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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte CHRISTIAN MOSER, GIOVANNA ASSERO, EPIFANIO FICHERA, DARIO VENTURA, LAURENCE LEMPEREUR, and DIANA FELNEROVA

Appeal 2015-005571
Application 11/666,633¹
Technology Center 1600

Before DONALD E. ADAMS, RYAN H. FLAX and DAVID COTTA,
Administrative Patent Judges.

COTTA, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a virosome. The Examiner rejected the claims on appeal as obvious under 35 U.S.C. § 103(a).

We reverse.

¹ According to Appellants, the real party in interest is Crucell Holland B.V. App. Br. 2.

STATEMENT OF THE CASE

Claims 1–7 and 27–35 are on appeal. Claim 1 is illustrative and reads as follows:

1. A virosome comprising:
a virosomal membrane comprising at least one lipid, an envelope protein of influenza virus, and an envelope protein of hepatitis B virus (HBV); and
nucleocapsid particles comprising HBc protein of HBV, wherein the nucleocapsid particles are attached to the envelope proteins of HBV through an interaction between the envelope proteins of HBV and the HBc proteins of HBV, wherein a first plurality of the nucleocapsid particles so attached are located on the inside of the virosome, wherein a second plurality of the nucleocapsid particles so attached are located on the outside of the virosome, wherein the nucleocapsid protein HBc lacks an exposed lipophilic domain, and wherein the virosome is able to induce a therapeutic Th1 response to HBV infection.

The claims stand rejected as follows:

Claims 1–7, 27–30, and 32–34 under 35 U.S.C. § 103(a) as unpatentable over the combination of Huckriede,² Rubido,³ Bagai,⁴ Wilschut,⁵ and Evans.⁶

² Huckriede et al., *Influenza Virosomes in Vaccine Development*, 373 METHODS IN ENZYMOLOGY 74–91 (2003) (“Huckriede”).

³ Rubido et al., EP 1 346 727 A2, published Sept. 24, 2003 (“Rubido”).

⁴ Bagai et al., *Effect of Substitution of Hemagglutinin-neuraminidase with Influenza Hemagglutinin on Sendai Virus F Protein Mediated Membrane Fusion*, 353 FEDERATION OF EUROPEAN BIOCHEMICAL SOCIETIES LETTERS 332-336 (1994) (“Bagai”).

⁵ Wilschut et al., WO 95/32706, published Dec. 7, 1995 (“Wilschut”).

⁶ Evans et al., *Enhancement of Antigen-Specific Immunity via the TLR4 Ligands MPL™ Adjuvant and Ribi.529*, 2(2) EXPERT REV. VACCINES 219–229 (2003) (“Evans”).

Claims 31, 34 and 35 under 35 U.S.C. § 103(a) as unpatentable over the combination of Huckriede, Rubido, Bagai, Wilschut, Evans, Page,⁷ and Hershberg.⁸

Claim 35 under 35 U.S.C. § 103(a) as unpatentable over the combination of Huckriede, Rubido, Bagai, Wilschut, Evans, and Hershberg.

ANALYSIS

Because the same issues are dispositive for all three rejections, we address all three rejections together.

The Examiner found that Huckriede disclosed virosomes comprised of a liposome membrane including a lipid and envelope proteins of influenza virus (hemagglutinin (HA) and neuraminidase (NA)). Ans. 2. The Examiner further found that while Huckriede disclosed that the virosome was “capable of being loaded with foreign protein,” Huckreide did not “suggest the incorporation of HBV surface antigen (HBsAg) into the liposome membrane.” *Id.* at 3.

The Examiner found that Rubido disclosed “aggregated antigenic structures that form particles comprised of HBsAg and other antigen(s) of interest, such as HBcAg, among other viral envelope antigens.” *Id.* Based on the combined teachings of Huckriede and Rubido, the Examiner concluded:

[I]t would have been obvious to have included HBsAg in the formation of Huckriede’s influenza virosomes, given the suggestion by Huckriede to include foreign antigens. One would have been motivated to increase the valency of the virosome to include HBsAg in view of the fact that HBV is a

⁷ Page et al., US Patent Publication No. 2004/0156863 A1, published Aug. 12, 2004 (“Page”),

⁸ Hershberg, US Patent No. 4,624,918, issued Nov. 25, 1986 (“Hershberg”).

known human pathogen that can cause acute or chronic disease. One would have had a reasonable expectation of success that the HBsAg would be incorporated into a membrane along with influenza HA, NA and phospholipids in view of [] Rubido's teaching that the HBsAg and other viral envelope antigens are capable of aggregation.

Id. The Examiner found that the person of ordinary skill in the art would have had a reasonable expectation of success in formulating virosomes with two different sources of proteins based on Bagai's disclosure, which shows the formation of virosomes with two different sources of proteins, influenza envelope protein and Sendai virus F protein. *Id.*

Appellants argue, *inter alia*, that the cited references do not provide the person of ordinary skill in the art a reasonable expectation of successfully producing a virosome in which nucleocapsid particles of HBc are attached to envelope proteins of HBV on the inside and outside of the membrane. App. Br. 8–10.

Appellants cite Glück⁹ for the proposition that “a defining characteristic of virosomes is the retention of the functional envelope glycoproteins *in authentic conformation.*” App. Br. 9 (quoting Glück at 1140). Based on the propensity of glycoproteins to retain their authentic conformation, Appellants argue that, “[a]t most, the person of ordinary skill would have expected that HBs would partition into virosome membranes in the same orientation that [they] partition[] into biological membranes; *i.e.*, facing inwards.” *Id.* Appellants contend, that “[w]ithout an indication that the HBV envelope proteins could be integrated into virosomes in an

⁹ Glück et al., *Influenza Virosomes as an Efficient System for Adjuvanted Vaccine Delivery*, 4 Expert Opin. Biol. Ther. 1139–45 (2004).

outward-facing orientation (unlike their natural orientation in virus membranes), one of skill in the art would not have expected that HBc could be surface-displayed through an interaction with HBs on the external surface of a virosome (which is necessary for triggering a therapeutic immune response).” Appellants note that this was not achieved in the prior art, which includes only examples where “the viral protein of interest is a transmembrane or membrane-anchored structure.” *Id.* at 10.

Appellants further argue that “[p]roteins are delicate structures, and the claimed virosomes require more than the simple passage of material through several different phase transitions of surrounding lipid molecules.” *Id.* at 10. Applicants argue that it “would be just as likely as anything else that conditions resulting in outward-facing HBs virosome proteins would denature or modify the proteins such that they could not complex with HBc.” *Id.*

Based on the record before us, we find that Appellants have the better position. The Examiner relies on Rubido’s teaching – i.e. that HBsAg is capable of forming aggregates with other antigens including HBcAg – as providing a reasonable expectation that HBsAg and HBcAg would be incorporated into the virosome as claimed. Ans. 3. But, as Appellants correctly point out, the Examiner does not explain why “the mere fact that the proteins associate under some conditions mean[s] that they would be integrated into the virosome membrane under the conditions of virosome formation, in opposite and unnatural orientations.” App. Br. 8.

The Examiner contends that it does not matter that a person of ordinary skill in the art would not have expected a virosome to have the claimed configuration of HBsAg and HBcAg so long as there was a

motivation to incorporate HBsAg and HBcAg in a virosome, because the claimed configuration is “a natural outcome of combining HBsAg and HBc in the same process used by Appellant.” Ans. 8. This argument fails because the Examiner does not sufficiently establish that the prior art process is the same as the process described in the Specification. *In re Spada*, 911 F.2d 705, 709 (Fed. Cir. 1990); *Compare*, Ans. 10 (asserting that the processes are the same because both involve “solubilization with detergent, reduction of detergent, addition of antigen and removal of detergent”); *with* Specification 21 (“efficient HB-virosome assembly can only occur under optimized biochemical conditions and the correct stoichiometry [sic] of the individual components”).

The Examiner’s argument that the claimed configuration is the “natural outcome” of combining HBsAg and HBcAg in a virosome also fails because the Examiner has not established that a person of ordinary skill in the art would have expected to be able to associate **both HBsAg and HBcAg** in a single virosome. Appellants assert that the nucleocapsid protein HBcAg does not associate with membranes. App. Br. 7. The Examiner does not identify any prior art virosomes in which an antigen other than an envelope protein – i.e. an antigen like nucleocapsid protein HBcAg – is incorporated into the membrane of the virosome. Nor does the Examiner identify any prior art virosomes in which an antigen like nucleocapsid protein HBcAg is attached to an envelope protein that is incorporated in a virosome membrane. Absent an expectation that it would work, a person of ordinary skill would not have been motivated to incorporate HBsAg and HBcAg in a virosome according to Appellants’ claimed invention.

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The Examiner failed to establish that any of Wilschut, Evans, Page and Hershberg, alone or in combination, make up for the deficiencies discussed above. Accordingly, we reverse the Examiner's rejection of claims 1–7 and 27–35.

SUMMARY

For the reasons set forth herein the Examiner's final decision to reject claims 1–7, and 27–35 is reversed.

REVERSED