

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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

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Appeal No. 2001-2379  
Application No. 08/931,666

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ON BRIEF

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Before WILLIAM F. SMITH, ADAMS, 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 1-15, all of the claims remaining. Claims 1 and 12 are representative and read as follows:

1. A method for targeting an intracellular protein in a cell comprising contacting said cell with a cationized antibody which thence enters said cell and immunologically binds with said intracellular protein.
12. A method for treating an individual infected by the HIV-1 virus comprising administering to said individual an effective amount of a cationized antibody which immunologically binds with an HIV-1 encoded trans-activating factor thereby reducing the reverse transcriptase activity associated with said HIV-1 virus.

The examiner relies on the following references:

Abrams et al. (Abrams), "Optimal Strategies for Developing Human-Human Monoclonal Antibodies," Methods in Enzymology, Vol. 121, pp. 107-119 (1986)

Barone et al. (Barone), "Reactivity of E. coli-derived trans-activating protein of human T lymphotropic virus Type III with sera from patients with acquired immune deficiency syndrome," The Journal of Immunology, Vol. 137, No. 2, pp. 669-673 (1986)

Triguero et al. (Triguero), "Blood-brain barrier transport of cationized immunoglobulin G: Enhanced delivery compared to native protein," Proc. Natl. Acad. Sci. USA, Vol. 86, pp. 4761-4765 (1989)

Fahey et al. (Fahey), "Status of immune-based therapies in HIV infection and AIDS," Clin. exp. Immunol., Vol. 88, pp. 1-5 (1992)

Fox, "No winners against AIDS," Bio/Technology, Vol. 12, p. 128 (1994)

Claims 1-15 stand rejected under 35 U.S.C. § 112, first paragraph, as not enabled by the specification.

Claims 1-15 stand rejected under 35 U.S.C. § 103 as obvious in view of Triguero, Barone, and Abrams.

We reverse both rejections.

#### Background

"Most antibodies have an isoelectric point of between about 5 to 6." Specification, page 6. "Cationization involves substituting basic groups in place of a sufficient number of surface carboxyl groups to increase the pI of the antibody to between 8.0 to 11.0." Id. "Cationization of proteins is known, in general, to enhance their cellular uptake. The prior art teaches that the uptake of cationized proteins is by endocytosis. . . . [P]roteins which are taken up by this method are sequestered in intracellular compartments." Id., page 5.

The specification discloses an “approach for the targeting of an intracellular protein which is based on the discovery that cationized proteins are not necessarily sequestered in intracellular vesicles when taken up by a cell.” Page 3. The disclosed method is “based on the discovery that a cationized antibody specific for the HIV-1[-]encoded Tat protein effectively inhibits replication of the HIV-1 virus when taken up by infected cells. . . . If the cationized anti-Tat antibody were sequestered in intracellular vesicles, as the prior art suggested, the antibodies would not come to contact with the Tat protein which is produced in the cytoplasm and transported into the nucleus.” Id. The specification provides examples showing that cationized anti-Tat monoclonal antibodies counteracted the growth inhibitory effect of exogenous Tat on lymphocytes in vitro. See pages 14-19.

### Discussion

The claims are directed to a method of targeting an intracellular protein such as the HIV-1 Tat transactivating factor, by contacting the cell with a cationized antibody. The examiner rejected the claims as nonenabled and as obvious.

#### 1. Enablement

The examiner rejected the claimed methods as nonenabled, on the basis that the “evidence is not sufficient to allow one skilled in the art to make and use the claimed invention with a reasonable expectation of success and without undue experimentation.” Examiner’s Answer, page 4. The examiner noted that Appellant had provided only in vitro data to support the claimed method, and had

not shown, e.g., “that antibody levels in vivo could be achieved which would allow sufficient uptake of antibody by endocytosis to achieve effective levels for therapy.” Id. The examiner also cited two references showing monoclonal antibody therapies and immune system-boosting therapies had not been effective in treating HIV infection. See id., page 5.

We conclude that the examiner has not carried the initial burden of showing nonenablement, by providing a reasonable explanation of why the claimed methods are not enabled. The examiner correctly notes that Appellant has not shown that the claimed method actually works in vivo. See the Examiner’s Answer, pages 4-5. Appellant, however, is not required to prove that the claimed method works. “Section 112 does not require that a specification convince persons skilled in the art that the assertions therein are correct.” In re Armbruster, 512 F.2d 676, 678, 185 USPQ 152, 153 (CCPA 1975).

Rather, the burden is on the examiner to set forth a reasonable explanation as to why he believes that the scope of the claims is not adequately enabled by the description of the invention provided in the specification. See In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The examiner cited two prior art references to support his position that those skilled in the art would not have expected the claimed methods to provide an effective treatment for HIV infection. See the Examiner’s Answer, page 5.

We do not agree that the cited references support the examiner’s conclusion. The examiner cites Fahey as showing that “clinical trials using monoclonal antibody therapies have not provided any clinical benefit.” Id. The

present specification shows, however, that native antibodies do not have the same Tat-inhibitory effect as cationized antibodies. See, e.g., Table 1. Thus, it is unclear why those of skill in the art would have expected the Fahey's results (which were apparently obtained using native antibodies) to be predictive of the results expected for the claimed method of using cationized antibodies.

The examiner's reliance on Fox also appears to be misplaced. The examiner cites Fox as discussing "[t]he failure of all immune-system-boosting therapies for treating AIDS." Examiner's Answer, page 5. The claimed methods, however, do not rely on boosting the immune system. The claimed methods involve administration of exogenous, cationized antibodies. Thus, it is unclear why those of skill in the art would have found Fox's results predictive with respect to the instant claims.

The examiner has not shown, by a preponderance of the evidence, that practicing the claimed methods would have required undue experimentation. We therefore reverse the rejection under 35 U.S.C. § 112, first paragraph.

## 2. Obviousness

The examiner also rejected all of the claims as obvious over the prior art. The examiner cited Triguero as teaching production of cationized antibodies and transport of such antibodies across the blood-brain barrier. According to the examiner, Triguero "establishes that those skilled in the art were well aware that 1) cationization of proteins enhanced cellular uptake, and 2) that during at least part of this cellular uptake process, the proteins diffused through the cytoplasm of

the cell.” Examiner’s Answer, page 6. The examiner based the latter assertion on Triguero’s statement that the

transport process is believed to be made up of three steps (11): (i) absorptive-mediated endocytosis at the luminal side of the capillary; (ii) diffusion through the 0.3  $\mu\text{m}$  of endothelial cytoplasm; and (iii) absorptive-mediated exocytosis at the antiluminal membrane of the brain capillary.

Pages 4764-4765 (citation omitted).

The examiner relied on Barone and Abrams for their disclosures of the HIV-1 Tat protein and methods of making monoclonal antibodies, respectively.

He concluded that it would have been obvious

to use the teachings of Barone et al. and Abrams et al. to produce human monoclonal antibodies which immunologically bind to tat protein of HIV and then to cationize the anti-tat antibodies to enhance the cellular uptake of the anti-tat antibodies according to the teachings of Triguero et al. One of ordinary skill in the art would have been motivated by the long felt need for improved therapeutic agents for treating HIV infection and would have had a reasonable expectation of success since tat is an intracellular protein critical for the replication of HIV virus and, thus, a target for therapeutic intervention, and since Triguero et al. established that cationization of antibodies enhanced cellular uptake of the antibodies.

Examiner’s Answer, page 7.

“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). “[A] proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out

the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have had a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1443 (Fed. Cir. 1991) (citation omitted)

In this case, the references cited by the examiner do not support a prima facie case of obviousness. The examiner has not adequately shown that the references would have suggested a method of treating HIV by administering cationized anti-Tat antibodies. First, the examiner has not shown that the references would have suggested Tat as a therapeutic target to those of skill in the art. Although Barone discloses that recombinant Tat was bound by antibodies in sera from 35% of the tested AIDS patients, the reference does not suggest that additional (exogenous) antibodies would be likely to have a beneficial effect. Barone simply concludes that the cloning of tat "should help in determining the role, if any, of this protein in the cytopathic activity of the HTLV-III [HIV] virus." Page 672. The examiner has not adequately explained why Barone would have led those skilled in the art to use anti-Tat antibodies as a treatment for HIV infection.

In addition, the examiner has not shown that the prior art would have led the skilled artisan to expect that a cationized antibody would bind to an intracellular target after being taken up by a cell. The examiner cites Triguero as teaching that cationized antibodies are taken up by cells of the blood-brain

barrier, and then diffuse across the cytoplasm before being exocytosed on the other side. See the Examiner's Answer, page 6. The examiner argues that this would have led those of skill in the art to expect that "this cytoplasmic stage of the transport process would then make the antibody available for binding to intracellular antigens." Id.

The evidence of record does not support the examiner's position. Appellant have provided evidence that those of skill in the art would not have expected cationized antibodies to be available for antigen binding during the cytoplasmic stage of traversing the blood-brain barrier. The instant specification cites Pardridge<sup>1</sup> as disclosing that transcytosis across the blood-brain barrier involves diffusion "presumably in nonclathrin-containing smooth vesicles." Thus, the evidence suggests that those of skill in the art would have understood Triguero's reference to cationized antibodies diffusing through the cytoplasm to mean diffusion of the antibodies in vesicles. The examiner has pointed to no evidence supporting an alternative reading of the reference, which would show that those skilled in the art would have expected the antibodies to diffuse freely through the cytoplasm and be available to bind to intracellular targets.

In addition, the evidence shows that many cells, including lymphoid cells, commonly degrade endocytosed material in lysosomes. See Renau-Piqueras, page 745 ("As is well known, lysosomal degradation of endocytosed material is common in many cell types, including resting and stimulated lymphoid cells.").

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<sup>1</sup> Pardridge, "Receptor-mediated peptide transport through the blood-brain barrier," *Endocrine Reviews*, Vol. 7, No. 3, pp. 314-330 (1986), of record.

Based on this evidence, it would appear that those of skill in the art would expect HIV-infected lymphocytes to endocytose and degrade cationized antibodies, rather than expecting the cationized antibodies to effectively bind to and inactivate intracellular Tat.

#### Other Issues

According to Appellant, the instant application is a continuation of application 08/137,183, filed March 21, 1994, which was a continuation-in-part of application 07/693,872, filed April 30, 1991. Thus, the effective filing date of the claimed invention may be either March 21, 1994 or April 30, 1991.

We have been unable to find any statement in the record by the examiner fixing the effective filing date of the instant claims. We note, however, that one of the references attached to the Appeal Brief cites references that might anticipate the instant claims. Specifically, Pardridge<sup>2</sup> cites three references (Pardridge et al. 1994a, Pardridge et al. 1994b, and Pardridge et al. 1994c) which have titles that suggest they may be anticipatory if the instant claims have an effective filing date of March 21, 1994, and if the references were published before March 21 of 1994.

Upon return of this case, the examiner should consider whether the “Pardridge et al. 1994” references are prior art with respect to the instant claims and, if so, whether they render the claims unpatentable.

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<sup>2</sup> Pardridge et al., “Cationized hyperimmune immunoglobulins: Pharmacokinetics, toxicity evaluation and treatment of human immunodeficiency virus-infected human-peripherabl blood lymphocytes-severe combined immune deficiency mice,” Journal of Pharmacology and Experimental Therapeutics, Vol. 276, pp. 246-252 (1996).

Summary

The examiner has not carried the initial burden of showing that the instant claims are unpatentable for either obviousness or lack of enablement. The rejections under 35 U.S.C. §§ 103 and 112, first paragraph, are reversed.

REVERSED

William F. Smith	)	
Administrative Patent Judge	)	
	)	
	)	
	)	BOARD OF PATENT
Donald E. Adams	)	
Administrative Patent Judge	)	APPEALS AND
	)	
	)	INTERFERENCES
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