the Lee-Huang publication.

The above conclusion as to unavailability to the ordinarily skilled worker of either the 7A7 antibody or the purified immunogen used to generate it is specifically confirmed by the statements of Dr. Lee-Huang in her PCT Application WO 85/03079 published July 18, 1985 (submitted as Applicant's Reference B-13). On page 1 of the published application, reference is first made to an alleged invention in cDNA clones of human erythropoietin, than to an "Anti-Ep Patent Application" (Serial No. 570,039, filed January 11, 1984) which relates to monoclonal antibodies to human erythropoietin, and finally to an "Ep Purification Patent Application" (Serial No. 570,075, filed January 11, 1984) which is said to relate to a novel method for purifying

human erythropoietin. The interrelationship between these patent applications is set forth at page 2, lines 14-20 of the published PCT Application:

> "The progress made by the present inventor in native human Ep purification (described in the Ep Purification Patent Application) by direct and reverse immunochromatography, and in preparation of monoclonal Anti-Ep (described in the Anti-Ep Patent Application) has made it possible to attempt cloning of human Ep gene which, upon expression, can produce Ep protein."

Clearly, Lee-Huang's position was that an "invention" in means for purifying erythropoietin was needed to secure the immunogen employed in practice of an "invention" in monoclonal, anti-erythropoietin antibody production, which, in turn allowed for a third "invention" in the isolation of an erythropoietin gene. Neither of the "enabling" inventions in erythropoietin purification and monoclonal antibody production is disclosed in the P.N.A.S. article. This conclusion is further borne out by the text of the published application at pages 29 through 36 and 37 through 42 which respectively describes "Ep Purification" and "Monoclonal Anti-Ep".

In the "Ep Purification" section, an erythropoietin purification process is set out wherein the erythropoietin obtained by hydrophobic interaction chromatography (HIC) according to the 1980 Lee-Huang publication (C-136) serves as the starting material of the process. The material is subjected to further processing by direct immunoaffinity chromatography (DIAC) and then by reversed immunoaffinity chromatography (RIAC) to secure the final product. The HIC/DIAC/RIAC purification process is not found in the P.N.A.S. publication.

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