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GROUP 120

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 - A. Tanenholtz

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

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

Sir:

This is in response to the Office Action dated June 21, 1987 in the above-identified application. Reconsideration and allowance of all claims is respectfully requested in view of the following amendments and remarks.

AMENDMENTS

IN THE SPECIFICATION

At page 25, following line 5 of the original text, delete the entire text of the insertion requested in the amendment dated October 3, 1986 and insert in place thereof the following:--Reference is made to FIGURES 1 through 21, wherein: FIGURE 1 is a graphic representation of a radio-immunoassay analysis of products of the invention; FIGURES 2 through 4 illustrate vector constructions according to the invention; and, FIGURES 5 through 21 are DNA and polypeptide sequences according to the invention.--

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At page 37 line 6, please delete the entire text of the insertion requested in the amendment dated October 3, 1982 [i.e., delete "duplicated as FIGURE 5 comprising portions 5A, 5B and 5C"].

-x-

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At page 37, line 6, please delete "Table V" and insert --FIGURE 5--.

At page 37, line 6, please delete "Table" and insert --FIGURE--.

Please delete the entire text of pages 38 through 40.

At page 41, line 1, please delete "Table V" and insert in place thereof --FIGURE 5--.

At page 42, line 25, please delete the entire text of the insertion requested in the amendment dated October 3, 1986 [i.e., ", duplicated as FIGURE 6 comprising portions 6A, 6B, 6C, 6D and 6E").

At page 42, line 25, please delete "Table VI" and insert in place thereof --FIGURE 6--.

Please delete the entire text of pages 43 through 47.

At page 48, line 1, please delete "Table VI" and insert in place thereof --FIGURE 6--.

At page 48, line 34, please delete "Table VI" and insert in place thereof --FIGURE 6--.

At page 49, line 1, please delete "Table" and insert in place thereof --FIGURE--.

At page 49, line 6, please delete "Table" and insert in place thereof --FIGURE--.

At page 49, line 8, please delete "Table 6" and insert in place thereof --FIGURE 6--.

At page 49, line 15, please delete "Table" and insert in place thereof --FIGURE--.

At page 49, line 16, please delete "Table VII, below," and insert in place thereof --FIGURE 9--.

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At page 49, line 18, please delete "Table" and insert in place thereof --FIGURE--.

At page 49, line 27, please delete "Table 6" and insert in place thereof --FIGURE 6--.

Please delete the entire text of page 50.

At page 63, line 35, please delete "Table 6" and insert in place thereof --FIGURE 6--.

At page 65, line 34, please delete "Table 6" and insert in place thereof -- FIGURE 6--.

At page 66, line 12, please delete "Tables VIII through XIV below" and insert in place thereof --FIGURES 10 through 15 and 7--.

Please delete the entire text of pages 67 through 72.

At page 73, line 1, please delete "Table VIII" and insert in place thereof --FIGURE 10--.

At page 73, lines 6 and 7, please delete "Table IX" and insert in place thereof --FIGURE 11--.

At page 73, line 21, please delete "(Tables XI and XIII)" and insert in place thereof --(FIGURES 13 and 15)--.

At page 73, line 23, please delete "Tables X and XII" and insert in place thereof --FIGURES 12 and 14--.

At page 73, line 26, please delete "Table XI" and insert in place thereof --FIGURE 13--.

At page 73, line 32, please delete the entire text of the insertion requested in the amendment of October 3, 1986 [i.e., "duplicated as Figure 7"].

At page 73, line 32, please delete "Table XIV" and insert in place thereof --FIGURE 7--.

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At page 74, line 29, please delete "Table XIV" and insert in place thereof --FIGURE 7--.

At page 75, line 28, please delete the entire text of the insertion requested in the amendment dated October 3, 1986 [i.e., "(the last-mentioned Table being duplicated as FIGURE 8)"].

At page 75, line 28, please delete "Tables XV through XXI" and insert in place thereof --FIGURES 16 through 21 and 8--.

At page 75, lines 30 and 31, please delete "Tables XV, XVII and XIX" and insert in place thereof --FIGURES 16, 18 and 20--.

At page 75, line 32, please delete "Tables XVI, XVIII and XX" and insert in place thereof --FIGURES 17, 19 and 21--.

Please delete the entire text of pages 77 through 82.

At page 83, line 21, please delete "Table XXI" and insert in place thereof --FIGURE 8--.

At page 89, line 16, please delete "Table VI" and insert in place thereof -- FIGURE 6--.

At page 90, line 15, please delete "Table V" and insert in place thereof --FIGURE 5--.

At page 90, line 16, please delete "Table VI" and insert in place thereof --FIGURE 6--.

At page 90, lines 29 and 30, please delete "Table V and VI" and insert in place thereof --FIGURES 5 and 6--.

At page 94, line 6, please delete "Tables V and VI" and insert in place thereof --FIGURES 5 and 6--.

At page 94, line 14, please delete "Tables V and VI" and insert in place thereof --FIGURES 5 and 6--.

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At page 94, line 33, please delete "mammlain" and insert in place thereof "--mammalian--".

IN THE DRAWING

Please enter drawing Figures 5 through 21 in accordance with the "Letter" submitted concurrently herewith.

IN THE CLAIMS

Please cancel claims 73-103 without prejudice.

Please insert new claims 104-134.

10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 841, 842, 843, 844, 845, 846, 847, 848, 849, 850, 851, 852, 853, 854, 855, 856, 857, 858, 859, 860, 861, 862, 863, 864, 865, 866, 867, 868, 869, 870, 871, 872, 873, 874, 875, 876, 877, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 888, 889, 890, 891, 892, 893, 894, 895, 896, 897, 898, 899, 900, 901, 902, 903, 904, 905, 906, 907, 908, 909, 910, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 923, 924, 925, 926, 927, 928, 929, 930, 931, 932, 933, 934, 935, 936, 937, 938, 939, 940, 941, 942, 943, 944, 945, 946, 947, 948, 949, 950, 951, 952, 953, 954, 955, 956, 957, 958, 959, 960, 961, 962, 963, 964, 965, 966, 967, 968, 969, 970, 971, 972, 973, 974, 975, 976, 977, 978, 979, 980, 981, 982, 983, 984, 985, 986, 987, 988, 989, 990, 991, 992, 993, 994, 995, 996, 997, 998, 999, 1000

104. A purified and isolated DNA sequence encoding erythropoietin, said DNA sequence selected from the group consisting of:

(a) the DNA sequences set out in Figures 5 and 6 or their complementary strands; and

(b) DNA sequences which hybridize under stringent conditions to the DNA sequences defined in (a).

105. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.

106. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding monkey erythropoietin.

107. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 104, 105 or 106 in a manner allowing the host cell to express erythropoietin.

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⁵
108. A biologically functional circular plasmid or viral DNA vector including a DNA sequence according to claim ¹104, ²105, or ³106.

⁶
109. A procaryotic or eucaryotic host cell stably transformed or transfected with a DNA vector according to claim ⁵108.

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⁷
110. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having ^{an amino acid sequence} ~~a primary structural conformation~~ sufficiently duplicative of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake.

⁸
111. A cDNA sequence according to claim ⁷110.

⁹
112. A monkey species erythropoietin coding DNA sequence according to claim ⁸111.

¹⁰
113. A DNA sequence according to claim ⁹112 and including the protein coding region set forth in Figure 5.

¹¹
114. A genomic DNA sequence according to claim ⁷110.

¹²
115. A human species erythropoietin coding DNA sequence according to claim ¹¹114.

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cont'd

¹³
~~116~~. A DNA sequence according to claim ¹²~~115~~ and including the protein coding region set forth in Figure 6.

¹⁴
~~117~~. A DNA sequence according to claim ⁷~~110~~ and including one or more codons preferred for expression in E.coli cells.

¹⁵
~~118~~. A DNA sequence according to claim ¹⁴~~117~~ coding for expression of human species erythropoietin.

¹⁶
~~119~~. A DNA sequence according to claim ¹⁵~~118~~ including the protein coding region set forth in Figure 7.

¹⁷
~~120~~. A DNA sequence according to claim ⁷~~110~~ and including one or more codons preferred for expression in yeast cells.

¹⁸
~~121~~. A DNA sequence according to claim ¹⁷~~120~~ coding for expression of human species erythropoietin.

¹⁹
~~122~~. A DNA sequence according to claim ¹⁸~~121~~ including the protein coding region set forth in Figure 8.

²⁰
~~123~~. A DNA sequence according to claim ⁷~~110~~ covalently associated with a detectable label substance.

²¹
~~124~~. A DNA sequence according to claim ²⁰~~123~~ wherein the detectable label is a radiolabel.

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²²
~~125~~. A single-strand DNA sequence according to
claim ²⁰~~122~~.

²³
~~126~~. A procaryotic or eucaryotic host cell trans-
formed or transfected with a DNA sequence according to claim
~~120~~, ~~121~~ or ~~124~~ in a manner allowing the host cell to
express said polypeptide.

²⁴
~~127~~. A transformed or transfected host cell
according to claim ²³~~126~~ which host cell is capable of
glycosylating said polypeptide.

²⁵
~~128~~. A transformed or transfected mammalian host
cell according to claim ²⁴~~127~~.

²⁶
~~129~~. A transformed or transfected COS cell
according to claim ²⁵~~128~~.

²⁷
~~130~~. A transformed or transfected CHO cell
according to claim ²⁵~~128~~.

²⁸
~~131~~. A biologically functional circular plasmid
or viral DNA vector including a DNA sequence according to
claim ⁷~~110~~.

²⁹
~~132~~. A procaryotic or eucaryotic host cell stably
transformed or transfected with a DNA vector according to
claim ²⁸~~131~~.

³⁰
~~133~~. A DNA sequence according to claim ⁷~~110~~ coding
for [Phe¹⁵]hEPO, [Phe⁴⁹]hEPO, [Phe¹⁴⁵]hEPO, [His⁷]hEPO,

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[Asn² des-Pro² through Ile⁶]hEPO, [des-Thr¹⁶³ through Arg¹⁶⁶]hEPO, or [A27-55]hEPO.

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134. A purified and isolated DNA sequence as set out in Figures 5 or 6 or the complementary strand of such a sequence.

REMARKS

Upon entry of the above-requested amendments to the specification, all of the original "Tables" in the specification, except for original Tables I through IV, will have been "converted" to Figures.

Upon entry of the above-requested amendments to the claims, claims 104 through 134 will remain in the application and will be correlated to prior claims 73 through 103 in the manner indicated in the following Table.

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<u>Prior Claim</u>	<u>New Claim</u>	<u>Prior Claim</u>	<u>New Claim</u>
73	104, 105, 106	90	122
74	107, 126-130	91	123
75	108	92	124
76	109	93	125
77	110	94	131
78	111	95	132
79	112	96	110
80	113	97	--
81	114	98	--
82	115	99	--
83	116	100	133
84	--	101	--
85	117	102	--
86	118	103	134
87	119		
88	120		
89	121		

The amendments to the claims are being made without prejudice to Applicant to pursue claims of the same or similar scope as those cancelled in a duly-filed continuing application.

A. The Claimed Subject Matter

As related in Applicant's prior communications, the claims remaining in this application relate to DNA sequences, DNA vectors, transformed and transfected host cells useful in the preparation of biologically active erythropoietin products including, e.g., polypeptide fragments and analogs of erythropoietin.

Independent claim 104 is thus directed to purified and isolated DNA sequences substantially defined by reference to the DNA sequences revealed in Figures 5 and 6 and independent claims 105 and 106 are specifically directed to

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purified and isolated DNA sequences encoding human and monkey erythropoietin. Dependent claims 107-109 respectively relate to host cells transformed or transfected with erythropoietin expressing DNA, to vectors including such DNA and to hosts transformed with such vectors.

Independent claim 110 is directed generally to DNA sequences which code for procaryotic or eucaryotic host expression of polypeptides having amino acid sequences sufficiently duplicative of that of erythropoietin to allow for specified erythropoietin properties. Dependent claims 111-134 are directed to presently preferred forms of DNA sequences, vectors, and transformed or transfected hosts based on the claim 110 DNA sequences. Claims 127-130 specifically relate to the host cell systems exemplified by Examples 7, 8 and 10.

B. The Outstanding Office Action, The Rejections Of The Claims And Applicant's Responses Thereto

In the communication dated March 12, 1987, Applicant responded to numerous outstanding objections to the specification and rejections to the claims under §§112, 101, 102 and 103. Applicant understands that the amendments and remarks set out in the March 12, 1987 communication have resulted in reconsideration and withdrawal of the following rejections propounded in the Action dated February 5, 1987:

- (1) The Section 112 (2nd paragraph) rejection of certain claims on grounds of their reference to drawings;
- (2) The "provisional" Section 101 rejection of claims based on copending parent patent applications;
- (3) The rejection of certain claims under Section 112 (2nd paragraph) for incorporation of brackets;

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(4) The rejection of certain claims under Section 112 (1st paragraph) due to alleged lack of specificity of reference to "hybridization";

(5) The rejection of certain claims under Section 103 based on the Sue et al. reference when considered with the Breslow et al. or Woods et al. references;

(6) The rejection of certain claims under Section 103 based on the Sue et al. reference and other specified secondary references; and

(7) The rejection of at least certain claims under Section 102(b) based on the Talmadge et al. reference.

Due to the number and variety of new objections and rejections set forth in the Action dated June 21, 1987, Applicant submits that the issues raised therein are best treated by means of responses which "track" the order of their appearance in the Action.

1. The Renewed Objections To The Disclosure Based On Reference To Drawings And Figures May Properly Be Withdrawn

As indicated above, application has now "converted" all Tables in the specification (other than Tables I through IV) into Figures. Applicant disagrees that the submission of these Figures 5 through 8 in a separate envelope labelled as an Exhibit was an inappropriate or improper way of presenting the drawings. Notwithstanding this disagreement, Applicant is concurrently submitting a complete set of new Figures 5-21 under cover of a "Letter" requesting entry of the same. Despite the fact that Applicant maintains that reference to Tables, in sequence in the Figures, would facilitate reading of the specification, none of the Figures include notations of their historical basis in Tables of the specification.

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? **No Basis Exists For Rejection
Of The Claims Under 35 U.S.C. §112
(First or Second Paragraphs)**

In the Action dated June 21, 1987, certain new rejections of prior claims 73 through 102 were propounded. More specifically, the Examiner first objected to element "(c)" of claim 73 as indefinite and unduly broad, stating that the recitation, "but for the degeneracy of the genetic code" was unclear, and that the recitation, "would hybridize" was improperly "permissive". Applicant respectfully disagrees with the Examiner's position. As clearly delineated in the specification (see, e.g., page 94, lines 15-24), element "(c)" of claim 73 (which has its origins in original claim 14) clearly delineates as within the scope of Applicant's invention those naturally-occurring allelic or manufactured or mutagenized genomic and cDNA sequences which, but for the degeneracy of the genetic code, would hybridize to the Figure 5 or Figure 6 sequences. Applicant submits that the specification fully "enables" such sequences (see, e.g., the ECEPO and SCEPO, E.coli and yeast preference codon DNA sequences) and that a person of ordinary skill in the art would clearly understand what was embraced by the recitations of claim. Clearly if one manufactures or mutagenizes a gene to include, e.g., a position 4 arginine-specifying codon AGG rather than CGC as in Figure 6, the prospects for hybridization between the manufactured sequence and the Figure 6 sequence are diminished. The same amino acid is encoded, however, and but for the degeneracy of the genetic code the three-base codon provided would hybridize.

Despite this position, Applicant acknowledges the Examiner's notation of equivalence in scope of alternatively worded claims:

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