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D E C I S I O N
of 12 February 2002

Case Number: T 0704/01 - 3.3.4

Application Number: 92903221.7

Publication Number: 0562020

IPC: A61K 37/22

Language of the proceedings: EN

Title of invention:
A vaccine against cholesterol to prevent hypercholesterolemia and atherosclerosis

Applicant:
EntreMed, Inc.

Opponent:
-

Headword:
Vaccine against cholesterol/ENTREMED,INC.

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (yes)"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T -0704/01 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 12 February 2002

Appellant: EntreMed, Inc.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 1 February 2001 refusing European patent application No. 92 903 221 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: A. L. L. Marie
S. U. Hoffmann

Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division to refuse the European Patent Application No. 92 903 221.7 under Article 97(1) EPC, because it does not involve an inventive step as required by Articles 52(1) and 56 EPC.

II. This decision was based on a set of 8 claims submitted with the letter of 30 June 1999, claim 1 of which read:

"1. Use of a composition comprising

A. biocompatible-biodegradable or biocompatible-nonbiodegradable liposomes, comprising

B. either,

(i) cholesterol; or

(ii) cholesterol and an adjuvant; or

(iii) cholesterol, phosphatidyl choline and an adjuvant; or

(iv) cholesterol, dimyristoyl phosphatidyl choline and adjuvant; or

(v) cholesterol and phosphatidyl choline; or

(vi) cholesterol and dimyristoyl phosphatidyl choline

for the manufacture of a vaccine for humans which

(a) prevents hypercholesterolemia and/or artherosclerosis caused by serum cholesterol or

(b) suppresses serum cholesterol and/or ameliorates artherosclerosis caused by serum cholesterol."

Claims 2 to 8 referred to further embodiments of the liposomes of claim 1.

III. The documents cited in the present decision are:

(1) G.M. Swartz Jr. et al., Proc. Natl. Acad. Sci. USA, March 1988, Vol. 85, pages 1902 to 1906

(6) J.M. Bailey et al., Nature, January 25, 1964, No. 4917, pages 407 to 408

(10) US 4,885,256

(16) Y. Charoenvit et al., Science, 8 February 1991, Vol. 251, pages 668 to 671

(17) S. Hoffman et al., Science, 26 April 1991, Vol. 252, pages 520 to 521

IV. The examining division considered that document (1), which was seen as the closest prior art, described the use of cholesterol enriched liposomes (71% cholesterol) to elicit upon injection in mice an immunogenic answer leading to the formation of antibodies against cholesterol and, after fusion of mice spleen cells with myeloma cells, to hybridomas secreting said anti-cholesterol antibodies. Document (1), quoting

"reference (4)" (which is in the present procedure referred to as document (6)), also mentioned that antibodies against cholesterol had already been reported to protect rabbits fed with a high cholesterol diet from induced atherosclerosis. The examining division defined the problem to be solved in view of the disclosure of document (1) as the extension of this teaching to humans. Considering that the finality of this kind of experiments was always the improvement of human healthcare, the examining division concluded that the technology transfer from animals (mice and rabbits, in this case) to humans was obvious and that success was to reasonably be expected.

V. In his grounds for the appeal the appellant followed several lines of argumentation in favour of the involvement of an inventive step in the application. He first argued that document (1) described the production of anti-cholesterol antibodies, but gave no hint to use the liposomes as vaccine for the treatment or prevention of atherosclerosis or diseases caused by high cholesterol concentrations and related this to the fact that epitopes may well lead to the production of antibodies, but not necessarily to an appropriate immune response resulting in the possibility of treating a given disease. In support of this argument, the appellant cited *inter alia* documents (16) and (17). Furthermore, contrary to those of the application, the antibodies of document (1) only reacted with "high cholesterol content"-liposomes, whereas the natural transport form of cholesterol in blood (LDL) had to be considered as a "low cholesterol content"-liposome, since it contained no more than 50% cholesterol.

Another line of argumentation related to the fact that

the antigen of document (6), referred to as "reference (4)" in document (1), a cholesterol ester-albumin conjugate, was different from the liposomes used in the application.

The applicant also pointed at the fact that the protection against diseases caused by high levels of cholesterol by anti-cholesterol antibodies as demonstrated in the application was surprising for the skilled person, since document (1) stated that antibodies to cholesterol could play a role in the pathogenesis of atherosclerosis and would amplify the disease instead of curing it. The immunization described in document (1) was also not comparable to the use, as in the application, of cholesterol-containing liposomes as vaccine against hypercholesterolemia and atherosclerosis, since hypercholesterolemia and atherosclerosis are not normal diseases for mice that would be considered as reasonable targets for preventive measures. Further, the cholesterol formulation was only injected once according to the immunization process of document (1) and the cholesterol content of the blood after injection was not determined.

The appellant also argued that the antibodies of document (10) are only specific for "high cholesterol content"-liposomes and they are used as probes and analytical tools for detecting high concentrations of cholesterol in biological specimens, but not as drugs for the treatment of hypercholesterolemia and/or atherosclerosis. Therefore, a combination of the teaching of documents (1) and (10) did not render the claimed subject-matter of the application deprived of inventive step.

VI. Oral proceedings have not been requested by the appellant.

The appellant requested that the decision under appeal be set aside and that the claims 1 to 8 submitted with the letter of 30 June 1999 be acknowledged as involving an inventive step over the cited prior art and thereby implicitly requested that a patent be granted.

Reasons for the Decision

Articles 123(2), 54, 84 EC

1. The examining division raised no objection against the claims submitted with the letter of 30 June 1999 in view of these Articles. Nor does the Board.

Article 56 EPC

2. The closest prior art is in the Board's view document (1), which discloses the production of anti-cholesterol antibodies after immunization of mice with liposomes containing high amounts of cholesterol (71 mol% relative to phosphatidylcholine) and lipid A as adjuvant. Immunization is performed with a single injection of the liposomes and, 3 days after immunization, mice spleen cells are fused with myeloma cell line P3-X63-Ag8.653 to produce hybridomas secreting said antibodies. These antibodies are able to bind crystalline cholesterol and "71% cholesterol"-liposomes, but are non-reactive with liposomes containing only 43% cholesterol. Furthermore, document (1), quoting document (6) as "reference (4)", indicates on pages 1902 and 1905 (left column) that

rabbits immunized with cholesteryl ester-albumin conjugates are resistant to development of atherosclerotic plaques induced by cholesterol feeding.

3. In view of this closest prior art, the technical problem to be solved can be defined as providing means for the prevention and/or cure of diseases related to high cholesterol concentrations in humans.

4. The claimed use of cholesterol containing liposomes as a vaccine for humans has solved this technical problem as demonstrated by Table 1 of the application in suit.

5. The question to be answered in view of Article 56 EPC is whether the use of cholesterol containing liposomes as a vaccine in humans was obvious for the skilled person as far as the prevention and/or cure of diseases due to high cholesterol concentrations are concerned. A basis for the answer to this question lies in the thorough analysis of the teaching of document (1) and document (6), to which document (1) makes reference, and thus in the result of the analysis of the two following points:

- does document (1) suggest the use of liposomes as vaccine against hypercholesterolemia and atherosclerosis, ie would the skilled person interpret document (1) in such a way as to make a link between anti-cholesterol antibodies and cholesterol-based diseases?

- does document (6) demonstrate that the antibodies resulting from the immunization process described react with cholesterol?

6. Document (1) is not concerned with the treatment of diseases related to cholesterol, such as hypercholesterolemia and/or atherosclerosis. It focuses on the production of antibodies specifically directed to cholesterol. Its purpose lies on the fundamental research level and aims at demonstrating that, contrary to the belief of the skilled person at that time, cholesterol is a potent immunogenic substance (abstract and introduction on page 1902). This target is achieved as soon as document (1) describes a method for preparing anti-cholesterol antibodies and the thus obtained antibodies. This constitutes what could be called the "factual teaching" of document (1).

7. Document (1) also mentions the context, in which this teaching has to be seen, and makes therefor reference to results, observations and/or hypotheses, which have been described or made by others. In that sense, document (1) refers to document (6), as "reference (4)" (page 1902), and to other documents (not cited in the present case), as "references (6, 9, 11)" (pages 1902 and 1906), which put the accent on a possible involvement of cholesterol and anti-cholesterol antibodies in the pathogenesis of atherosclerosis and/or its treatment. This constitutes what could be called the "reported teaching" of document (1).

8. This "reported teaching" is in the Board's opinion confusing, contradictory in itself and teaches away from the solution given in the claims of the application.

9. First of all, it is unclear **which** role could play the activation of complement by antibodies to cholesterol in the pathogenesis of atherosclerosis (document (1),

page 1906, left column, last paragraph, second sentence). It cannot be excluded that antibodies to cholesterol could play a **negative** role, ie amplify said pathogenesis.

10. Further, a negative impact of anti-cholesterol antibodies can also be drawn from the "reported teaching" of document (1) concerning "references 6, 9, 11" (page 1906) indicating that an IgG antibody specifically reacting with crystalline cholesterol activated the classical pathway of complement in a patient with ulcerating atherosclerosis and precising that complement activation by crystalline cholesterol might serve as a potential amplifier of atherosclerotic ischemic damage. The skilled person would thus assume that anti-cholesterol antibodies by activating the complement pathway might amplify the atherosclerosis pathogenesis.

11. In the Board's view this would hardly prompt the skilled person to use cholesterol containing liposomes as a vaccine to prevent or cure atherosclerosis and in fact teaches away from the solution proposed in the present application.

12. Furthermore, this part of the "reported teaching" of document (1)(cf. points 9 and 10) appears to be in contradiction with another part of the "reported teaching" of document (1) concerning document (6), mentioned as "reference (4)", which seems to imply a curative effect of anti-cholesterol antibodies (page 1902 left column, first paragraph, penultimate sentence).

13. Therefore, the Board considers that document (1) is, as

far as the possibilities of using compositions resulting in the production of anti-cholesterol antibodies for the prevention and/or cure of diseases related to high cholesterol concentrations, confusing and self-contradictory. Thus the skilled person is not led to assume that such compositions and/or the resulting anti-cholesterol antibodies may be efficient in the prevention and/or treatment of diseases caused by high cholesterol concentrations. Document (1) only demonstrates the binding of the antibodies obtained to cholesterol, however, it is part of the common general knowledge that not all the antibodies which bind to a given molecule may prevent or cure a disease related to said molecule, as shown *inter alia* by documents (16) and (17), cited as expert opinions.

14. On the other hand, as far as the reference to document (6) is concerned, it should first be determined what precisely is its teaching and, then, whether its combination with document (1) would lead the skilled person in an obvious way to the claimed solution.

15. Document (6) describes an immunization process with cholesterol ester-bovine albumin conjugates containing 9.5 moles of cholesterol per mole of albumin and its influence on the atherosclerotic process in rabbits fed with a high cholesterol diet. No antibody possibly resulting from this immunization process has been characterized.

16. First of all, the antigen used in document (6) is not the same as that of the present application: it is not a liposome composed of cholesterol, phosphatidyl choline, dimyristoyl phosphatidyl choline and/or lipid A, but a cholesterol ester-albumin conjugate.

Document (6) thus does not use cholesterol as in the present application, but cholesterol esters, the increase of which is said to be more closely related to atherosclerosis than that of free cholesterol (page 407, left column). Document (6) hence already points at a difference between cholesterol (used as an antigen in the present application) and cholesterol esters in relation to atherosclerosis.

17. Further, document (6) does not demonstrate that cholesterol esters conjugated to albumin immunologically behave as the cholesterol of the present application.

18. Moreover, nothing can be drawn from document (6) about the influence of the albumin moiety of the conjugate on the "presentation" of the cholesterol esters to the immune system. This "presentation" may result in the fact that an epitope may be recognized on the cholesterol ester molecule which is different from that of the cholesterol contained in the liposomes of the application. It may as well result in the fact that the epitope(s) on the cholesterol molecule is (are) no longer accessible for the immune system.

19. The necessity of a very cautious attitude in drawing conclusions from document (6) in view of the described immunization process is even strengthened by the analysis of Table 2, which summarized the comparative results obtained with immunized and non-immunized rabbits fed with a diet enriched in cholesterol by reference to four parameters: the total lipid content, the total cholesterol content, the ratio cholesterol ester/free cholesterol and the atherosclerotic plaque.

Whereas the total cholesterol content and the ratio cholesterol ester/free cholesterol are modified, the main impact of this immunization process seems nevertheless to be on the **total lipid concentration** (page 407, bottom of right column). Indeed, whereas the total cholesterol content between Groups III and IV animals goes from 1362 mg/100 ml to 1020 mg/100 ml (ie a 25% change) and the ratio cholesterol ester/free cholesterol from 1.8 to 2.2 (ie a 33% change), the total lipid concentration goes from 4497 mg/100 ml to 2682 mg/100 ml (ie a **40%** change). Albumin, which is, as a high molecular weight protein, immunogenic by itself, is generally known as a carrier molecule for (among others) lipids and steroids. Antibodies reacting with albumin would thus most probably also induce modifications of the total lipid, cholesterol content, cholesterol ester/free cholesterol ratio and plaque grade. So that it is not possible in the Board's opinion to conclude from document (6) that the results disclosed in Table 2 can be explained by the presence of antibodies directed against cholesterol esters as a result of the immunization process. They could as well be explained by the production of antibodies directed against the albumin moiety. This explanation appears even more likely, since the main impact of said immunization process is, according to Table 2, on the total lipid concentration. It has to be kept in mind, in this context, that, in document (6), the specificity of the antibodies has not been checked: they have been assumed to be directed to cholesterol, but document (6) does not demonstrate that they interact with, for instance, crystalline cholesterol, cholesterol containing liposomes or even with cholesterol esters.

20. Therefore, the skilled person would not consider for

sure that the immunization process of document (6) leads to the production of anti-cholesterol antibodies and would hence not combine the teachings of documents (1) and (6).

21. The Board further shares the applicant's view concerning document (10) and its reference to the importance of the anti-cholesterol antibodies in the **treatment** of disease states involving accumulation of cholesterol or disorder of cholesterol or lipoprotein metabolism (column 5, lines 36 to 40). Indeed, apart from the fact that said disease states are not precisely defined, it can be deduced from the sentence in column 5, lines 24 to 36 that the characteristics, which make these antibodies suitable for diagnosis and treatment, are their excellent specificity for high cholesterol liposomes and their unreactivity to low cholesterol liposomes, which results in their ability to determine the presence and location of high cholesterol concentrations. In other words, these antibodies are only useful in the treatment of atherosclerosis as **diagnosis tools**, but not as therapeutic drugs. Thus, document (10) does not add anything to the teaching of document (1): it only confirms said teaching by showing that anti-cholesterol antibodies bind to cholesterol. However, as document (1), document (10) does not demonstrate or suggest that anti-cholesterol antibodies may be used as therapeutic drugs for the prevention and/or treatment of diseases related to high cholesterol concentrations. Therefore, the skilled person would have had no reason to combine the teachings of documents (1) and (10).

22. Therefore, the Board is of the opinion that it was not obvious to use the liposomes of document (1),

considered alone or in combination with documents (6) and/or (10), as a vaccine to prevent and/or cure atherosclerosis and/or hypercholesterolemia in humans and that the teaching of document (1), combined or not with document (6), would even have taught away from such an use. The Board therefore concludes that claims 1 to 8 submitted with the letter of 30 June 1999 fulfil the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to grant a patent based on claims 1 to 8 submitted with the letter of 30 June 1999, and a description adapted thereto.

The Registrar: The Chairwoman:

P. Cremona U. Kinkeldey