

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opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.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. 41

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte BENJAMIN L. WOLOZIN
and HAYDEN G. COON

Appeal No. 95-4464
Application 07/605,788¹

ON BRIEF

Before RONALD H. SMITH, WILLIAM F. SMITH and ELLIS,
Administrative Patent Judges.

ELLIS, **Administrative Patent Judge.**

DECISION ON APPEAL

This is an appeal from the final rejection of claims 20, 21 and 23, all the claims pending in the application.

Claim 20, which is illustrative of the subject matter on appeal, reads as follows:

¹ Application for patent filed October 30, 1990. According to appellants, this application is a continuation-in-part of Application 07/487,894, now abandoned.

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20. A method of diagnosing Alzheimer's disease comprising the steps of:

- i) isolating human tissue containing olfactory neurons;
- ii) growing said tissue in a suitable medium under a first membrane comprising collagen and laminin, establishing a human olfactory neuron culture;
- iii) separating said first membrane from neurons;
- iv) replating said neurons on a surface coated with a second membrane comprising collagen and laminin;
- v) culturing said neurons of step (iv) under conditions allowing replication;
- vi) contacting said cultured neurons with a calcium salt;
- vii) contacting said neurons of step (vi) with an ionophore;
- viii) detecting AD-specific changes in amyloid precursor protein or A68 as compared to normal; and
- ix) diagnosing tissue as AD afflicted, if any AD-specific changes of said proteins of step (viii) are detected.

The references relied on by the examiner are:

Talamo, et al., (Talamo) "Pathological Changes in Olfactory Neurons in Patients with Alzheimer's Disease", **Nature**, Vol. 337, pp. 736-739 (1989).

Coon, et al., (Coon) "Cell Cultures of Neuroblasts from Rat Olfactory Epithelium that Show Odorant Responses", **Proc. Natl. Acad. Sci. USA**, Vol. 86, pp. 1703-1707 (1989).

Wolozin, et al., (Wolozin) "A Neuronal Antigen in the Brains of Alzheimer Patients", **Science**, Vol. 232, pp. 648-650 (1986).

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Cole, et al., (Cole) "Stimulated Platelets Release Amyloid β -Protein Precursor", **Biochem. Biophys. Res. Commun.**, Vol. 170, No. 1, pp. 288-295 (1990).

A reference relied on by the appellants and this merits panel is:

Microbiology, Second Edition, "Characterization of Cultures of Animal Cells", (Harper & Row, N.Y. 1973), pp. 1122.

Claims 20, 21 and 23 stand rejected under 35 U.S.C. § 103 as being unpatentable over Talamo in view of Coon, Wolozin and Cole.

We reverse.

The claimed invention is directed to a method of diagnosing Alzheimer's disease (AD) which involves isolating and growing human olfactory neurons *in vitro*, contacting said neurons first with a calcium salt and then an ionophore, and detecting AD-specific changes in amyloid precursor protein (APP) or A68.

Talamo discloses that "nasal epithelium tissue taken at autopsy shows unique pathological changes in morphology, distribution, and immunoreactivity of neuronal structures in patients with Alzheimer's disease." Talamo, p. 736, para. 1. Talamo reports that "[n]euritic masses in AD olfactory epithelium were also stained in some cases with antibody ALZ50, which was reported to be completely specific to Alzheimer's tissue." Talamo, p. 738, para. 2. Talamo suggests neurons in the

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olfactory epithelium could be used as source of living nerve cells for the study of Alzheimer's disease provided "they can be shown to have the characteristics of this disease." Talamo, p. 736, para. 1. Specifically, Talamo states that because olfactory neurons "have the unusual property of arising from stem cells throughout the life of the organism, they are good candidates for the development of cell cultures or cell lines which may express the disorder from living patients." *Id.*

Coon discloses a method of isolating and culturing neuroblasts derived from rat olfactory epithelium. Coon, p. 1703, the abstract.

Wolozin discloses the preparation of a monoclonal antibody (Alz-50) which recognizes a single antigen (with a molecular weight of 68,000) which is said to be present in much higher concentrations in certain regions of the brain of Alzheimer's patients than in normal brain. Wolozin, p. 232, the abstract.

Cole discloses that the platelets of Alzheimer's patients can be stimulated with thrombin or ionomycin to secrete soluble truncated amyloid β -protein precursor (APP) and particulate membrane fragments which contain C-terminal and N-terminal immunoreactive amyloid β -protein precursor. Cole, p. 288,

para. 1.

The examiner argues that

[i]t would have been **prima facie** obvious to one of ordinary skill in the art at the time of the invention to culture human olfactory epithelial neurons using Coon's method of culturing olfactory epithelial neurons obtained from rats because Talamo suggests that neurons in the olfactory epithelium are good candidates for development of cell culture of cell lines for studying Alzheimer's disease and Coon teaches a method of establishing continuous cultures of the neuronal stem cells using olfactory epithelial tissue. Thus one would have reasonably expected to successfully culture neuron-containing olfactory epithelium from humans using Coon's method which has been show [sic, shown] to allow for continuously [sic, continuous] culture [of] the same cells isolated from another vertebrate species. It would have been obvious to detect AD-specific changes as taught by Talamo et al in the cultured cells because Talamo teaches that olfactory epithelium from patients with Alzheimer's disease exhibits differential binding as compared to normal olfactory tissue using antibody ALZ50 which Wolozin teaches is specific for AD. One would have been motivated to add an ionophore as taught by Cole et al to cultured cells as a means of increasing calcium-mediated expression of APP as an AD marker because Cole teaches that ionomycin causes release of C-terminal APP in membrane fragments [Answer, p. 6].

In response, the appellants focus their arguments primarily on whether the combined teachings of Talamo and Coon would have suggested to one of ordinary skill in the art, the culturing of human AD olfactory neurons and whether said person would have had a reasonable expectation of success of culturing human olfactory neurons using the disclosed rat medium. ***In re O'Farrell***, 853

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F.2d 894, 904-905, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

Specifically, the appellants argue that (1) "Dr. Kohn's expert opinion that a medium specifically designed to maintain the growth of a cell type of one species, would not be expected to be useful in the maintenance and growth of a cell type of a different species,"² (Brief, p. 8) and (2) it is unpredictable as to whether the response of cells to stimuli in culture will mimic their response to the same stimuli *in situ* (Brief, p. 10).

Although argued extensively by the appellants in the Brief (Paper No. 32), Reply Brief (Paper No. 35) and supplemental Reply Brief (Paper No. 37), and by the examiner in the Answer (Paper No. 33), supplemental Answer (Paper No. 36), and second supplemental Answer (Paper No. 38) we find it unnecessary to pass on the merits of the relative positions with respect to issue (1). Rather, we find conspicuous in its absence, any rebuttal by the examiner to the appellants' second argument. That is, the examiner fails to contest the appellants' position that due to the potential differences between the neurons disclosed by Talamo which are derived from autopsies (and, therefore, comprise fully differentiated neurons), those skilled in the art would not have

² The appellants refer to the declaration of Dr. Kohn, executed March 23, 1993, Paper No. 23.

expected that **neuroblasts** derived from AD patients and cultured **in vitro** to express AD-specific markers.

Thus, even if we assume, arguendo, that the culturing of human olfactory neurons would have been obvious to one of ordinary skill in the art in view of the teachings of Talamo and Coon, the question remains as to whether the neuroblasts derived from AD patients would, after their adaptation to tissue culture conditions and/or differentiation **in vitro**, express AD-specific markers. Here, the appellants have presented evidence that the phenotype and genotype of animal cells may be altered when they are placed in culture.³ Thus, on this record, it appears that the mere fact that Talamo reports that the neurotic masses in olfactory epithelium comprising differentiated cells derived from AD patients and taken at autopsy, could be stained with the AD-specific monoclonal antibody, ALZ-50, would not necessarily have suggested that neuroblasts derived from AD patients, or neuroblasts from AD patients and placed in culture, would express the antigen recognized by ALZ-50.

Similarly, even if we assume, arguendo, that the culturing

³ The appellants have submitted an excerpt from the textbook **Microbiology**, Second Edition, Davis, et al., Harper & Row, publishers, NY, p. 1122 (1973).

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of human olfactory neurons would have been obvious to one of ordinary skill in the art in view of the teachings of Talamo and Coon, it would appear, on this record, that the mere fact that Talamo observed morphological differences and staining with the monoclonal antibody ALZ-50 in olfactory neurons taken from AD patients at autopsy, would not necessarily have suggested to those of ordinary skill in the art the release of APP from neuroblasts derived from AD patients, or neuroblasts from AD patients and placed in culture, in response to an ionophore as described by Cole.

Accordingly, on this record, we reverse the examiner's rejection.

The decision of the examiner is reversed.

REVERSED

RONALD H. SMITH)	
Administrative Patent Judge)	
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)	
)	BOARD OF PATENT
WILLIAM F. SMITH)	APPEALS AND
Administrative Patent Judge)	INTERFERENCES
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JOAN ELLIS)	
Administrative Patent Judge)	

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