

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

## UNITED STATES PATENT AND TRADEMARK OFFICE

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### BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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Ex parte MEIR STRAHILEVITZ

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Appeal No. 2006-2146  
Application No. 08/451,120

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ON BRIEF

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Before GRIMES, GREEN, and LEBOVITZ, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

#### DECISION ON APPEAL

This appeal involves claims to delivering a ligand to a targeted site in a patient, which the examiner has rejected as obvious. We have jurisdiction under 35 U.S.C. § 134. Because the examiner has not adequately explained how the cited references would have suggested the claimed method, we reverse.

#### Background

“One of the major strategies utilized for the improvement of treatment and diagnosis of cancer is to increase the concentration of the anticancer drug in the cancer, by targeting the drug to the cancer, utilizing antibodies and antibody fragments specific to epitopes (antigens) on the cancer cells.” Specification, page 1.

The specification discloses methods for directing a therapeutic or visualization ligand to a targeted site *in vivo*. One approach is shown in the application's Figure 3, which is reproduced below:

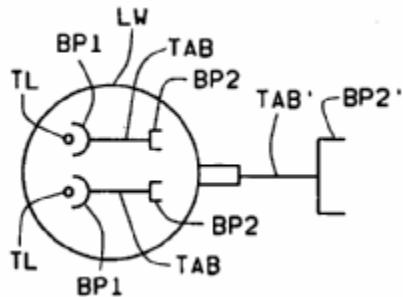


Figure 3 is said to be a "a diagrammatic view showing hybrid antibodies [TAB] bound to a drug [TL] and entrapped in a liposome, with a targeting antibody [TAB'] covalently bound to the liposome wall [LW]." Specification, page 10. The hybrid antibodies have "one specific binding site directed to the targeted antigen [BP2 in Figure 3] and one binding site directed to the TL [BP1 in Figure 3]." Id., page 9. Hybrid antibodies can be made by "utilizing two distinct Fab's and joining them to [form] a hybrid F(ab')<sub>2</sub>." Id.

### Discussion

#### 1. Claims

Claims 87, 90, and 92-99 are on appeal. Claims 88, 89, and 91 are also pending but have been withdrawn from consideration by the examiner. Claim 87 is the only independent claim on appeal and reads as follows:

87. A method of delivering a ligand to a site in an organism, the method comprising a step of binding to the surface of a moiety selected from the group consisting of a liposome and a microcapsule a first molecule targeting the site, a step of entrapping a ligand in the moiety, the ligand being bound to a second molecule targeting the site, and thereafter a step of introducing the moiety into the organism.

Claim 87 is directed to a method of delivering a ligand to a specific site in vivo by administering a liposome or microcapsule that has on its surface a first molecule (e.g., an antibody) targeting the site and that contains a second molecule (e.g., an antibody) that (a) targets the same site and (b) is bound to the ligand to be delivered.

## 2. Obviousness

The examiner rejected claims 87, 90, and 94-99 under 35 U.S.C. § 103 as obvious in view of Wong,<sup>1</sup> either of Caras<sup>2</sup> or Martin,<sup>3</sup> and Allen.<sup>4</sup>

The examiner cited Wong for its disclosure of “a method of delivering . . . antiviral antibody against type A influen[za], to a site in an organism wherein said antibody is entrapped within a liposome” and “a method of delivering a radioactive tracer ligand conjugated to an antibody to a site in an organism for the determination of organ distribution of the antibody for optimum targeting of said antiviral antibody.” Examiner’s Answer, page 4. The examiner acknowledged that Wong does not teach “a liposome with an antibody attached . . . [or] that the entrapped antibody is bound to a ligand to be delivered to the site.” Id.

The examiner relied on Caras<sup>5</sup> and Martin for teaching the targeting of liposomes to cell types of interest by attaching antibodies or antibody fragments to the liposomes. Examiner’s Answer, pages 4-5. The examiner cited Allen as teaching the advantages

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<sup>1</sup> Wong et al., “Enhanced protection against respiratory influenza A infection in mice by liposome-encapsulated antibody,” Immunology, Vol. 81, pp. 280-284 (1994)

<sup>2</sup> Caras, U.S. Patent 5,374,548, issued December 20, 1994

<sup>3</sup> Martin et al., “Immunospecific targeting of liposomes to cells: A novel and efficient method for covalent attachment of Fab’ fragments via disulfide bonds,” Biochemistry, Vol. 20, pp. 4229-4238 (1981)

<sup>4</sup> Allen et al., “Antibody-mediated targeting of long-circulating (Stealth<sup>®</sup>) liposomes,” Journal of Liposome Research, Vol. 4, pp. 1-25 (1994)

<sup>5</sup> In explaining the rejection, the Examiner’s Answer cites U.S. Patents 5,372,548 and 5,473,548. We understand these citations to refer to Caras (U.S. Patent 5,374,548) since neither of the other patents is remotely related to the method claimed here.

of targeting a liposome-encapsulated ligand with antibodies, rather than attaching the ligand directly to the targeting antibody: “liposomes carry several hundred-fold more drug, reducing the cost of antibody production” and “some liposomes have long circulation half-lives and protect the immunogenicity of foreign antibodies attached to the liposomes.” Id., page 5.

The examiner concluded that it would have been obvious, in view of the cited references, “to have targeted the liposomes of Wong et al. containing antiviral antibodies with the same antiviral antibodies or Fab fragments thereof,” because Allen teaches that liposomes carry several hundred-fold more drug than antibody drug conjugates and protect their targeting antibodies from in vivo degradation. Id., pages 5-6. The examiner also concluded:

It would have further been prima facie obvious and one of ordinary skill in the art would have been motivated to conjugate the tracer ligand of Wong et al[.] to the entrapped anti-type A influenza virus IgG of the combined references:

In order to follow the organ distribution of the anti[-]type A influenza virus IgG and to determine the optimum targeting of the antiviral antibody at the site to be treated.

Id., page 6.

Appellant acknowledges that “[t]he prior art has long suggested either attaching a targeting molecule to the ligand (e.g., drug or tracer) which is to be delivered to a site or else attaching a targeting molecule to a liposome carrying the free ligand.” Appeal Brief, page 5. Appellant argues, however, that “[n]othing in the prior art suggests applicant’s double targeting of both the ligand and the liposome, and nothing in the prior art even suggests a reason for such double targeting.” Id.

We agree with Appellant that the cited references, viewed without the benefit of the present disclosure, would not have suggested incorporating a ligand bound to a target-specific antibody into liposomes that are targeted with an antibody having the same target specificity. The examiner pointed to an experiment described in Wong as suggesting the claimed method but we do not agree with the examiner's reasoning.

Wong describes an experiment in which radiolabelled IgG was encapsulated in (non-targeted) liposomes and administered to mice by various routes. See page 281, right-hand column: "The organ distribution of radioactive tracer following intravenous, intranasal and intratracheal administrations was evaluated using  $^{125}\text{I}$ -IgG. For each of the three routes of administration, liposomes containing a total of 1  $\mu\text{mol}$  total lipid and 0.2  $\mu\text{Ci}$  of  $^{125}\text{I}$ -IgG were administered to each mouse." The radiolabelled IgG was not specific to any particular target. See page 280, right-hand column ("Goat IgG labelled with  $^{125}\text{I}$  . . . was obtained from ICN Biochemicals.").

Wong explains that the purpose of the experiment was "to optimize the delivery of liposome-encapsulated antibody into the lungs." Page 282, left-hand column. The "[l]iposome-encapsulated  $^{125}\text{I}$ -IgG was used as a radiolabelled tracer for antibody molecules." Id. Wong discloses that "intranasal and intratracheal administrations were equally effective. . . . These results indicated that optimum targeting of antiviral antibody was achieved with intranasal administrations using negatively charged liposomes as carriers." Page 282, right-hand column.

The examiner argues that this experiment would have suggested labelling, with  $^{125}\text{I}$ , the anti-influenza virus antibodies used by Wong to treat influenza virus infection and encapsulating the labelled antibodies into liposomes that display the same

anti-influenza virus antibodies “in order to follow the organ distribution of the anti[-]type A influenza virus IgG and to determine the optimum targeting of the antiviral antibody at the site to be treated.” Examiner’s Answer, page 6.

We do not agree that Wong’s disclosure would have suggested the experiment described by the examiner. The point of Wong’s experiment was to determine which route of administration – intranasal, intratracheal, or intravenous – optimized delivery of liposomes to the lungs. See page 282, left-hand column: “In order to optimize the delivery of liposome-encapsulated antibody into the lungs, various routes of administration . . . were evaluated.”

The examiner has not adequately explained how Wong’s disclosure would have suggested the proposed experiment, for at least two reasons. First, Wong’s experiment generated the desired data – Wong reports that both intratracheal and intranasal administration efficiently delivered liposomes to the lungs. Because Wong’s experiment answered the question it was intended to address, there would seem to be no point to a skilled artisan repeating the experiment with the variations proposed by the examiner.

Second, the labelled immunoglobulin ( $^{125}\text{I}$ -IgG) used in Wong’s experiment was not specific for any particular antigen; the immunoglobulin served merely as a carrier for the  $^{125}\text{I}$  that was later detected as an indication of where the liposomes went. The examiner has not explained what would have led those skilled in the art to replace the generic IgG used by Wong with an anti-influenza virus antibody, when the binding properties of the antibody were irrelevant to the purpose for which it was used.

“The PTO has the burden under section 103 to establish a prima facie case of obviousness. It can satisfy this burden only by showing some objective teaching in the

prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.” In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988) (citations omitted).

In this case, we conclude that the examiner has not adequately shown that those of ordinary skill in the art, without knowledge of the present disclosure, would have found it obvious to practice the instantly claimed method. We therefore reverse the rejection of claims 87, 90, and 94-99 under 35 U.S.C. § 103.

The examiner also rejected all of the claims on appeal, including claims 92 and 93, as obvious in view of the references discussed above, combined with Maddock<sup>6</sup> and Lear.<sup>7</sup> The examiner relied on Maddock and Lear for teaching the “further step of removing at least one of the moiety and the ligand by affinity adsorption” recited in claims 92 and 93. Since this rejection relies on the same reasoning as the rejection discussed above, it suffers from the same deficiency and must be reversed for the same reason.

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<sup>6</sup> Maddock, U.S. Patent 5,474,772, issued December 12, 1995

<sup>7</sup> Lear et al., “Improved tumor imaging with radiolabeled monoclonal antibodies by plasma clearance of unbound antibody with anti-antibody column,” Radiology, Vol. 179, pp. 509-512 (1991)

Summary

The examiner has not adequately explained how the cited references would have suggested the instantly claimed method. We therefore reverse the rejections under 35 U.S.C. § 103.

REVERSED

Eric Grimes	)
Administrative Patent Judge	)
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	) BOARD OF PATENT
Lora M. Green	)
Administrative Patent Judge	) APPEALS AND
	)
	) INTERFERENCES
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Richard M. Lebovitz	)
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