EXHIBIT H-4

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#4 JM 4/25/

IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

Application of	)	"PRODUCTION OF
	)	
FU-KUEN LIN	)	ERYTHROPOIETIN"
	)	
Serial No. 675,298	)	Group Art Unit 127
	)	
Filed November 30, 1984	)	Examiner: J. Martinell

Information Disclosure Statement
Under 37 C.F.R. §1.97 Including Form PTO-1449

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

In compliance with Title 37 of the Code of Federal Regulations, Sections 1.97, et seq., applicant hereby files a Form PTO-1449 listing references cited in the specification.

Applicant preliminarily notes that items A-1 to A-16, B-1 to B-11, and C-1 to C-129 are references cited in the specification of the application as filed. Items A-17 and A-18 are additional references listed herein as a result of their having been relied upon during PTO examination of parent application Serial No. 561,024. Items A-19 to A-21 and C-130 to C-134 are additional references cited by Examiner Martinell during preliminary examination of PCT Application US84/02021 (published June 20, 1985, as WO85/02610). Some degree of duplication appeared unavoidable. Thus, certain U.S. patent applications cited in the text (Itmes A-13 through A-16) are also cited as their corresponding EPC or PCT published patent applications (B-5, B-11, B-9 and B-12, respectively).

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U.S. 4,377,512 (A-8) is essentially equivalent to GB 2,085,877 (B-10). Previously uncited U.S. 4,558,005 (A-22) is essentially cumulative of Weiss, et al. (C-123). Previously uncited PCT WO85/03079 (B-13) corresponds to C-68 and was published after the filing date of the application, as was U.S. 4,568,488 (A-21) which is apparently based on a U.S. Application cited in B-13. Previously uncited WO85/04419 (B-14) was also published after the filing of the present application.

REFERENCES RELATING TO ERYTHROPOIETIN PRODUCTION THROUGH MANIPULATION OF GENETIC MATERIALS

and

REFERENCES RELATING TO SYNTHETIC PEPTIDES STRUCTURALLY RELATED TO ERYTHROPOIETIN AND TO ANTIBODIES RAISED AGAINST SUCH PEPTIDES

Applicant, by his counsel, respectfully submits that the art most relevant to patentability of essentially all the claims herein (and particularly to provisionally elected claims 14, 15, 17-36, 58, and 61-72) is that which bears upon the state of knowledge in the art with respect to: (1) use of genetic manipulations in the production of erythropoietin; and (2) the primary structural conformation of erythropoietin as isolated from natural sources.

Five references appear to have a bearing on the state of the art with regard to producing erythropoietin through genetic manipulation.

Reference No. C-31

Farber, Clin.Res., 31(4), 769A (1983)

Reference No. C-32

Farber, et al., Exp. Hematol., 11, Supp. 4, Abstract No. 101 (1983)

Reference No. C-33

Farber, et al., Blood, 62, No. 5, Supp. No. 1, Abstract 392, 1129 (1983)

Reference No. C-68

Lee-Huang, Proc. Nat'l. Acad. Sci. (USA), 81, 2708-2712 (1984)

Reference No. B-13

Lee Huang, Published PCT Appln. WO85/03079 (7/25/85).

As set forth in the specification at page 17, line 30 through page 18, line 21, the Farber, and Farber, et al. references (C-31, 32, 33) relate generally to in vitro systems designed for transitory expression of messenger RNA obtained from baboon and human kidney cells. The systems described in this reference, simply put, are incapable of placing in the hands of a skilled artisan DNA serving to substantially define the subject matter of claims 14, 15, 17-36, 58 and 61-72.

As set forth in the specification at page 18, lines 21 through 31, the Lee-Huang P.N.A.S. reference (C-68) was published after filing of parent application Serial Nos. 561,024 (December 13, 1983) and 582,185 (February 21,

1984). The newly cited Lee-Huang published PCT Application WO85/03079 (Reference B-13) was published July 25, 1985, and reflects a priority claim based on U.S. Patent Application S.N. 570,040 filed January 11, 1985. Applicant submits, at the outset, that neither reference is properly deemed as prior art with respect to any claim in the present application. Moreover, applicant submits that the refrences do not place the skilled artisan in possession of any erythropoietin-specifying DNA material whatever because they are wholly lacking in enabling description of the "Anti-Ep" antibody substances employed as a verification of the asserted erythropoietin-like translation products of DNA sequences cloned. Applicant notes that, in all likelihood, these references reflect a "failed experiment" which did not even place erythropoietin-specifying DNA in the hands of the investigator.

These references cited at page 16 of the specification relate to synthetic peptides having structures based on prior attempts at identification of the sequence of amino acids at the amino terminal of urine-derived erythropoietin. Antibodies to such peptides are also discussed in these references.

Reference No. A-13 (B-5)

Egrie, Published EPC Application 0116446 (8/22/84)

Reference No. C-103

Sue, et al., Proc. Nat'l. Acad. Sci (USA), 80, 3651-3655 (1983

Reference No. C-106

Sytowski, et al. J. Immunol. Methods, 69, 181-186 (1984)

Of these, only the Egrie reference (A-13/B-5) describes the correct (20-mer) amino terminal sequence of human erythropoietin. As such, it is pertinent to but does not adversely affect, patentability of peptide and anti-peptide antibody claims 47-49 and 51-54. Note that the first twenty residues of human EPO are specifically dealt with by "exclusionary" terms in independent claims 48, 49 and 51. Note also that amino acid sequence information concerning the initial twenty residues of erythropoietin was not employed in the manufacture of hybridization probes for identification of human genomic DNA encoding erythropoietin as described in Example 4. Rather, probes based on sequence analysis of specification Table I tryptic digest fragments T35 and T38 were used. (See page 30.) Fragment T35 is now known to span residues 46-52 of human EPO as disclosed in Table VI and fragment T-38 is now knownto span residues 86 to 106 of human erythropoietin.

REFERENCES RELATING TO ISOLATION OF NATURALLY-OCCURRING ERYTHROPOIETIN BY IMMUNOLOGICAL MEANS

Certain references were noted in the specification as relating to immunological methods for isolation of erythropoietin from natural sources. None are believed to be relevant to patentability of the claims, but appears to have been referred to by Serial No. in B-13.

Reference	Specification Page
C-9	14
C-69	14
C-123	15
C-99	15
C-129	15
C-130	15
A-12	15

Newly cited reference A-23 by Goldwasser, et al. is essentially cumulative of previous reference C-123 by Weiss, et al. Newly cited reference A-22 is not seen to be relevant to any of the pending claims.

REFERENCES GENERALLY RELATING TO ISOLATION OF NATURALLY-OCCURRING ERYTHROPOIETIN BY NON-IMMUNOLOGICAL MEANS

A number of references cited as background to the present invention refer to prior isolative methods for obtaining erythropoietin from cells and body fluids. As such, they are not seen to be directly relevant to the claimed subject matter.

Reference	Specification Page
A-1	12
A-2	12
C-79	13, 16
A-10	13
B-10 (A-8)	13
C-53	13
C-107	13
C-57	13
C-47	13
C-11	13

REFERENCES RELATING TO THE PROPERTIES AND USES OF ERYTHROPOIETIN

A large number of references cited in the specification relate generally to the properties and uses of erythropoietin and with the content of proposed therapeutic compositions involving erythropoietin.

Reference	Specification Page
C-109	10
C-110	10
C-40	11
C-35	11
C-105	11
C-83	11
C-124	11
C-64	11
C-3	11
C-81	11

Reference	Specification Page
C-24	11
C-29	11
C-91	11
C-45	11
C-30	11
C-59	11
C-80	11
C-115	12
C-116	12
C-20	12
C-46	12
C-15	12
C-28	12
C-78	12
C-112	12
C-73	12
C-21	12
C-100	12
C-93	88
C-75	88
C-90	88
C-62	88
C-26	88
C-122	88
C-55	88
C-101	88
C-36	88
C-113	88
C-6	88
C-84	88

Reference	Specification Page
C-18	88
C-16	88
C-17	88
C-96	88
C-49	92

While all of these references are generally pertinent to erythropoietin, its formulations and uses, none have any foundation in recombinant methodologies or provide any significant insights into the primary structural conformation of erythropoietin as described for the first time in this application.

Reference C-131 was cited during preliminary examination of WO85/02610. Although designated as being of "particular relevance", is is believed to provide only further background information concerning properties of erythropoietin.

REFERENCES RELATING TO SYNTHETIC PEPTIDES, THEIR BIOLOGICAL AND IMMUNOLOGICAL PROPERTIES IN GENERAL

Certain references cited in the specification provide general background concerning the biological and immunological properties of synthetic peptides. Most of these references are cited at page 15 of the specification, as indicated in the Table below. None of the references relate to erythropoietin.

Reference	Specification Page
C-71	15
C-95	15
C-121	15
C-72	15
C-120	15
C-125	15
C-44	15
C-86	15
C-4	15
C-25	15
C-70	15
C-54	15
C-14	89

REFERENCES RELATING TO
HYBRIDIZATION PROBE TECHNOLOGIES GENERALLY

A number of references were cited in the specification as providing background information relative to DNA hybridization procedures practiced in carrying out the present invention. All teachings of these references are believed to be manifestly distinct from the improved detection method of claim 60.

Reference	Specification Page
A-9	6
C-118	6
C-94	6
C-52	6
A-7	6
B-1	6
B-2	6
C-23	6
C-38	6
C-117	7
C-104	7
C-10	7
C-61	7
C-87	7
C-58	7
C-117	7
C-102	7
C-65	8
C-56	8
C-7	8
C-34	8
C-22	8
C-2	8
C-38	33
C-108	95

Applicant submits that Reference C-2 is of particular relevance to the patentability of claim 60 in that it teaches away from the claimed invention. (See specification page 9, lines 4-20.)

REFERENCES GENERALLY RELATING TO
MANIPULATIVE PROCEDURES, ASSAYS AND THE LIKE

A substantial number of the references cited in the specification are believed to be pertinent to the claimed invention in the sense that they constitute publications of manipulative procedures and assays or analyses practiced or practicable in the course of work providing illustrative examples of the invention. These references are listed below by item number appearing on Form PTO-1449. Their respective pertinence is believed to be manifest from the text portions associated with their citation in the specification, principally spanning pages 28 through 89. If further comment with respect to any reference would be of assistance to the Examiner, advice of same is solicited.

Reference	Specification Page
C-50	16
C-5	30
C-8	32
C-74	32
C-88	33
C-119	34
C-98	35
C-76	35
C-51	41
C-63	41
C-12	41
C-13	41
C-65	41
C-126	41

Reference	Specification Page
C-37	41
C-74	41
C-41	58
C-19	58
C-48	58
C-114	59
C-92	61
C-67	65
C-85	65
A-16	74
A-15	83
C-77	85
C-51	89
C-27	89
C-60	89
C-97	89
C-82	89
C-39	89

REFERENCES RELATING TO RECOMBINANT DNA TECHNIQUES IN GENERAL

A number of references cited in the specification are believed to be pertinent to the claims insofar as they generally relate to "background" methods and materials concerning application of recombinant techniques for generation of biologically active polypeptides related to naturally occurring materials in a variety of procaryotic and eucaryotic hosts.

Reference	Specification Page
A-3	3
A-4	4
A-5	4
A-6	4
B-4	4
A-14 (B-11)	5
C-111	22
A-11	59
B-6	59
B-7	59
B-8	59
B-9 (A-15)	83
C-89	93
B-3	90
C-42	90
C-43	95

None of these references relate to application of such techniques to erythropoietin production.

Certain references relating to recombinant techniques generally were cited by the Examiner in prosecution of parent application Serial No. 561,024. These references, A-17 and A-18, do not relate to erythropoietin and are not believed to be relevant to patentability of any claim.

Certain other refrences were cited during preliminary examination of PCT US84/02021 (WO85/02610). These are references C-130 and C-132 through C-134, and references A-19 through A-21. While they were noted to be of "particular relevance", it is submitted that they do not refer in any way to erythropoietin and thus are not relevant to patentability of any of the claims.

Newly cited reference B-14 was published October 10, 1985 and mentions recombinant production of erythropoietin (see claim 10), but only in the context of a litany of polypeptides which might be expressed in claimed vectors. No other disclosure concerning erythropoietin is contained in the references and it is believed to be pertinent only as a "background" recombinant methodology reference.

Respectfully submitted,

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