

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Ex parte ANTONIO MOLINAR, MARCO GERNA, CARLA GIORGETTI,
JACQUELINE LANSEN, and ROMEO RONCUCCI

Appeal No. 2001-1730
Application No. 08/603,182

ON BRIEF

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

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 22-26, which are all the claims pending in the application.

Claims 22 and 24 are illustrative of the subject matter on appeal and are reproduced below:

22. An immunogen consisting essentially of a set of hirudin polymers being devoid of any heterologous carrier protein and having sufficient immunogenicity, in the absence of conjugation to said carrier protein, to elicit an antibody which binds specifically to a natural or recombinant hirudin, and, the majority of said polymers having at least three monomer units, said monomers selected from the group consisting of HV1 (SEQ. ID NO:1), HV2 (SEQ. ID NO:2), and HV3(SEQ. ID NO:3).

24. A method of making an immunogen according to claim 22, consisting essentially of polymerizing said monomers of hirudin under conditions

such that a majority of polymers formed have at least 3 monomer units, said conditions including a molar excess of cross-linking agent relative to said monomers, and an absence of carrier protein.

The references relied upon by the examiner are:

Schlaeppli et al. ('443) EP 0,380,443 Aug. 1, 1990

Man et al. (Man), "Treatment of Human Muscle Creatine Kinase with Gluteraldehyde Preferentially Increases the Immunogenicity of the Native Conformation and Permits Production of High-Affinity Monoclonal Antibodies which Recognize Two Distinct Surface Epitopes," J. Immunological Methods, Vol. 125, pp. 251-259 (1989)

Maurer et. al. (Maurer), "Proteins and Polypeptide as Antigens," Methods in Enzymology, Vol. 70, pp. 49-70 (1980)

Schlaeppli J. (Schlaeppli), "Preparation of Monoclonal Antibodies to the Thrombin/Hirudin Complex," Thrombosis Research, Vol. 62, No. 5, pp. 459-470 (1991)

Spinner et al. (Spinner), "Quantitative Enzyme-Linked Immunosorbant Assay (ELISA) for Hirudin," J. Immunological Methods, Vol 87, pp. 77-83 (1986)

GROUND OF REJECTION

Claims 22-26 stand rejected under 35 U.S.C. § 103 as being unpatentable over '443 in view of Maurer and Man. Claims 22-26 stand rejected under 35 U.S.C. § 103 as being unpatentable over Schlaeppli in view of Maurer and Man. Claims 22-26 stand rejected under 35 U.S.C. § 103 as being unpatentable over Spinner in view of Maurer and Man.

We reverse.

DISCUSSION

As set forth in In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991), to establish a prima facie case of obviousness, there must be both some suggestion or motivation to modify the references or combine

reference teachings and a reasonable expectation of success. According to Appellants (Reply Brief, page 1), the claimed invention is drawn to a hirudin immunogen devoid of carrier protein. In this regard, Appellants allege the examiner erred finding all claims unpatentable under 35 U.S.C. § 103 because the references do not teach or suggest their combination and because the references do not provide a reasonable expectation of success of their combination. For the following reasons, we agree with Appellants.

I. '443 IN VIEW OF MAURER AND MAN:

According to the examiner (Answer, page 7), '443 discloses an immunogen conjugate comprising hirudin linked to a carrier protein. In this regard, the examiner finds (Answer, page 7):

Although ['443] does not specifically teach the presence of aggregated (i.e. polymerized) hirudins or hirudin peptides (i.e., hirudin-hirudin or hirudin peptide-hirudin peptide conjugates) in their immunogen preparation, it would have been obvious to one of ordinary skill in the art, as suggested in a specific example of ['443], that such aggregates would have been expected in those hirudin immunogen conjugates in which the formation of such aggregates was not specifically blocked by the optional step of blocking undesired reactive groups, amino groups in particular. . . . The teachings of ['443] differ from the invention as instantly claimed in conjugating hirudin or hirudin peptides with an additional carrier protein for use as an immunogen.

To make up for the deficiency in '443, the examiner relies on Maurer and Man. According to the examiner (Answer, page 8), Maurer teach the general proposition that “the greater the molecular weight and the more complex the structure of the macromolecule, the greater the immune response one would reasonably expect to obtain.” Therefore, the examiner concludes (Answer, page 9), that Maurer teaches, “it is advisable to aggregate a protein artificially in order

to enhance the immunogenicity of the protein.” Similarly, the examiner finds (id.), Man teach, “it is notoriously old and well known in the art that aggregated (i.e. polymerized) forms of monomeric proteins are more immunogenic.”

Based on this evidence, the examiner concludes (id.), it would have been obvious to one of ordinary skill in the art at the time of the instant invention was made to apply the teachings of Man or of Maurer for the purpose of enhancing immunogenicity. However, in contrast to the claimed invention, the examiner recognized that ‘443 took measures to ensure no hirudin polymerization took place. (Answer, page 7). As we understand the facts in evidence on this record, the relevant question is not whether a person of ordinary skill in the art at the time the invention was made could expect hirudin to polymerize or whether hirudin did in fact polymerize in the immunogen preparation of ‘443, but it is whether the prior art, taken as a whole, would have suggested to a person of ordinary skill in the art that the carrier molecule technique of ‘443 be abandoned in favor of the polymerizing/aggregating technique taught in Maurer and Man.

On the facts of this case, a proper 35 U.S.C. § 103 analysis requires consideration of two questions: was there a suggestion in the prior art to forgo the carrier protein in the method of ‘443 in favor of a hirudin polymer, and if so does the prior art provide a reasonable expectation of success that a hirudin polymer would elicit a favorable immune response? Vaeck.

We remind the Examiner, “[i]n determining whether the claimed invention is obvious, a prior art reference must be read as a whole and consideration must be given where the reference teaches away from the claimed invention. Akzo

N.V., Aramide Maatschappij v.o.f. v. United States Int'l Trade Comm'n, 808 F.2d 1471, 1481, 1 USPQ2d 1241, 1246 (Fed. Cir. 1986). In this regard, Appellants note (Reply Brief, bridging page 3 and 4), Man teach the lack of predictability of success in aggregating proteins. As we understand the reference, Man teaches (page 252) that aggregating large proteins is not generally advisable or necessary. We also note Man's observation (page 258) that similar proteins (creatine kinase) derived from different sources (human muscle and human brain), responded very differently to attempts at increasing immunogenicity through polymerization; polymerizing the muscle kinase increased immune response while polymerizing the brain kinase did not. Thus, to the extent that a hirudin polymer would have been contemplated by one of ordinary skill in the art, Man demonstrates that the results are unpredictable enough to yield very different results with two similar proteins. In our opinion, Man demonstrates that the prior art does not provide a reasonable expectation of success in producing an immunogenic hirudin polymer.

While Maurer teach both the carrier protein method and the polymerization method for the immunogenicity of molecules, Maurer provides no suggestion that the two methods are equivalent for hirudin or hirudin-like molecules. Consistent with the teachings of Man, Appellants note (Reply Brief, page 4), Maurer teach (page 57) that there is no absolute correlation between increased antigen size and increased immunogenicity. Furthermore, even if there was a suggestion in the art to combine the cited references, as we understand the evidence of record, neither Maurer nor Man support a finding that a person of ordinary skill in the art

would have had a reasonable expectation of success in producing an immunogenic hirudin polymer by modifying '443 with the teachings of Maurer and Man.

Accordingly, we reverse the rejection of claims 22-26 under 35 U.S.C. § 103 as being unpatentable over '443 in view of Maurer and Man

II. SCHLEAPPI IN VIEW OF MAURER AND MAN:

According to the examiner (Answer, page 7 bridging 8), Schlaeppi teach that conjugating hirudin to a carrier protein increases its immunogenicity. The examiner recognizes (id.), however, that Schlaeppi does not teach the blocking step used in '443. To make up for this deficiency, the examiner relies on Maurer and Man as set forth above. As we understand the examiner's position, Schlaeppi differs from '443 only in the omission of the optional step of protecting the hirudin amino groups. This difference, however, does not make up for the deficiencies set forth above. Accordingly, for the reasons set forth above, we reverse the rejection of claims 22-26 under 35 U.S.C. § 103 as being unpatentable over Schlaeppi in view of Maurer and Man

III. SPINNER IN VIEW OF MAURER AND MAN:

Spinner like '443 and Schlaeppi teach that a hirudin preparation is somewhat immunogenic (Answer, page 8). That hirudin is immunogenic, however, is not the issue. Instead, the issue is whether it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the teachings of Spinner with those of Maurer and Man to produce an immunogenic hirudin polymer. For the reasons set forth above, it is

our opinion that it is not. Accordingly, we reverse the rejection of claims 22-26 under 35 U.S.C. § 103 as being unpatentable over Spinner in view of Maurer and Man.

REVERSED

Sherman D. Winters)	
Administrative Patent Judge)	
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