EXHIBIT 15

PATENT

IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

Application of:	)	"PRODUCTION OF
	)	
FU-KUEN LIN	)	ERYTHROPOIETIN"
	)	
Serial No: 113,179	)	Group Art Unit 184
	)	
Filed: October 23, 1987	)	Examiner Tanenholtz

SEP 27 1988

APPLICANT'S REPLY UNDER 37 C.F.R. 1.111

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

Sir:

This is in response to the Office Action dated August 3, 1988 in the above-identified application, wherein all presently pending claims (65 through 69) were rejected under 35 U.S.C. §103 as unpatentable in view of the teachings of Yokota et al., U.S. Letters Patent No. 4,695,542. Reconsideration and allowance is respectfully requested in view of the following remarks.

REMARKS

Applicant acknowledges with thanks the interview kindly granted to Applicant's counsel, Mr. S. Odre, on September 14, 1988. As indicated in the Interview Summary Record, attached as Exhibit "A" hereto, no agreement was reached concerning patentability.

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The Claimed Subject Matter

Claims 65 through 129 are pending. Briefly summarized, independent claim 65 relates to a novel series of process steps wherein a mammalian host cell[1] capable of glycosylating the expressed polypeptides is first transformed or transfected with a DNA sequence[2] encoding a specifically delineated polypeptide, i.e., one having sufficient amino acid sequence homology to natural human erythropoietin to allow it to qualify, amino acid sequence-wise, for potential in vivo biological activity. (The DNA reagent employed in the transformation/transfection process is itself the novel and unobvious subject matter of claim 7 of U.S. Patent 4,703,008 and the resulting host cells are as recited in claim 24 of the Patent.) The claim 65 process calls for host cell growth in culture under conditions wherein transcription, translation and glycosylation processing occurs. More particularly, the claim calls for mRNA transcript formation according to the per se unique directions provided by the recited DNA sequence. (Illustratively, the formation of a full length coding region transcript of erythropoietin cDNA ordinarily involves no less than 582 specifically ordered nucleotide additions for the formation of the mRNA polymer.) Also delineated by claim 65 is performance of a specific sequence of translational events giving rise to polypeptide formation. (Again, a minimum of 193 specific alignments of tRNA's to the mRNA and 192 peptide bond formations are involved to link, in

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1 Including such non-human, non-kidney cells as COS and CHO cells as specified in claims 66 and 67.

2 Including, e.g., cDNA and genomic DNA as specified in claims 68 and 69.

order, the amino acids constituting the full length primary structural conformation.) Further required by claim 65 is the glycosylation processing of the translated polypeptide at sites directed by the order of amino acids of the translated polypeptide so that the resulting product, upon isolation, will have the pattern of glycosylation which is also required for in vivo biological activity.

The Outstanding Rejection

It was the Examiner's position that Yokota et al. teach a process as set forth in claims 65 through 69

> "differing only in using a mammalian DNA sequence that encodes a different polypeptide. More specifically, Yokota et al teach growing a mammalian host cell which is capable of effecting post-translational glycosylation of polypeptides expressed therein and which has been transformed with an isolated DNA sequence encoding the protein GMCSF under nutrient conditions to allow, in sequence, transcription, translation and glycosylation and then isolating the resulting glycosylated GMCSF. It is noted that the erythropoietin of the claims and the GMCSF of Yokota et al are proteins that both stimulate the production of blood cells."

The Examiner noted that the PTO files did not contain Exhibit "E" to the prior response. A copy of the Exhibit is attached hereto.

Patentability Argument

Applicant respectfully disagrees with the Examiner's reliance upon the Yokota et al. reference as providing a basis for application of In re Durden to deny patentability of the present method claims.

As noted in Applicant's Second Preliminary Amendment, the core patentability issue is whether the prior

art extant at the time of the present invention provided the skilled artisan with a reasonable expectation of success in securing the recombinant production of a human obligate glycoprotein, i.e., a human protein which must be properly glycosylated in order to display in vivo biological activity. Applicant submits that this was not the case. the cited Yokota, et al. reference is simply another example of expression of a non-human (i.e., mouse) protein ("Multi-CSF" or "IL-3") in a glycosylated form and in a context wherein therein is no indication of either the need for proper glycosylation in order for the molecule to possess in vivo biological activity or the actual possession by the mouse CSF product of such obligatory glycosylation. The Summary of the Invention of Yokota et al. notes only in vitro activity (column 4, lines 47-49) and all of the assays in column 22-24 are in vitro assays.

Indeed, subsequent experimentation has revealed that glycosylation is not necessary in order for Multi-CSF to possess in vivo biological activity. Exhibits B and C hereto [Metcalf et al., Blood, 68:46-57 (1986) and Exp. Hematol., 15:288-295 (1987)] address the in vivo biological activity of non-glycosylated, bacterially produced recombinant murine Multi-CSF and respectively report:

> "In the present study, purified, bacterially synthesized Multi-CSF was injected for up to 6 days into normal adult mice. The results indicated that injected Multi-CSF of this type is able to induce various changes in hematopoietic tissues, in agreement with expectations from the known actions of Multi-CSF in vitro." [Blood, 68:46]

> "Previous studies [7-9] showed that unpurified glycosylated recombinant Multi-CSF had in vitro properties similar to those of native Multi-CSF. The present studies have documented the functional equivalence in vitro of

> purified native and non-glycosylated bacterially synthesized recombinant Multi-CSF, and have validated the use of purified non-glycosylated Multi-CSF to determine the in vivo effects of infected Multi-CSF." [Exp.Hematol., 15:293]

As set forth in detail at pages 16 through 20 of the Second Preliminary Amendment, it appears that Applicant may have been the first to have successfully produced a human obligate glycoprotein by recombinant methods. Whether Applicant's recombinant erythropoietin was the first such product or Genentech's tPA was, it is abundantly clear that there did not exist any body of information in the art which would be at all analogous to that existing in the Durden case, providing a basis for asserting that the transformation/transfection, transcription, translation, glycosylation and isolation as described by the present claims could reasonably have been expected to succeed in yielding a human erythropoietin product having the amino acid sequence and glycosylation required for in vivo biological activity.

Attached hereto as Exhibit "D" is a Table describing the proteins which are the subject of expression in the references reviewed for the purposes of Applicant's previous submission. As will be apparent from consideration of the Table, no public reports of recombinant expression of an obligate human glycoprotein appeared before the December 13, 1983 filing of parent application Serial No. 561,024.

Applicant respectfully submits that the processes herein claimed were in no way obvious when originally practiced by Applicant and, accordingly, that no proper basis exists for rejection of the claims under 35 U.S.C. §103. Allowance of the claims is in complete legal harmony with the ruling of the C.A.F.C. in In re Durden because the

process herein claimed could not have been expected to provide the valuable product attained.

CONCLUSION

The foregoing amendments and remarks are believed to establish that claims 65-69 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,

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Sept. 27, 1988