

THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today
(1) was not written for publication in a law journal and
(2) is not binding precedent of the Board.

Paper No. 32

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte HANS RINK, MANFRED LIERSCH,
PETER SIEBER, WERNER RITTEL,
FRANCOIS MEYER, URSULA SEEMULLER,
HANS FRITZ, WALTER MARKI
and SEFIK ALKAN

Appeal No. 94-2592
Application 07/707,265¹

ON BRIEF

Before WILLIAM F. SMITH, GRON, and ELLIS, **Administrative
Patent Judges.**

ELLIS, **Administrative Patent Judge.**

DECISION ON APPEAL

¹ Application for Patent filed May 24, 1991. According to applicants, this application is a continuation of Application 07/186,828, filed April 27, 1988; which is a continuation of Application 06/736,601, filed May 21, 1985, which is a continuation-in-part of Application 06/673,951, filed November 21, 1984, all abandoned.

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This is an appeal from the final decision of the Primary Examiner rejecting claims 31 through 33. Claims 20 through 26 and 34 are also pending, but have been withdrawn by the examiner under 37 CFR § 1.142(b).

Claim 31 is illustrative of the subject matter on appeal and reads as follows:

31. A process for the preparation of an eglin compound having the following amino acid sequence:
N-acetyl-Thr-Glu-Phe-Gly-Ser-Glu-Leu-Lys-Ser-Phe-Pro-Glu-Val-
Val-Gly-Lys-Thr-Val-Asp-Gln-Ala-Arg-Glu-Tyr-Phe-Thr-Leu-His-
Tyr
-Pro-Gln-Tyr-Asp-Val-W-Phe-Leu-Pro-Glu-Gly-Ser-Pro-Val-Thr-
Leu-
Asp-Leu-Arg-Tyr-Asn-Arg-Val-Arg-Val-Phe-Tyr-Asn-Pro-Gly-Thr-
Asn
-Val-Val-Asn-His-Val-Pro-His-Val-Gly

(Formula XIV')

in which W is Tyr or His, said process comprising:

a) transforming host cells of *Escherichia coli* or *Saccharomyces cerevisiae* with an expression vector, said expression vector comprising a promoter of host cell origin and a DNA sequence coding for said eglin compound, wherein said DNA sequence is directly and operably linked to and in proper reading frame relative to said promoter, in a liquid medium containing assimilable sources of carbon and nitrogen,

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b) culturing the transformed host cells in a liquid medium containing assimilable sources of carbon and nitrogen suitable for expression of said expression vector, and
c) isolating said eglin compound.

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The references relied on by the examiner are:

Riggs	4,431,739	Feb. 14, 1984 (filed Jul. 30, 1982)
DeBoer	4,551,433	Nov. 5, 1985 (filed Jan. 11, 1982)
Seemüller et al. (Seemüller '87)	4,636,489	Jan. 13, 1987 (filed Jul. 6, 1984)

Seemüller et al. (Seemüller '80), "Structure of the Elastase-Cathepsin G Inhibitor of the Leech *Hirudo medicinalis*," **Z. Physiol. Chem.**, Vol. 361, pp. 1841-1846 (December, 1980).

Miyanohara et al. (Miyanohara), "Expression of Hepatitis B Surface Antigen Gene in Yeast," **Proc. Natl. Acad. Sci., USA**, Vol. 80, pp. 1-5 (January, 1983).

Knecht et al. (Knecht), "Sequence Determination of Eglin C Using Combined Microtechniques of Amino Acid Analysis, Peptide Isolation, and Automatic Edman Degradation," **Analytical Biochemistry**, Vol. 130, pp. 65-71 (1983).

The references relied on by the appellants are:

Waller et al. (Waller), "Selective Acetylation of the Terminal Amino Group of Corticotrophin," **Biochem. Journal**, Vol. 75, pp. 320-328 (1960).

Brown et al. (Brown), "Evidence that Approximately Eighty per Cent of the Soluble Proteins from Ehrlich Ascites Cells are N^o-Acetylated," **The Journal of Biological Chemistry**, Vol. 251, No. 4, pp. 1009-1014 (February, 1976).

Roth et al. (Roth), "Acetylation of the NH₂-terminal Serine of Prostaglandin Synthetase by Aspirin," **The Journal of Biological Chemistry**, Vol. 253, No. 11, pp. 3782-3784 (June, 1976).

Smyth et al. (Smyth), "Endorphins are Stored in Biologically Active and Inactive Forms: Isolation of ^o-N-acetyl Peptides,"

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Nature, Vol. 279, pp. 252-254 (May, 1979).

Ross, "Production of Medically Important Polypeptides Using Recombinant DNA Technology," in **Insulins, Growth Hormone, and Recombinant DNA Technology**, John L. Gueriguian, ed., Raven Press, pp. 33-48 (May, 1981).

Wetzel et al. (Wetzel), "Synthesis of Polypeptides by Recombinant DNA Methods," in **The Peptides**, Academic Press, NY, Vol. 5, pp. 1-65 (1983).

Tsunasawa et al. (Tsunasawa), "Amino-Terminal Acetylation of Proteins: An Overview," in **Methods in Enzymology**, Academic Press, NY, Vol. 106, pp. 165-170 (1984).

Märki et al. (Märki), "Isolation and Characterization of 'Native' and Rec. Eglin C From *E. coli*, Selective Proteinase Inhibitors for Human Leucocyte Elastase, Cathepsin G and Chymotrypsin," in **Peptides: Structure and Function**, Proceedings of the Ninth American Peptide Symposium, Deber et al., eds., pp. 385-388 (1985).

Persson et al. (Persson), "Structures of N-terminally Acetylated Proteins," **European Journal of Biochemistry**, Vol. 152, No. 3, pp. 523-527 (Nov., 1985).

Tsunasawa et al. (Tsunasawa), "Amino-terminal Processing of Mutant Forms of Yeast Iso-1-cytochrome *c*," **The Journal of Biological Chemistry**, Vol. 260, No. 9, pp. 5382-5391 (May, 1985).

Huang et al. (Huang), "Specificity of Cotranslational Amino-Terminal Processing of Proteins in Yeast," **Biochemistry**, Vol. 26, No. 25, pp. 8242-8246 (Dec., 1987).

Winnacker, **From Genes to Clones: Introduction to Gene Technology**, translated by Horst Ibelgaufts, pp. 279-293 (June,

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1989).

Hallewell et al. (Hallewell), "Amino Terminal Acetylation of Authentic Human Cu, Zn Superoxide Dismutase Produced in Yeast," **Biotechnology**, Vol. 5, pp. 363-366 (April, 1987).

Claims 31 through 33 stand rejected under 35 U.S.C. § 103 as being unpatentable over Riggs and either Knecht, Seemüller('87) or Seemüller ('80), in view of DeBoer or Miyanochara.

Having considered the entire record which includes, **inter alia**, the appellants' main Brief (Paper No. 25) and Reply Brief (Paper No. 29), the examiner's Answer (Paper No. 26) and Supplemental Answer (Paper No. 30), as well as the declaration of Dr. Schmitz, we find ourselves in substantial agreement with the appellants' position. Accordingly, we **reverse** the examiner's rejection for the reasons set forth in the appellants' Brief and Reply Brief. In so doing, we especially direct the examiner's attention to the appellants' statements with respect to the negative teachings in the prior art as to the direct expression of proteins less than 100 amino acids in length. Brief, pp. 5-7; Reply Brief, pp. 3-4. Moreover, in our view, based on the record before us, one of ordinary skill

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in the art would have had no expectation that the claimed eucaryotic protein (eglin) which is not N-acetylated in its natural state, would be acetylated when expressed in microorganisms which do not generally acetylate the N-termini of their own endogenous proteins. Brief, pp. 9-10; Reply Brief, pp. 7-8. We find statements by the examiner such as

[i]t is considered that such a state of the art does not clearly teach away from appellants' invention because the state of the art was unsettled, there were both successes and failures at expression of heterologous proteins, and the successes were sufficient to give those of ordinary skill in the art a reasonable expectation of successful expression of any given protein with recombinant methods [Answer, p. 7];

and

[t]he state of the art of acetylation of proteins was unsettled at the time the invention was made. It was known, however, as appellants point out (Brief, page 9, line 16), that E. coli and S. cerevisiae do acetylate some proteins. Because the state of the art at the time the invention was made was not sufficiently predictive, it would have been expected by one of ordinary skill that any given protein may or may not be acetylated [Answer, p. 8];

to show inconsistent reasoning and to be contrary to the interpretation of obviousness as set forth in the prevailing case law. If the state of the art with respect to (i) the direct expression of small proteins in a recombinant host cell, and (ii) the acetylation of proteins, was unsettled and

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unpredictable, then it would not have been reasonable for one of ordinary skill in the art to expect success in producing either one.

Rejection under 37 CFR § 1.196(b)

Under the provisions of 37 CFR § 1.196(b) we make the following new ground of rejection.

Claims 31 through 33 are rejected under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which the appellants regard as the invention.

Claims 31 through 33 are confusing and misdescriptive in the recitation of an eglin compound having the "amino acid sequence: N-acetyl-Thr. . . ." Since the "N-acetyl" is not an amino acid, it is not clear whether the appellants intend to claim just the eglin amino acid sequence or an "N-acetylated eglin." An amendment inserting "N-acetylated" between "following" and "amino" on line 2 of claim 31 would obviate this rejection.

A similar problem exists in withdrawn claim 34. Since the DNA sequence in paragraph a) encodes "said eglin compound," it is not clear whether the appellants intend to

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claim the eglin amino acid sequence alone or an "N-acetylated eglin." An amendment inserting the phrase "N-acetylated" between "An" and "eglin" on line 1 of claim 34 would remedy this defect.

Other Issues

In our review of the application we note that the examiner's search of the prior art appears to have been limited to a word search of the term "eglin." We find no indication that the examiner searched (i) the protein data bases for the amino acid sequence of the claimed protein, or (ii) the protein by its other name, hirudin. Upon return of this application to the corps, we suggest the examiner consider whether all the relevant data bases have been properly explored.

The decision of the examiner is reversed.

REVERSED

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	WILLIAM F. SMITH)	
	Administrative Patent Judge)	
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PATENT	Administrative Patent Judge)	APPEALS AND
)	INTERFERENCES
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