

*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opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.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. 19

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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*Ex parte* ALAN F. COOK

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Appeal No. 1995-2831  
Application No. 07/908,376

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ON BRIEF

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Before WINTERS, WILLIAM F. SMITH, and SPIEGEL, *Administrative Patent Judges*.  
SPIEGEL, *Administrative Patent Judge*.

*DECISION ON APPEAL*

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 9, 26 and 53 through 55, which are all of the claims pending in this application. Claims 9 and 53 are illustrative:

53. An oligonucleotide wherein each nucleotide unit of the oligonucleotide includes a sugar moiety, a purine or pyrimidine base, and a phosphorus-containing moiety, wherein said oligonucleotide is conjugated to at least one sugar phosphate moiety which is independent of a nucleotide unit, wherein said at least one sugar

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phosphate moiety is attached at said purine or pyrimidine base, at said phosphorus-containing moiety, or at said sugar moiety of said oligonucleotide.

9. The oligonucleotide of Claim 53 wherein said sugar phosphate is selected from the group consisting of mannose-6-phosphate, glucose-6-phosphate, galactose-6-phosphate, mannose-1-phosphate, glucose-1-phosphate, galactose-1-phosphate, 6-0-phosphoryl-"-D-mannopyranosyl-(1-2)-D-mannopyranose, 6-0-phosphoryl-"-D-mannopyranosyl-(1-3)-mannopyranose, 6-0-phosphoryl-"-D-mannopyranosyl-(1-6)-mannopyranose, 6-0-phosphoryl-"-D-mannopyranosyl-(1-2)-D-mannopyranosyl-(1-2)-D-mannopyranose, and pentamannose-6-phosphate.

The references relied on by the examiner are:

Hoflack et al. (Hoflack), "Purification and Characterization of a Cation-dependent Mannose 6-Phosphate Receptor from Murine P388D<sub>1</sub> Macrophages and Bovine Liver," 260 *The Journal of Biological Chemistry* 22, 12008-12014 (October 5, 1985).

Leamon et al. (Leamon), "Delivery of macromolecules into living cells: A method that exploits folate receptor endocytosis," 88 *Proceedings of the National Academy of Sciences USA* 5572-5576 (July 1991).

Lemaitre et al. (Lemaitre), "Specific antiviral activity of a poly(L-lysine)-conjugated oligodeoxyribonucleotide sequence complementary to vesicular stomatitis virus N protein mRNA initiation site," 84 *Proceedings of the National Academy of Sciences USA* 648-652 (February 1987).

Vestweber et al. (Vestweber), "DNA-protein conjugates can enter mitochondria via the protein import pathway," 338 *Nature* 170-172 (1989).

Claims 9, 26 and 53-55 stand rejected under 35 U.S.C. § 103 as being unpatentable over Lemaitre in view of Vestweber, Leamon and Hoflack. We REVERSE.

In reaching our decision in this appeal, we have given careful consideration to the appellant's specification and claims and to the respective positions articulated by the appellant and the examiner.

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We make reference to the examiner's answer (Paper No. 18, mailed November 1, 1994) for the examiner's reasoning in support of the rejection and to the appellant's brief (Paper No. 16, filed August 22, 1994) for the appellant's arguments thereagainst.

#### *THE INVENTION*

Appellant's claimed invention is directed to oligonucleotides which are conjugated to at least one sugar phosphate moiety which is independent of a nucleotide unit (claim 53), a composition for binding to an RNA, a DNA, a protein or a peptide which comprises the conjugated oligonucleotide described in claim 53 and an acceptable pharmaceutical carrier (claim 54), and a probe for determining the presence of a target DNA or RNA sequence which comprises the conjugated oligonucleotide described in claim 53 (claim 55). Claims 9 and 26 specify selected sugar phosphate moieties. [Brief, page 1, last paragraph - page 2, first full paragraph.]

#### *OPINION*

Lemaitre describes conjugates of a *polypeptide* (i.e., poly(L-lysine)) and an oligonucleotide (i.e., antisense oligodeoxyribonucleotide sequence) used to deliver antisense sequences to intact cells, thereby promoting a specific and efficient antiviral activity. Little is known about the pathway of their internalization. Lemaitre states that oligonucleotide could conceivably be conjugated to other polypeptides, thus allowing targeting of the conjugated sequences to cells bearing specific cell-surface determinants. [Abstract; page 652.]

Vestweber discloses that mitochondria import most of their proteins and small molecules from the cytoplasm; and, that there is some tentative evidence that they import some of their RNA. However, it is not known how nucleic acids enter the mitochondria. [Abstract]. Vestweber showed that at least short pieces of DNA conjugated to a mitochondrial precursor *protein* can be processed and transported across the mitochondrial membranes of isolated yeast mitochondria (page 170, col. 2; page 172, last para.).

Leamon discloses that by conjugating the *vitamin* folic acid to macromolecules, such as proteins, enzymes and antisense oligonucleotide, the natural endocytosis pathway for internalizing folate can also internalize the macromolecules into cultured cells (abstract; page 5572, col. 2; page 5576, col. 1).

Hoflack discloses that phosphomannosyl residues (i.e., phosphorylated (phosphate) mannose (sugar) residues) on newly synthesized lysosome enzymes (i.e., acid hydrolases) bind to mannose-6-phosphate receptors in the Golgi which (1) facilitates sorting these lysosomal enzymes from the proteins which are to be secreted and (2) transports the bound enzymes via coated vesicles to a prelysosomal acidic compartment where the low pH releases the enzymes. The enzymes are packaged into lysosomes and the mannose-6-receptors return to the Golgi. Thus, the phosphomannosyl residues on the acid hydrolase enzymes serve to target these specific enzymes to lysosomes. Hoflack isolated a second, cation dependent 46 kDa mannose-6-phosphate receptor which is different from the 215 kDa

cation independent mannose-6-phosphate receptor that is widely distributed among cell types. [Page 12008]

The examiner bears the initial burden of establishing a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, there must be both some suggestion or motivation to modify the reference or combine reference teachings and a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

According to the examiner, “the combined teachings of the references reasonably suggest that conjugation of sugar phosphates to an oligonucleotide would facilitate entrance of the oligonucleotide into a cell via the mannose 6-phosphate receptor for used in affecting intracellular gene expression” (emphasis in the original, answer, page 5). However, the examiner has failed to explain how Hoflack’s disclosure of a mannose-6-phosphate receptor in a Golgi or other vesicle *inside a cell* would have provided a specific cell-surface determinant *on a cell* membrane for targeting of the conjugated oligonucleotide sequences to cells bearing specific cell-surface determinants as arguably suggested by Lemaitre or would have provided a receptor-mediated *endocytosis* as discussed by Leamon. The examiner has not pointed out and we do not find were Lemaitre, Vestweber, Leamon or Hoflack disclose or suggest that mannose-6-phosphate receptor is a *cell surface* receptor. Therefore, based on this record, the examiner has not established a sufficient factual basis for concluding that the sugar

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phosphate moiety, i.e., a phosphomannosyl residue, would have been reasonably expected to facilitate entry of an oligonucleotide into a cell.

Thus, we find the examiner has not carried his burden of establishing a *prima facie* case of obviousness and has relied on impermissible hindsight in making his determination of obviousness. *In re Fritch*, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992) (“It is impermissible to engage in hindsight reconstruction of the claimed invention, using the applicant’s structure as a template and selecting elements from references to fill the gaps.”).

Accordingly, the rejection of claims 9, 26 and 53-55 under 35 U.S.C. § 103 over Lemaitre in view of Vestweber, Leamon and Hoflack is reversed.

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*CONCLUSION*

To summarize, the decision of the examiner to reject claims 9, 26 and 53-55 under 35 U.S.C. § 103 is reversed.

**REVERSED**

SHERMAN D. WINTERS	)	
Administrative Patent Judge	)	
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	)	
	)	BOARD OF PATENT
WILLIAM F. SMITH	)	APPEALS
Administrative Patent Judge	)	AND
	)	INTERFERENCES
	)	
	)	
CAROL A. SPIEGEL	)	
Administrative Patent Judge	)	

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APPLICATION NO. 07/908,376

APJ SPIEGEL

APJ WILLIAM F. SMITH

APJ WINTERS

DECISION: **REVERSED**

Prepared By:

**DRAFT TYPED:** 02 Feb 01

**FINAL TYPED:**