

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 30

**UNITED STATES PATENT AND TRADEMARK OFFICE**

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

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Ex parte ALI KANDIL, OLIVE A. JAMES,  
MICHEL H. KLEIN, and PELE CHONG

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Appeal No. 2002-0616  
Application No. 08/261,194

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ON BRIEF

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Before WINTERS, ADAMS, and GREEN, Administrative Patent Judges.

GREEN, 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, 5, 11, 15 and 26.<sup>1</sup> Claim 1 is representative of the subject matter on appeal, and is drawn to an adjuvant composition consisting essentially of a mineral salt adjuvant selected from the group consisting of aluminum hydroxide, aluminum phosphate, calcium phosphate, zinc hydroxide

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<sup>1</sup> Claims 1, 5, 11, 15 and 19-29 are pending, and claims 19-25 and 27-29 have been indicated to be allowable. See Paper No. 29. In addition, although the examiner has indicated that the amendment after final has been entered, see Paper No. 29, it has not been entered into the record. Upon return of the application, the examiner should have the amendment entered.

and calcium hydroxide, combined with at least one other adjuvant selected from the group consisting of a glycosylamide of a specified formula, an octadecyl ester of an aromatic amino acid, and a lipopeptide which is tripalmityl-S-glyceryl-cysteinylserin or N-palmityl-S-[2,3-(bis(palmitoxy))-2-(RS)propyl-[R]-cysteine.

The examiner relies upon the following references:

Gupta et al. (Gupta), "Adjuvants – A balance between toxicity and adjuvanticity," Vaccine, Vol. 11, No. 3, pp. 294-306 (1993).

Richards et al. (Richards), "Liposomes, Lipid A, and Aluminum Hydroxide Enhance the Immune Response to a Synthetic Malaria Sporozite Antigen," Infection and Immunology, Vol. 56, No. 3, pp. 682-686 (1988)

Masihi et al. (Masihi), "Immunobiological Activities on Nontoxic Lipid A: Enhancement of Nonspecific Resistance in Combination with Trehalose Dimycolate Against Viral Infection and Adjuvant Effects," International Journal of Immunopharmacology, Vol. 8, No. 3, pp. 339-345 (1986)

Stünkel et al. (Stünkel), "Synthetic Glycolipids with Immunopotentiating Activity on Humoral Immunity: Evaluation In Vivo," Cellular Basis in Immune Modulation: Progress in Leukocyte Biology, Vol. 9, pp. 575-579, Alan R. Liss, Inc. (1989)

Penney et al. (Penney), "Analysis of the immunoadjuvant octadecyl tyrosine hydrochloride," Journal of Biological Standardization, Vol. 14, No. 4, pp. 345-349 (1986)

Weismüller et al. (Weismüller), "Novel low-molecular weight synthetic vaccine against foot-and-mouth disease containing a potent B-cell and macrophage activator," Vaccine, Vol. 7, No. 1, pp. 29-33 (1989)

Ramasamy et al. (Ramasamy), "Peptides Derived from a Malaria Parasite Surface Antigen – Effect of Adjuvants and Number of Immunizations on the Total Antibody Response in Mice," J. Natn. Sci. Coun. Sri Lanka, Vol. 21, No. 1, pp. 125-140 (1993)

Claims 1, 5, 11 15 and 26 stand rejected under 35 U.S.C. § 103(a) over the combination of Gupta, Richards, Masihi, Stünkel, Penney, Weismüller and Ramasamy. After careful review of the record and consideration of the issue before us, we reverse.

#### DISCUSSION

Claims 1, 5, 11 15 and 26 stand rejected under 35 U.S.C. § 103(a) over the combination of Gupta, Richards, Masihi, Stünkel, Penney, Weismüller and Ramasamy.

Gupta is relied upon for teaching that adjuvants are well known in the art, and for teaching the use of combinations of adjuvants, specifically, “ that the incorporation of MPL into liposomes along with recombinant antigen and mixed with alum stimulated a high antibody response to the antigen with no pyrogenicity or toxicity in humans.” Examiner’s Answer, page 5. The rejection acknowledges that “Gupta does not teach the particular claimed combination of adjuvants of the class of mineral salts with adjuvants of the class of glycosylamides, or octadecyl esters of aromatic amino acids, or the recited lipopeptides.” Id.

Richards, according to the rejection, “teaches adjuvant effects of liposomes, lipid A, and aluminum hydroxide (alum) are additive or synergistic, and results in the strongest immunization antibody response when compared to liposome alone, alum-adsorbed liposome, or liposome containing A.” Id. at 5-6.

Masihi is cited for teaching that the combination of adjuvants MPL and trehalose dimycolate resulted in complete protection against lethal influenza

virus infection, while the use of each adjuvant alone was ineffective. See id. at 6.

Stünkel is cited for teaching that the adjuvant glycosylamide N-2(deoxy-2-L-leucylamino- $\beta$ -D-glucopyranosyl)-N-octadecyldodecanomide acetate is known in the art, and is more effective than Freund's adjuvant and aluminum hydroxide. See id.

Penney is cited that octadecyl tyrosine hydrochloride is an effective organic adjuvant, and does not induce side effects such as granulomata as the site of injection as does aluminum. Id.

Weismüller is cited for teaching tripalmitoyl-S-glycerol-cyteinylserine covalently linked to a synthetic virus peptide vaccine, producing "long-lasting high protection against foot and mouth disease and serotype-specific virus-neutralizing antibodies in guinea-pigs after a single administration." Id.

Ramasamy is cited for teaching the linking of antigenic peptides to bovine serum albumin in combination with Freund's adjuvant or aluminum hydroxide to elicit antibodies. See id. at 8.

The rejection concludes:

It would have been prima facie obvious to one skilled in the art at the time the invention was made to generate an adjuvant composition, an immunogenic composition, and a kit comprising a mineral salt adjuvant, and an adjuvant selected from the group consisting of a glycosylamide, an ester of an aromatic amino acid, and a lipopeptide for the purpose of enhancing immunological responses of vaccinees [sic] to various antigens. Gupta teaches claimed adjuvants aluminum hydroxide, aluminum phosphate, calcium phosphate, and stearyl tyrosine, and the use of such adjuvants with antigens such as influenza hemagglutinin and pertussis toxoid, and the use of combinations of adjuvants.

Richards teaches adjuvant effects are additive or synergistic, and results in the strongest immunization antibody response when compared to adjuvants being used alone. Masihi also teaches combining adjuvants resulted in better protection against lethal influenza challenge, and the effectiveness of MPL adjuvant with influenza hemagglutinin subunit vaccine. . . . One skilled in the art would have been motivated to combine a mineral salt adjuvant with a second adjuvant for additive and synergistic effect for use in a vaccine formulation with a reasonable expectation of success. The use of adjuvants was well-known in the art. Combining adjuvants for enhancing immunological responses was also well known in the art, as evidenced by the applied prior art. All claimed adjuvants were known immunoadjuvants. Absent of evidence to the contrary, appellants' claimed invention would have been prima facie obvious to one of ordinary skill in the art at the time of the instant invention in view of the teachings of the prior art applied herein with a reasonable expectation of success.

Id. at 7-8.

Appellants argue there is no motivation provided in the references to combine a glycosylamide, an octadecyl ester of an aromatic amino acid, or a lipopeptide adjuvant with a mineral salt adjuvant as required by the claimed invention, and Stünkel and Penney suggests using the adjuvants they describe in the place of mineral salt adjuvants. See Appeal Brief, page 7. Thus, appellants conclude that the invention of the claims is not disclosed or suggestion by the combination of references relied upon. See id. at 8. We agree.

“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).

With respect to an obviousness rejection based on a combination of references, as the court has stated, “virtually all [inventions] are combinations of old elements.” Environmental Designs, Ltd. V. Union Oil Co., 713 693, 698, 218 USPQ 865, 870 (Fed. Cir. 1983); see also Richdel, Inc. v. Sunspool Corp., 714 F.2d 1573, 1579-80, 219 U.S.P.Q. (BNA) 8, 12 (Fed. Cir. 1983) (“Most, if not all, inventions are combinations and mostly of old elements.”). Therefore, an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. The United States Court of Appeals for the Federal Circuit, our reviewing court, however, has stated that “the best defense against hindsight-based obviousness analysis is the rigorous application of the requirement for a showing of a teaching or motivation to combine the prior art references.” Ecolchem, Inc. v. Southern California Edison Co., 227 F.3d 1361, 1371, 56 USPQ2d 1065, 1073 (Fed. Cir. 2000).

Gupta, Richards and Masihi are relied upon by the rejection as teaching the use of combinations of adjuvants. Richards, in particular, is used to provide the motivation to arrive at a combination of adjuvants as required by the instant claims. Specifically, according to the rejection, Richards teaches adjuvant effects are additive or synergistic, and results in the strongest immunization antibody response when compared to adjuvants being used alone.

Gupta teaches that “MPL [monophosphoryl lipid A] when incorporated into liposomes along with recombinant antigen of Plasmodium falciparum and mixed with alum, stimulated a high antibody response to the antigen with no

pyrogenicity or toxicity in humans.” Gupta, page 299. But Gupta also teaches that liposomes prolong the clearance of antigens, and the use of “consisting essentially of” in the claims excludes the use of liposomes, and there is no general teaching of the use of a mixture of two adjuvants.

Richards teaches that the combined effects of liposomes, lipid A and ALUM may induce antibody responses greater than those induced by ALUM alone, see Richards, page 685, and that “the adjuvant effects of liposomes, lipid A, and ALUM were additive or synergistic,” abstract. Again, there is no general teaching of the use of a mixture of two adjuvants.

Masihi, as recognized by the rejection, teaches that the combination of adjuvants MPL and trehalose dimycolate (TDM) resulted in complete protection against lethal influenza virus infection, while the use of each adjuvant alone was ineffective. See Masihi, abstract. The reference teaches that “[b]inding of MPL by the hydroxyl groups of TDM which remain anchored to the squalane droplet by embedded mycolic acid chains may prolong the retention of MPL and induce a persistent stimulation of the host system for a longer duration.” Id. at 344.

Therefore, each of the references relied upon by the examiner as teaching a combination of adjuvants, and thus providing motivation to arrive at the claimed combination of adjuvants, are drawn to a specific combination of adjuvants, and do not provide motivation to combine other adjuvants. In addition, as pointed out by appellants, Stünkel and Penney suggest using the adjuvants they describe in the place of mineral salt adjuvants, and thus teach away from the claimed combination.

In addition, the examiner appears to be asserting, that the teaching of a specific combination of adjuvants, such as those taught by Gupta, Richards and Masihi, would render obvious any combination of adjuvants. However, a broad disclosure of a genus does not render any species that falls within it obvious.

See In re Jones, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992); In re Baird, 16 F.3d 380, 382-83, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994).

CONCLUSION

Because the examiner has not set forth a prima facie case of obviousness, the rejection is reversed.

REVERSED

SHERMAN D. WINTERS	)	
Administrative Patent Judge	)	
	)	
	)	
	)	BOARD OF PATENT
DONALD E. ADAMS	)	
Administrative Patent Judge	)	APPEALS AND
	)	
	)	INTERFERENCES
LORA M. GREEN	)	
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