

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 34

**UNITED STATES PATENT AND TRADEMARK OFFICE**

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**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

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Ex parte TSE WEN CHANG

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Appeal No. 2001-2497  
Application No. 08/855,744

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ON BRIEF

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Before WILLIAM F. SMITH, SCHENER, and GRIMES, Administrative Patent Judges.

GRIMES, 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 1 and 3, all of the claims in the application. Claim 1 and 3 read as follows:

1. A method of enhancing delivery of a therapeutic agent selected from the group consisting of tumor necrosis factor and interleukin-1 to a solid tissue site, comprising:  
  
administering to a patient a conjugate consisting of two individual single chain  $V_H$ - $V_L$  binding molecules which are conjugated with a hydrophilic peptide linker, one single chain binding molecule having specificity for a solid tissue antigen and the other for the therapeutic agent, and waiting until the conjugate concentration in the

extravascular space reaches equilibrium between the extravascular space and the capillaries;

administering a liposome conjugated with antibodies specific for the conjugate which binds circulating conjugate;

administering the therapeutic agent.

3. The method of claim 1 further including the step of administering the liposome conjugated with antibodies at least one more time after time is allowed for the conjugate(s) in the extravascular space and the blood circulation to reach equilibrium.

The examiner relies on the following references:

Huston et al. (Huston)                      WO 88/09344                      Dec. 1, 1988

Goodwin, "Pharmacokinetics and Antibodies," The Journal of Nuclear Medicine, Vol. 28, No. 8, pp. 1358-1362 (1987)

Colcher et al. (Colcher), "In Vivo Tumor Targeting of a Recombinant Single-Chain Antigen-Binding Protein," Journal of the National Cancer Institute, Vol. 82, No. 14, pp.1191-1197 (1990)

Claims 1 and 3 stand rejected under 35 U.S.C. § 112, first paragraph, for nonenablement.

Claims 1 and 3 stand rejected under 35 U.S.C. § 103 as obvious in view of Goodwin combined with either of Huston or Colcher.<sup>1</sup>

We reverse both rejections.

### Background

Immunoconjugates and immunotoxins – monoclonal antibodies conjugated with a therapeutic agent or toxin – have been investigated for treatment of cancer. See the specification, pages 1 and 2. These agents,

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<sup>1</sup> As further discussed *infra*, we construe the examiner's rejection under § 103 to be based on Goodwin combined with either of Huston or Colcher, rather than, as stated in the Examiner's Answer, Goodwin combined with Huston and Colcher.

however, have proven more effective in treating leukemia or lymphoma than solid tumors. See id., page 2. “One plausible explanation for this difference in efficacy is that malignant cells in blood or lymphoid tissues are more accessible than those in solid tumors. . . . In addition, even where the toxin is in contact with the target cells, only a very small fraction will actually enter the cell and thus, not all cells in a solid tumor will be killed.” Id. This problem cannot be solved by increasing the dosage of immunotoxin, because the immunotoxin is also taken up by reticuloendothelial cells and phagocytic cells of the liver, and therefore “the total amount of toxin which can be administered is sever[e]ly limited.” Id.

The specification discloses a method for increasing the amount of therapeutic agent delivered to a target site such as a tumor, without causing systemic toxicity. “The invention includes using bifunctional two-domain binding molecules to recruit a therapeutic agent to a solid tissue target site, where the binding molecules have one specificity for the target site and the other specificity for the therapeutic agent.” Specification, page 6. The binding molecules and therapeutic agent are administered in separate steps. The binding molecules are administered first and allowed to bind to the target site. **Cite specification.** A remover substance (e.g., a liposome conjugated to antibodies against the binding molecules) is then administered to facilitate clearing of the binding molecules from the circulation. See id., page 6. After the last administration of remover has had time to clear from circulation, the therapeutic agent is administered and bound by the binding molecules bound to the target site. Thus, the toxic effects

of the therapeutic agent are confined to the target site and systemic toxicity is minimized.

### Discussion

The claims are directed to a method of treating a patient with either tumor necrosis factor (TNF) or interleukin-1 (IL-1). In the claimed method, the patient is first administered a conjugate that consists of two  $V_H$ - $V_L$  binding molecules connected by a peptide linker. One of the binding molecules in the conjugate binds specifically to the therapeutic agent (TNF or IL-1) and the other binds to a target site antigen. After it is administered, the conjugate is allowed to reach equilibrium between the capillaries and extravascular space. A liposome conjugated with conjugate-specific antibodies is then administered (one or more times) to bind circulating conjugate and, finally, the therapeutic agent is administered.

### 1. Enablement

The examiner rejected the claims for as nonenabled. The statement of the rejection in the Examiner's Answer reads as follows: "Claims 1 and 3 stand rejected under 35 U.S.C. § 112, first paragraph. . . . This rejection is set forth in prior Office action, Paper No. 5; please also see the Office action in paper No. 10." Examiner's Answer, page 3. Paper No. 5 (mailed July 29, 1992), in turn, provides the following statement of rejection:

[T]he specification does not provide any probative evidence for the operability of the claimed methods. . . . [I]t is unclear as to the operability of the methods since the delivery of the therapeutic

agents which are highly toxic occurs after being administered separately. Furthermore, all of the species being administered such as the binding molecules, remover substances, and the therapeutic agents are immunogenic and would appear to hinder long term administrations. Therefore, in the absence of further guidelines, it would be undue experimentation to determine the conditions in which bifunctional binding molecules with which remover and which therapeutic agents would be operable as broadly claimed in the instant application.

Paper No. 5, pages 4-5.<sup>2</sup> As we understand it, the examiner's reasoning is that the claimed method encompasses inoperative embodiments and undue experimentation would have been required to determine what embodiments within the scope of the claims are and are not operable.

The examiner bears the initial burden of establishing nonenablement. See In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (“[T]he PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement.”).

That burden is not met by a bare assertion that a claimed method has not been shown to work. “Section 112 does not require that a specification convince persons skilled in the art that the assertions therein are correct.” In re

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<sup>2</sup> Paper No. 5 includes an additional basis of nonenablement: “The specification improperly incorporates the essential material required to make and use the claimed invention.” Page 4, lines 25-27. This basis, however, was apparently withdrawn in the next Office action. See Paper No. 10 (mailed Jan. 13, 1993), page 3: “[C]laims 1-3 . . . remain rejected under 35 U.S.C. §112,

Armbruster, 512 F.2d 676, 678, 185 USPQ 152, 153 (CCPA 1975). If the specification “contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented[, it] must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.” In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971), emphasis in original.

Further, a conclusion of nonenablement must be supported by evidence or scientific reasoning. See Armbruster, 512 F.2d at 677, 185 USPQ at 153 (“[T]he Patent and Trademark Office must substantiate its rejection for lack of enablement with reasons.” (emphasis in original)). See also Marzocchi, 439 F.2d at 224, 169 USPQ at 370 (“[It] is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.”).

In this case, the examiner has provided no Wands-based analysis to support the conclusion of nonenablement and has pointed to no evidence in the record to support the assertion that the claimed method is likely to be inoperative. With regard to the asserted requirement for undue experimentation, we note that

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first paragraph, for the reasons previously set forth on page 4, line 28 to page 5 of [Paper No. 5]” (emphasis added).

the claims as they presently stand encompass only two therapeutic agents (TNF and IL-1) in combination with a single remover substance (liposomes). In short, the examiner has not carried the initial burden of showing a prima facie case of nonenablement. The rejection under 35 U.S.C. § 112, first paragraph, is reversed.

## 2. Obviousness

The examiner also rejected the claims as obvious over the prior art. The statement of the rejection in the Examiner's Answer reads as follows: "Claims 1 and 3 stand rejected . . . under 35 USC 103 over Goodwin in view of Huston et al, and Colcher et al. This rejection is set forth in prior Office action, Paper No. 5; please also see the Office action in paper No. 10." Examiner's Answer, page 3.

This statement of rejection leaves us somewhat at a loss, since neither of Paper No. 5 or Paper No. 10 contains a rejection based on Goodwin, Huston, and Colcher. The § 103 rejection in Paper No. 5 is based on "Goodwin (1987) in view of Huston et al.," while Paper No. 10 contains two rejections under § 103, one being the Goodwin-and-Huston rejection from Paper No. 5, and the other based on "Goodwin (1987) in view of Huston et al . . . or Colcher et al (1990) and further in view of Glennie . . . and Chang et al." We also note that in the next Office action, the latter rejection morphed one based on "Goodwin (1987) in view of Huston et al . . . or Colcher et al (1990) essentially for the reasons of record." See Paper No. 16, mailed June 17, 1993.

Thus, other than the Examiner's Answer, the record nowhere contains a rejection under § 103 based on Goodwin, Huston, and Colcher. Thus, the

rejection as stated in the Examiner's Answer would constitute a new ground of rejection that could not be raised for the first time on appeal; the examiner would have had to reopen prosecution.

Since the examiner expressly referred to prior Office actions, however, we assume the examiner intended to state the rejection as it had been set out in previous Office actions, i.e., a rejection under 35 U.S.C. § 103 based on Goodwin in combination with either Huston or Colcher. Our review of the rejection is based on this understanding of its basis.

Goodwin discloses a method of detecting cancers "in which the antibody and the radiolabel are administered separately." Page 1361. Goodwin describes the method as follows:

Nonradioactive antibody is given first (pretargeted) and allowed time to reach maximum tumor concentration, usually at least one day. At the time of maximum tumor concentration of nonradioactive antibody, the blood is quickly cleared of excess circulating nonradioactive antibody using a special intravenous "chase". Shortly after (30-60 min) the radiolabel is given and images made in 1-3 hr.

Id.

Goodwin also teaches that "[a]n obvious improvement in this system is the development of bifunctional antibodies that could bind both a chelate and a tumor antigen. . . . Either hybrid antibodies or antibody conjugates could be used for this application." Id.

Huston and Colcher both disclose single-chain  $V_H$ - $V_L$  molecules with potential diagnostic and/or therapeutic applications. Huston describes the molecule as a "multifunctional protein" having affinity for a preselected antigen.

See the abstract. The proteins are disclosed to bind the target antigen via a “biosynthetic antibody binding site” and are disclosed to optionally “include other polypeptide sequences which function, e.g., as an enzyme, toxin, binding site, or site for attachment to an immobilization medi[um] or radioactive atom.” Id. Thus, Huston’s multifunctional proteins comprise separate domains that (1) bind to the target antigen and (2) carry out enzymatic or toxic reactions.

Colcher discloses “in vivo targeting of tumors with a single-chain antigen-binding protein.” Abstract. The disclosed protein was “composed of a variable light-chain ( $V_L$ ), amino acid sequence of an immunoglobulin tethered to a variable heavy-chain ( $V_H$ ) sequence by a designed peptide.” Id. This protein was disclosed to bind to the appropriate tumor antigen. See id. Colcher suggests that “it may be possible, for more efficient therapeutic and/or diagnostic applications, . . . to add drugs or specific combining sites for drugs and radionuclides (i.e., bifunctional chelates).” Page 1196.

The examiner concluded that

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the method of pretargeted radiolabel of Goodwin using the functionally equivalent bifunctional antibodies . . . which can be made as single chain as taught by Huston et al[.] or Colcher et al[.] since Goodwin teaches the use of bifunctional antibodies . . . and since Huston et al[.] and Colcher et al[.] teach the advantages of having single chain chimeric antibodies over the antibody fragment conjugates . . . with the expected benefit of reduced immunogenicity and increased bioavailability. See Page 3, the last paragraph of Huston et al[.] and page 1196 of Colcher et al.

“In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant.” In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993).

In this case, the examiner has not made out a prima facie case of obviousness. One obvious defect in the examiner’s rejection is that it fails to account for several of the limitations of the claims. In addition to a conjugate made up of two VH-VL binding molecules, the claims require the use of either TNF or IL-1 as the therapeutic agent, in combination with liposomes conjugated with antibodies specific for the conjugate. The examiner’s rejection, however, does not explain why it would have been obvious to use TNF or IL-1 as the therapeutic agent, nor why it would have been obvious to use antibody-conjugated liposomes. Obviousness is determined based on the claimed “subject matter as a whole.” 35 U.S.C. § 103. Express limitations of the claims cannot be ignored. See General Foods Corp. v. Studiengesellschaft Kohle mbH, 972 F.2d 1272, 1275, 23 USPQ2d 1839, 1840 (Fed. Cir. 1992) (“[E]ach claim is an entity which must be considered as a whole.” (emphasis in original)).

In addition, the examiner has not adequately explained how the combination of the reference disclosures would have suggested the claimed method. In the imaging method disclosed by Goodwin, a tumor-binding molecule is administered and allowed to bind its target, then the blood is cleared of excess binding molecule, and finally, a radiolabel is administered. Since Goodwin’s

method depends on the tumor-binding activity and the effector activity (radiolabel for imaging, toxin for therapy) being administered at different times, it is essential that those activities be carried out by different molecules.

Colcher and Huston, however, disclose or suggest multifunctional proteins that both bind to an antigen and carry out the effector function. Since both functions reside in the same protein, it would appear that the proteins disclosed by Colcher and Huston could not be used in the multistep procedure of Goodwin, since there would be no way to administer the tumor-binding part of the protein separately from the effector part of the protein. The examiner has not explained how the multifunctional proteins disclosed by Colcher and Huston could be combined with Goodwin's method in such a way as to yield the instantly claimed invention.

Summary

The examiner has not carried the initial burden of supporting a prima facie case of nonenablement or obviousness. We therefore reverse the rejections under 35 U.S.C. § 112, first paragraph, and 35 U.S.C. § 103.

REVERSED

WILLIAM F. SMITH	)	
Administrative Patent Judge	)	
	)	
	)	
	)	BOARD OF PATENT
TONI R. SCHEINER	)	
Administrative Patent Judge	)	APPEALS AND
	)	
	)	INTERFERENCES
	)	
ERIC GRIMES	)	
Administrative Patent Judge	)	

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Application No. 08/855,744

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