

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 18

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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Ex parte ANANTHACHARI SRINIVASAN, LEON R. LYLE,  
and RAGHAVEN RAJAGOPALAN

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Appeal No. 1997-4379  
Application No. 08/278,437

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ON BRIEF

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Before WINTERS, SCHEINER, and ADAMS, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1 through 5 and 14 through 18. Claims 6 through 13 and 19 through 26, which are the only other claims remaining in the application, stand withdrawn from further consideration by the examiner as directed to a non-elected invention (office action entered August 21, 1995, Paper No. 4, page 2).

Claim 1 is illustrative of the subject matter on appeal and is reproduced in

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Appendix A, attached.

The references relied on by the examiner are:

Dean et al. (Dean)	5,225,180	Jul. 6, 1993
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Jost et al. (Jost), "Amino Acids and Peptides. C. The Effect of the Presence of Sulphur Atoms on the Biological Activity of Oxytocin; Synthesis of Deamino-Carba<sup>6</sup>-Oxytocin and Deamino-Dicarba-Oxytocin," Collection Czechoslov. Chem. Commun., Vol. 36, pp. 234-245 (1971)

Rivier et al. (Rivier), "Biological Action of Somatostatin," Rec. Progm. Horm. Res., Vol. 31, pp. 369-371 (1975)

Edwards et al. (Edwards), "In Vitro Activity Profiles of Cyclic and Linear Enkephalin Pseudopeptide Analogs," Biochemical and Biophysical Research Communication, Vol. 136, No.2, pp.730-736 (1986)

Mather et al. (Mather), "What Lessons for Antibody-Mediated Targeting?," Cell Biophysics, Vol. 21, pp. 93-107 (1992)

The references relied upon by appellants are:

Blake et al. (Blake)	5,439,792	Aug. 8, 1995
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Belinka, Jr. et al. (Belinka)	5,449,761	Sep. 12, 1995
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#### Grounds of Rejection

The appealed claims stand rejected as follows:

1. Claims 1 through 5 and 14 through 18 under 35 U.S.C. § 112, first paragraph, as based on a non-enabling disclosure.
2. Claims 1 through 5 and 14 through 18 under 35 U.S.C. § 103. As evidence of obviousness, the examiner relies on Dean, Edwards and Jost.

On consideration of the record, we reverse the rejection under 35 U.S.C. § 112, first paragraph and vacate the rejection under 35 U.S.C. § 103.

### Background

The present invention is directed to "conformationally and chemically stable analogs of cyclic bioactive peptides containing disulfide linkages" (Specification, page 6). According to appellants, "disulfide bonds exist primarily to ensure conformational rigidity" (Specification, page 1). When subject to "even mild reducing conditions," the destruction of the disulfide bond "usually destroys the bioactivity of the peptide" (id.). The invention provides "analogues of cyclic bioactive peptides containing disulfide linkages which have improved chemical and biological activity while substantially retaining the overall 3-dimensional peptide conformation and bioactivity" (Specification, page 2). This is done by modifying the disulfide bond by "one of four methods: (a) sulfide contraction, (b) isoteric substitution, (c) thioketal expansion, or (d) alkylation expansion" (Specification, paragraph bridging pages 2 and 3).

### Discussion

#### Rejection under 35 U.S.C. § 112, first paragraph:

The examiner rejected claims 1 through 5 and 14 through 18 under 35 U.S.C. § 112, first paragraph, as based on a non-enabling disclosure (Examiner's Answer, page 4). We shall not sustain this rejection.

It is well settled that the examiner bears the initial burden of providing reasons why a supporting disclosure does not enable a claim. In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). It has long been held that "[t]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" Genentech, Inc. v.

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Novo Nordisk, A/S, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997)

(quoting In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)).

As set forth in In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404, (Fed. Cir. 1988):

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman, [230 USPQ 546, 547 (Bd. Pat. App. Int. 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. (footnote omitted).

However, as set forth in Enzo Biochem., Inc. v. Calgene, Inc., 188 F.3d 1362, 1371, 52 USPQ2d 1129, 1136 (Fed. Cir. 1999) “the Wands factors ‘are illustrative, not mandatory. What is relevant depends on the facts.’ [citation omitted]”

The examiner’s position with respect to the rejection under 35 U.S.C. § 112, first paragraph, is that it would require undue experimentation to use the claimed compositions. Specifically, the examiner argues (Examiner’s Answer, pages 4-5) that

The claimed ... alpha amino acids would read on a myriads [sic, myriad] of natural or synthetic amino acids, singly or in combination that have neither been described, taught nor contemplated in the spec.

...

[I]t is not clear as to the kind of modifications ... the ones that are modified without the peptide losing its bioactivity and at the same time having the desired improved chemical and biological stability.

...

[T]he spec. fails to show whether such modifications in disulfide bridge result in the retention of the bioactivity of the peptide and more importantly, in the desired stability of the peptide.

...

Except for the method of modifying the single peptide, malformin, the spec. is devoid of any enabling disclosure for any other disulfide modified peptide or for the activity of even the single disulfide modified peptide.

...  
One skilled in the art would therefore, have not likely deemed applicants mere statements or the method for making a single peptide as predictive or conclusive for all or any disulfide containing compounds especially in view of the known unpredictability in the peptide art.

Therefore, in the examiner's opinion the specification fails to adequately teach how to use the claimed compounds because "[n]o data has been provided in the spec. to show that such modification [of the disulfide bond] did not result in the destruction of the peptide bioactivity but rather in the stability of the modified compound in a biological system" (Examiner's Answer, paragraph bridging pages 4 and 5). In other words, it would require undue experimentation to use the claimed compounds for the intended purpose of "diagnosis and therapy" (Specification, page 1).

In response to the examiner's position, appellants argue that "[a]n assertion by the Patent and Trademark Office that the enabling disclosure is not commensurate in scope with the protection sought in the Claims must be supported by evidence or reasoning substantiating the doubts so expressed" (citations omitted) (Appeal Brief, page 4). Specifically, appellants state that "[t]he Examiner's statements that the claimed analogs would encompass "myriads" of amino acids is not evidence nor would such assertions be reasoning sufficient to support a rejection of the present Claims" (Appeal Brief, page 5). According to appellants, the compounds encompassed by the claims "are well within the level of skill in the art" (*id.*).

In support of this position, appellants rely on Blake, Belinka and Edwards, to exemplify "the state of the art with respect to amino acid chemistry" (*id.*). These references allegedly teach methods of making peptides of 7, 50 and even 100 amino

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acids (id.). According to appellants,

"[t]he present invention would require very little if any experimentation and certainly would not require ingenuity beyond that expected of one of ordinary skill. The peptides can be made by the skilled artisan using the chemical reaction "Schemes" detailed in the Specification and techniques of peptide chemistry and synthetic procedures long known to skilled artisans, as shown in the Edwards reference cited in the present file. The Specification is replete with experimental procedures containing detailed reactions conditions and a discussion of the procedures needed to synthesize the claimed peptides, e.g., Scheme 1 on page 12 of the Specification... There is little if any unpredictability in making the claimed peptides. Such work is done numerous times each day, as shown by a careful reading of the cited references (Appeal Brief, page 6).

The examiner counters that

"the prior art peptide is not the same as the instant peptide and does not contain any of the instant various modifications that can be done on the disulfide bridge and the amino acids structures surrounding the disulfide bridge are defined. Accordingly, as argued, one can easily synthesize the prior art peptide by the known solid or solution phase synthesis since the residues flanking the disulfide bridge are known and the disulfide bridge is not modified by any means (as compared to the instant unknown amino acids and various disulfide bridge modifications)" (Examiner's Answer, page 9).

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Appellants also argue (Appeal Brief, page 7) that:

[T]he breath of the Claims is not overreaching. The Claims are limited to peptides having about 45 amino acids. A narrow scope when compared to the 100 amino acids disclosed in Belinka (U.S. 5,449,761) as discussed above. Claims 4 and 17 are certainly enabled. Claims 4 and 17 claim the compound octreotide.

In response, the examiner argues (Examiner's Answer, page 10) that:

However, the number of amino acids contained in the peptide sequence is irrelevant. It cannot be said as matter of law that 100 or a number of examples are sufficient to support a claim embracing thousands of compounds. It is the nature, not the number, of the claimed compounds which determines the sufficiency of the supporting disclosure.

On reflection, based on a careful review of the record, we find that the examiner has not provided adequate reasons to doubt the objective truth of statements made in appellants' specification. The examiner's arguments are insufficient to establish that the specification does not enable any person skilled in the art to use the claimed invention, taking into account the relevant factors set forth in Wands. First, the examiner's position that the destruction of the disulfide bond results in loss of bioactivity misapprehends the invention as disclosed and claimed. The purpose of the disulfide bond is "to insure conformational rigidity" (Specification, page 1). Due to the instability of this bond in mild reducing conditions (id.), the appellants seek to modify the disulfide bond in a manner that improves the stability of the compound without loss of conformation and bioactivity (Specification, page 2).

We are not persuaded by the examiner's reliance on Mather and Rivier. According to the examiner, Mather "discloses that octreotide appears to be more

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selective in its inhibitory actions. This evidence taken together with other findings, suggests heterogeneity in receptor type. Since it is fundamental that the structure of a peptide, i.e., amino acid order and chemical linkages, is what determines its function, the ordinarily skilled worker would have recognized that the different structures of the claimed cyclic peptides would have precluded any expectations about how they would behave" (Examiner's Answer, page 6). Mather's discloses the use of an octreotide, a synthetic analog of somatostatin, as an inhibitor (abstract). Mather specifically discloses that "some of [the octreotides] are in the (D) configuration in order to enhance the stability of the molecule in vivo" (id.). The main purpose of using this analog is to increase the half-life to avoid rapid secretion by the liver and the kidney experienced by the somatostatin which "severely limited [its] therapeutic application" (Mather, page 94). At best, Mather teaches that adopting a specific configuration (conformation) can increase the stability of analogs while retaining its bioactivity. We fail to see how the examiner's position with respect to Mather serves as evidence that appellants' modification of the disulfide bond destroys the bioactivity of the peptide.

According to the examiner, Rivier "states that '... potency is decreased as a result of the loss of groups which are important either to maintaining the conformation of the molecule or to the binding and activation of the receptor ... thus, there appear to be strict structural requirements for high potency ...'" (id.). The examiner's position, however, does not take into account that appellants' invention does not lead to "loss of groups." What appellants' invention does is modify an existing disulfide bond so as to maintain the conformation and bioactivity of the peptide. Again, we fail to see how the

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examiner's position with respect to Rivier serves as evidence that appellants' modification of the disulfide bond destroys the bioactivity of the peptide.

All in all, we conclude that appellants' specification provides sufficient knowledge and guidance to enable any person skilled in the art to make and use the claimed invention without resorting to undue experimentation. In view of the foregoing, we believe that the examiner has not established that claims 1 through 5 and 14 through 18 are based on a non-enabling disclosure. The examiner's reliance on Mather and Rivier is not sufficient to support the conclusion that the modified sulfide bond would not serve the analogous function of the disulfide bond; that is, that the peptide with the modified sulfide bond would not retain its bioactivity.

Accordingly, the rejection under 35 U.S.C. § 112, first paragraph, is reversed.

Rejection under 35 U.S.C. § 103:

Claims 1 through 5 and 14 through 18 stand rejected under 35 U.S.C. § 103 as unpatentable over Dean in view of anyone of Edwards or Jost.

We note that this rejection is different from the rejection under 35 U.S.C. § 103 advanced in the Final office action entered October 11, 1996 (Paper No. 10). In the Final office action, the examiner rejected only claim 1 under 35 U.S.C. § 103 as "unpatentable over Lyle et al in view of Dean et al and anyone of Edwards et al or Jost" (Paper No. 10, page 5). On page 2 of the examiner's answer, the examiner withdrew "the rejection of the claims over Lyle." In its place, the examiner now advances a rejection under 35 U.S.C. § 103 affecting all the claims pending under appeal with Dean replacing Lyle as the primary reference (Examiner's Answer, page 7). This rejection is

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not labeled as a new ground of rejection and the examiner explicitly states that the "Examiner's Answer does not contain any new ground of rejection" (Examiner's Answer, page 8).

Based on this procedural history, we are confused as to why this rejection does not constitute a new ground. It appears that the examiner withdrew the only prior art rejection made in the Final office action, the one rejecting claim 1 over the combined disclosures of Lyle, Dean, Edwards and Jost. The rejection now before us not only affects all of the claims under appeal, but it is also based on a different primary and, apparently, a different rationale. Without further clarification from the examiner, we are unable to address the merits of this rejection since it has not been adequately briefed.

Accordingly, because of the conflict between the Final office action and the examiner's answer, we vacate the examiner's rejection under 35 U.S.C. § 103.<sup>1</sup>

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<sup>1</sup> Lest there be any misunderstanding, the term "vacate" in this context means to set aside or to void. When the Board vacates an examiner's rejection, the rejection is set aside and no longer exists.

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If, upon further review, the examiner believes that the rejection over the combined disclosures of Dean, Edwards and Jost is still appropriate, the examiner may reinstate the rejection. In doing so, the examiner must follow the established Office procedures and afford appellants an opportunity to respond to the rejection.

Conclusion

The examiner's rejection under 35 U.S.C. § 112, first paragraph is reversed. The examiner's rejection under 35 U.S.C. § 103 is vacated.

REVERSED

SHERMAN D. WINTERS	)	
Administrative Patent Judge	)	
	)	
	)	
	)	BOARD OF PATENT
TONI R. SCHEINER	)	
Administrative Patent Judge	)	APPEALS AND
	)	
	)	INTERFERENCES
	)	
DONALD E. ADAMS	)	
Administrative Patent Judge	)	

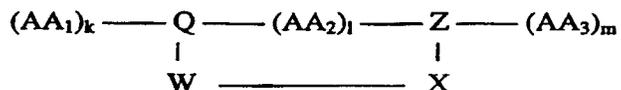
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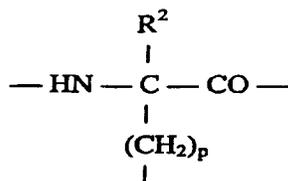
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### Appendix A

1. A cyclic peptide analog having the following general formula:



wherein  $(AA_1)_k$ ,  $(AA_2)_l$ , and  $(AA_3)_m$  are  $\alpha$ -amino acids in the peptide and the bonds connecting  $(AA_1)_k$ , Q,  $(AA_2)_l$ , Z, and  $(AA_3)_m$  are conventional peptide bonds; k, l, and m are the number of  $\alpha$ -amino acids and may range from 0 to 15 with the proviso that at least two of k, l, and m are greater than zero; W and X are -S- or  $-\text{CHR}^1-$ , such that when W is -S-, then X is  $-\text{CHR}^1-$  and when W is  $-\text{CHR}^1-$ , then X is -S-;  $\text{R}^1$  is  $-(\text{CH}_2)_n-$ ; n is from 0 to 10; Y is a reactive functional group capable of being coupled to a bifunctional effector molecule; and Q and Z may be the same or different and have the following general structure:



wherein p may range from 0 to 3 and  $\text{R}^2$  is H, alkyl, aryl, hydroxyalkyl, alkoxyalkyl, and carboxyl wherein the carbon containing portions contain from 1 to 10 carbon atoms or the side chain portion of naturally occurring  $\alpha$ -amino acids.