

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opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.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. 26

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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Ex parte TAMAS JANAKY, ATTILA JUHASZ, SANDOR BAJUSZ  
and ANDREW V. SCHALLY

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Appeal No. 1996-2431  
Application 08/008,186<sup>1</sup>

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ON BRIEF

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Before WINTERS, ROBINSON and SCHEINER, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1 through 23, all the claims remaining in the application.

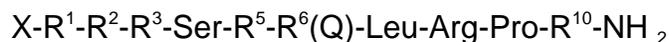
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<sup>1</sup> Application for patent filed January 25, 1993. According to appellants, this application is a continuation-in-part of Application 07/505,517, filed April 6, 1990, now abandoned; which is a continuation-in-part of Application 07/404,667, filed September 7, 1989, now abandoned; which is a continuation-in-part of Application 07/260,994, filed October 21, 1988, now abandoned.

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Claims 1, 2, 5, 13 and 14 are representative of the subject matter on appeal and read as follows:

1. A peptide selected from the group of peptides having the formula:



wherein

R<sup>1</sup> is pGlu or D-Nal(2),

R<sup>2</sup> is His or D-Phe(4Cl),

R<sup>3</sup> is Trp, D-Trp or D-PAI(3),

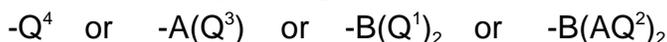
R<sup>5</sup> is Tyr or Arg

R<sup>6</sup> is D-Lys or D-Orn

R<sup>10</sup> is Gly or D-Ala,

X is a hydrogen or a lower alkanoyl group of 2-5 carbon atoms,

Q is a cytotoxic moiety having the formula



wherein

A is  $-NH-(CH_2)_n-CO-$  or  $-OH-(CH_2)_n-CO-$

where n is 2-6,

B is  $-HN-CH_2-(CH_2)_m-CH(NH)-(CH_2)_n-CO-$

where

m is 0 or 1,

n is 0 or 1,

the  $-CO$  moiety of A- and of B- being bonded to the epsilon or delta amino group of R<sup>6</sup> when R<sup>6</sup> is Lys or Orn respectively, and in the group  $-B(AQ^2)_2$ , the  $-CO$  moiety of A being bonded to an amino group on B,

Q<sup>1</sup> is D or L-melphalanyl, cyclopropanecarbonyl, aziridine-2-carbonyl, epoxyalkyl or 1,4-naphthoquinone-5-oxycarbonyl-ethyl,

Q<sup>2</sup> is Q<sup>1</sup>:2-anthraquinonyl-methylenoxy or doxorubicinyl,

Q<sup>3</sup> is Q<sup>2</sup>, mitomicinyl, esperamycinyl or methotrexoyl,

Q<sup>4</sup> is Q<sup>1</sup> or methotrexoyl,

and pharmaceutically acceptable salts thereof.

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2. A peptide of Claim 1 wherein Q is Q<sup>4</sup>.
5. A peptide of Claim 1 wherein Q is A(Q<sup>3</sup>).
13. A peptide according to Claim 2 wherein Q<sup>4</sup> is D- or L-Mel, CPC or methotrexoyl.
14. A peptide according to Claim 5 wherein A is 6-aminohexanoyl or glutaryl, and Q<sup>3</sup> is 2-anthraquinonyl-methylenoxy, doxorubicinyl or methotrexoyl.

The references relied on by the examiner are:

Sela et al. (Sela)	4,263,279	Apr. 21, 1981
Rivier et al. (Rivier)	4,652,550	Mar. 24, 1987
Stevens	4,713,366	Dec. 15, 1987
Anderson et al. (Anderson)	5,169,933	Dec. 8, 1992

Lin et al. (Lin), "2-Methylantraquinone Derivatives as Potential Bioreductive Alkylating Agents," J. Med. Chem., Vol. 23, pp. 1237-1242 (1980).

Varga, "Hormone-Drug Conjugates," in Methods in Enzymology, Vol. 112, pp. 259-269 (1985).

Bajusz et al. (Bajusz), "Highly potent analogues of luteinizing hormone-releasing hormone containing D-phenylalanine nitrogen mustard in position 6," Proc. Natl. Acad. Sci. USA, Vol. 86, pp. 6318-6322 (August 1989).

Channabasavaiah et al. (Channabasavaiah), "New Potent Agonist and Antagonist Analogs of Luteinizing Hormone Releasing Hormone," Peptides, Proceedings of the Sixth American Pept. Symp., E. Gross and J. Meienhofer (eds.), pp. 803-806.

The claims stand rejected as follows:

I. Claims 1 through 4 and 13 under 35 U.S.C. § 103 as unpatentable over Channabasavaiah, Bajusz and Rivier.

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II. Claims 5 through 7, 12 and 14 under 35 U.S.C. § 103 as unpatentable over Channabasavaiah, Bajusz, Rivier, Sela and Varga.

III. Claims 8 through 10, 12 and 15 under 35 U.S.C. § 103 as unpatentable over Channabasavaiah, Bajusz, Rivier and Stevens.

IV. Claims 16 through 18 under 35 U.S.C. § 103 as unpatentable over Channabasavaiah, Bajusz, Rivier, Sela, Varga and Stevens.

Claims 11, 13, 14 and 19 through 23 under 35 U.S.C. § 103 as unpatentable over Channabasavaiah, Bajusz, Rivier, Stevens, Lin and Anderson.

#### DISCUSSION

The present invention is directed to cytotoxic agonists and antagonists of luteinizing hormone releasing hormone (LHRH). In each of the claimed LHRH decapeptide analogs, a cytotoxic agent is conjugated directly or indirectly to the amino acid residue at position six, and the amino acid at position six is always D-Lys or D-Orn. We note that both the examiner and appellants have focused throughout the prosecution on those LHRH agonists and antagonists wherein the cytotoxic moiety is D-melphalan (D-Mel), anthraquinoyl or methotrexoyl. As this board functions as a board of review, not a de novo examination tribunal, we shall do likewise.<sup>2</sup>

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<sup>2</sup> 35 U.S.C. § 7(b): "The [board] shall . . . review adverse decisions of examiners upon applications for patents . . ."

There are five rejections under 35 U.S.C. § 103, and each is founded on the combination of Channabasavaiah and Bajusz. We view the examiner's proposed combination of these two references as the dispositive issue in each of the rejections.

Channabasavaiah discloses a number of agonist and antagonist analogs of LHRH, including "[DLys(Chlorambucil)<sup>6</sup>]-LRH," wherein the amino acid at position six of the native decapeptide is replaced by D-Lys, and the D-Lys is conjugated in turn to the alkylating agent, chlorambucil (Chl); and "[Dphe<sup>2</sup>,DLys(Chlorambucil)<sup>6</sup>]-LRH," wherein the amino acid at position two is additionally replaced by D-Phe. According to the examiner, "Channabasavaiah does not expressly teach other alkylating agents such as D-Mel as claimed." Examiner's Answer, page 5.

Bajusz teaches that "highly potent alkylating analogues of LH-RH" were obtained when "the D enantiomer of Mel was incorporated into position 6 of the native hormone and some of its antagonistic analogues." In addition, "[D-Mel<sup>6</sup>]LH-RH . . . showed high affinities for the membrane receptors of . . . human breast cancer cells, human prostate cancer cells, and rat Dunning R-3327 prostate tumor cells" and "exerted cytotoxic effects on human and rat mammary cancer cells in vitro." Abstract.

The examiner believes that "it would have been obvious to one having ordinary skill in the art at the time the invention was made to replace the alkylating agent, Chl in the peptide sequence of Channabasavaiah with another alkylating agent [such] as D-Mel such that a peptide with high affinity to cancer receptor cells is obtained as per the teachings of

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Bajusz.” Examiner’s Answer, page 5. If we understand the examiner’s position correctly, it is that it would have been obvious for one of ordinary skill in the art to conjugate D-Mel, rather than Chl, to the amino acid at position six of one of Channabasavaiah’s analogs (for example, [Dlys(Chlorambucil)<sup>6</sup>]-LRH)) to obtain a peptide with high affinity to cancer cells.

Appellants point out that D-Mel replaces the amino acid at position six of Bajusz’s “highly potent alkylating analogues,” rather than being conjugated to it. Brief, page 12.

Nevertheless, the examiner maintains that:

[T]he findings of Channabasavaiah i.e., conjugating an alkylating agent to D-Lys at position 6 results in high bioactivity coupled with the teachings of Bajusz that the presence of an alkylating agent, Mel or Chl, at position six . . . of the LHRH sequence, even in an unconjugated form, results in increase in bioactivity would certainly motivate a person skilled in the art to make the modification called for by the claims (Examiner’s Answer, page 10).

In our view, Bajusz’s observations are of little relevance in establishing a nexus between conjugating an alkylating agent to position six of an LHRH analog and replacing position six of the LHRH analog with the same (or a related) alkylating agent. As discussed above, Bajusz teaches that replacing amino acid position six with D-Mel produces highly potent alkylating analogs of LH-RH with high affinities for cancer cell membrane receptors. On the other hand, the reference teaches that compounds “prepared by linking Chl, as an N-Acyl moiety, to the complete amino acid sequence of agonistic and antagonistic analogues . . . showed much lower potency than their

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congeners carrying other acyl groups.”<sup>3</sup> Abstract. Neither teaching suggests anything, negative or positive, about the effects of conjugating D-Mel to position six of the analogs.

It is well settled that the initial burden of establishing unpatentability rests on the examiner, In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992).

As stated in Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ 1626, 1629, (Fed. Cir. 1996) (citation omitted):

[B]efore a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead an inventor to combine those references.

In our judgment, the examiner’s proposed reasons for combining Channabasavaiah and Bajusz are not sufficient to support a conclusion of obviousness. This insufficiency is not remedied by any of the remaining references relied on by the examiner.

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<sup>3</sup> Contrary to appellants’ arguments in the Brief (e.g., page 12), this portion of Bajusz appears to refer to the effects of conjugating Chl to the N-terminal amino acids of LHRH agonist and antagonist analogs, not to the effects of conjugating Chl to position six of LHRH analogs.

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Accordingly, we find that the examiner's initial burden of establishing a prima facie case of obviousness has not been met. On this record, we reverse the rejections of the claims under 35 U.S.C. § 103.<sup>4</sup>

REVERSED

SHERMAN D. WINTERS	)	
Administrative Patent Judge	)	
	)	
	)	
	)	BOARD OF PATENT
DOUGLAS ROBINSON	)	
Administrative Patent Judge	)	APPEALS AND
	)	
	)	INTERFERENCES
	)	
TONI R. SCHEINER	)	
Administrative Patent Judge	)	

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<sup>4</sup> Having determined that a prima facie case of obviousness has not been established, we do not find it necessary to comment on the declaration of Dr. Tetsu Yano (submitted July 31, 1995, under 37 CFR § 1.132), or appellants' arguments regarding unexpected results attributable to an embodiment of the present invention.

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Omri M. Behr  
325 Pierson Avenue  
Edison, NJ 08837