

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 37

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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Ex parte JOHN R. RHODES

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Appeal No. 1997-3019  
Application No. 08/404,122<sup>1</sup>

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ON BRIEF

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Before WINTERS, ROBINSON, and SCHEINER, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

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<sup>1</sup> Application for patent filed March 14, 1995.



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Application No. 08/404,122

Gao et al. (Gao), "An Essential Role for Constitutive Schiff Base-Forming Ligands in Antigen Presentation to Murine T Cell Clones," Journal of Immunology, Vol. 144, No. 8, pp. 2883-2890 (April 15, 1990)

### DISCUSSION

The claims stand rejected as follows:

I. Claims 1, 2, 4, 5, 10, and 11 under 35 U.S.C. § 103 as unpatentable over Knop, Lipkowitz, Rhodes, Gao, Roitt and Ada.

II. Claim 3, under 35 U.S.C. § 103 as unpatentable over Knop, Lipkowitz, Rhodes, Gao, Roitt, Ada and the Sigma Catalog.

III. Claims 6 through 8 under 35 U.S.C. § 103 as unpatentable over Knop, Lipkowitz, Rhodes, Gao, Roitt, Ada and UK Patent 1,569,003.

We reverse all three rejections. In addition, we raise an issue for the consideration of the examiner upon return of the application to the examining group.

### BACKGROUND

A vaccine, in the context of the claims, and in general, "stimulate[s] a specific immune response consisting of protective antibodies and T cell immunity," and upon administration to a non-immune individual, "induces active immunity."<sup>2</sup> An adjuvant is a

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<sup>2</sup> Illustrated Dictionary of Immunology, J.M. Cruse and R.E. Lewis, CRC Press, Inc. Boca Raton, FL, 1995, page 309 ("vaccine") attached.

component of a vaccine which “facilitates or enhances the immune response to an antigen with which it is combined.”<sup>3</sup> According to the specification (pages 1 through 3):

Materials having adjuvant activity are well known. Currently, however, [a]lum . . . and similar aluminum gels are the only adjuvants licensed for human use . . . Other material are also known to have adjuvant activity, and these include: Freund’s complete adjuvant, . . . Freund’s incomplete adjuvant, . . . saponin, . . . nonionic block copolymer surfactants, . . . and muramyl dipeptide . . .

With all of these agents toxicity, and unacceptable chronic reactions, depending on dose, are a feature which currently limit their use as potential alternatives to alum. Alum, on the other hand, will not stimulate cell-mediated immunity, and although having a broad spectrum of activity, is not effective in all potential vaccines, since in peptide vaccines, adsorption onto the alum may be poor due to the small size of the peptide. Occasionally, alum may induce the degradation of antigens by proteases with great efficiency. Thus it is apparent that there is a need for new adjuvants.

NAGO, a combination of neuraminidase and galactose oxidase, is known in the art to induce T lymphocyte proliferation by the induction of aldehydes on cell membranes.

The present inventors have now discovered that a combination of neuraminidase and galactose oxidase (NAGO) possesses potent adjuvant properties. NAGO has been found to be a non-reactogenic adjuvant of unprecedented potency in the induction of T-cell responses. In particular it was as effective or better than Freund complete adjuvant in the induction of cytotoxic T-cells induced with peptide by recogni[z]ing cells infected with live virus. It was also more effective than Freund complete adjuvant in priming T-cells to the envelope glycoprotein gp120 of human immunodeficiency virus. Strong adjuvant effects were exemplified with peptide and protein and polysaccharide antigens of bacterial, viral and protozoal origin. Local reactions produced by NAGO were very mild and were no different to, or less than, those induced by alhydrogel, the only adjuvant licensed for human use.

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<sup>3</sup> Illustrated Dictionary of Immunology, J.M. Cruse and R.E. Lewis, CRC Press, Inc. Boca Raton, FL, 1995, page 7 (“adjuvant”) attached.

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Preferably the ratio of neuraminidase to galactose oxidase in terms of the units of activity is from 1:2 to 1:10 but optimally is about 1:5. The amount of NA per 100 µl of material for injection may be from 0.05 to 12u, preferably from 0.2 to 1.2u. The amount of GO per 100 µl of material for injection may be from 0.1 to 25u, preferably from 2 to 8u. The optimal amount is 1u NA and 5u GO per 100 µl of material for injection.

Finally, the specification demonstrates that in vivo administration of NAGO with various antigens enhances several antigen-specific responses: antibody response, T-cell priming, and induction of cytotoxic T-cells (e.g., specification pages 12-14).

#### DISCUSSION

All of the claims stand rejected under 35 U.S.C. § 103. With respect to claims 1, 2, 4, 5, 10, and 11 the examiner relies on Knop, Lipkowitz, Rhodes, Gao, Roitt and Ada as evidence of obviousness; with respect to claim 3, the examiner relies on the same combination further in view of the Sigma catalog; with respect to claims 6 through 8, the examiner relies on the same combination further in view of UK Patent 1,569,003. We view the examiner's proposed combination of Lipkowitz, Rhodes, Gao, Roitt and Ada as the dispositive issue in all three rejections, so we will discuss them together.

The Examiner's Answer refers to the Final Office action, paper 21, pages 2 through 4, from which we quote the essentials of the examiner's position:

[Knop] teach[es] that neuraminidase is a valuable immunostimulating agent, i.e an adjuvant, when administered with a variety of antigens (column 1, lines 27-30 and column 4, lines 52-57) . . . [Knop] do[es] not teach the addition of galactose oxidase in the adjuvant composition.

[Lipkowitz] teach[es] that the generation of aldehyde moieties on cell surface structures by treatment with neuraminidase and galactose oxidase induce[s] marked proliferation of lymphocytes (p 2702, column 1). [Lipkowitz] also teach[es] that oxidized macrophages are potent stimulators of T cells and that oxidized B and T cells can also stimulate T cell proliferation provided macrophages or macrophage-dependent soluble mediators are present in the cell culture medium (p 2702 column 2).

Rhodes teaches that T cells may be activated by generating aldehydes (via oxidation) on membrane glycoproteins by means of galactose oxidase reacting with the galactosyl or N-acetylgalactosaminy residues exposed after neuraminidase treatment. These aldehydes then react covalently with ligands on class II positive accessory cells to form Schiff bases and the result is a vigorous T cell proliferative response (p 1482, column 2, paragraph 2).

[Gao] teach[es] that Schiff base-forming ligands play an essential role in the inductive interaction between Class II<sup>+</sup> antigen presenting cells and T helper cells (p 2889 column 2, last paragraph).

[Roitt] teach[es] that T helper cells recognize antigen processed by antigen presenting cells and provide help to B cells which then secrete antibody (Figure 8.8).

Ada teach[es] that the activation of antigen presenting cells, T cells and B cells are all requirements of a vaccine (p 525, column 1).

It would have been obvious to one of ordinary skill in the art to include galactose oxidase in the neuraminidase adjuvant composition taught by [Knop] because neuraminidase and galactose oxidase result in biochemical changes of membrane glycoproteins which, in turn, result in inducing the activation of T cells and the interaction between antigen presenting cells and T helper cells, as taught by [Lipkowitz] and Rhodes and [Gao]. Furthermore, the activation of these cells is important in the production of antibodies and is a requirement of a vaccine as taught by Roitt and Ada. Therefore, one of ordinary skill in the art would expect that the combination of neuraminidase and galactose oxidase would act as an adjuvant in a vaccine formulation by enhancing the interactions between antigen presenting cells and T cells and potentiating the immune response . . .

Appellant argues (Brief, page 7) that “[a]djuvants may be tested in vitro and in vivo,” but “when used as an adjuvant with a vaccine, their administration would be in vivo.” “At the date of the invention,” however, “only in vitro data were published concerning NAGO and its behavior and effects in vivo were unexplored.” According to appellant (Brief, page 10), “[t]he generation of a non-specific response by NAGO in vitro does not enhance the weak specific response elicited by the vaccine or antigen but masks it.” On the other hand (Brief, page 11), “administration of NAGO in vivo does not provoke the general proliferation of T cells . . . [r]ather, in vivo, NAGO has the completely opposite effect,” it “enhances the specific proliferation of T-cells elicited by antigen or vaccine.” This is also the position advanced in two declarations submitted by Dr. Rhodes under 37 CFR § 1.132 (dated May 22, 1995 and May 16, 1996).

The examiner summarizes (inaccurately, in our view) appellant’s arguments as follows (Examiner’s Answer, page 7):

The main argument against the secondary references is that they are directed to in vitro experiments and thus should not be combined with the teaching in the primary reference which is directed to in vivo experiments.

Nevertheless, the examiner maintains that “it is well known [that] reagents are tested using more simplistic and readily accessible in vitro studies prior to in vivo applications” and “the combination of neuraminidase and galactose oxidase (NAGO) was known to be

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immunostimulating . . . thus using galactose oxidase in the formulation containing neuraminidase as taught in Knop would have been obvious.”

Needless to say, the examiner’s response does not come to grips with appellant’s contention that NAGO, which produces an apparently non-specific response in vitro, produces the opposite response in vivo, i.e., an antigen-specific immune response, and that “[i]t is this specificity that was unexpected and that is key to the usefulness of NAGO as an adjuvant.” Brief, page 12. Given the apparent lack of a specific immune response to NAGO in vitro, the examiner has not explained why one skilled in the art would combine NAGO with an antigenic component to form a vaccine composition, much less why one would combine neuraminidase and galactose oxidase in the specific amounts or ratios required by the claims.

To establish a prima facie case of obviousness, there must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the modifications required. That knowledge cannot come from appellant’s disclosure of the invention itself. Diversitech Corp. v. Century Steps, Inc., 850 F.2d 675, 678-79, 7 USPQ2d 1315, 1318 (fed. Cir. 1988); In re Geiger, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987); Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985). On the record before us, we find no reasonable suggestion for combining or modifying the teachings of the references

relied on in the manner proposed by the examiner. Accordingly, all three of the rejections of the claims under 35 U.S.C. § 103 are reversed.

#### AN ADDITIONAL MATTER

It is axiomatic that one cannot patent what is old. “The discovery of a new property or use of a previously known composition, even when that property and use are unobvious from the prior art, can not impart patentability to claims to the known composition.” In re Spada, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990) (citations omitted).

The composition of claim 10, unlike the compositions of claims 1 through 8, does not require an antigenic component, nor does it require a specific amount of either component of NAGO or a specific ratio of the two components. While the recitation “[a] vaccine adjuvant” does impose a functional limitation on the claimed composition, the limitation is simply that the composition is capable of functioning as a vaccine adjuvant, not that it is actually used as such.

According to the specification (page 2), compositions comprising neuraminidase and galactose oxidase (NAGO) are known in the art; indeed, several references of record describe such compositions.<sup>4</sup> The specification further teaches that the ratio of neuraminidase to galactose oxidase in vaccine adjuvants should be from 1:2 units of activity to 1:10 units of activity, while the amount of neuraminidase per 100 µl of material for injection may be from 0.05 to 12 units, and the amount of glucose oxidase per 100 µl of

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<sup>4</sup> Lipkowitz, Rhodes and Gao, for example.

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material for injection may be from 0.1 to 25 units. It does not appear that any reference of record describes a composition within the specified ranges, but it is not clear whether NAGO is capable of functioning as a vaccine adjuvant outside these ranges.

The relevant question, then, is whether any of the NAGO formulations already known in the art are capable of enhancing immune response to an antigen in vivo. Should that be the case, then the recitation “[a] vaccine adjuvant” would be insufficient to distinguish the composition of claim 10 from NAGO formulations known in the prior art.

REVERSED

Sherman D. Winters )  
Administrative Patent Judge )  
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) BOARD OF PATENT  
Douglas W. Robinson )  
Administrative Patent Judge ) APPEALS AND  
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