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D E C I S I O N
of 3 November 2004

Case Number: W 0023/03 and W 0018/03 - 3.3.2

Application Number: PCT EP01/11485

Publication Number: W0 02/24194

IPC: A61K 31/22

Language of the proceedings: EN

Title of invention:
Use of statins (HMG-CoA reductase inhibitors) for the preparation of medicament as a novel type of immunomodulator, immunosuppressor and anti-inflammatory agent"

Patentee:
NOVIMMUNE S.A.

Opponent:
-

Headword:
Use of statins/NOVIMMUNE S.A.

Relevant legal provisions:
PCT Art. 17(3)a, 34(3)a
PCT R. 40, 68.3(e), 13.1

Keyword:
"Consolidation request granted: same claims, analogous argumentation"
"The different pathways are not reflected in distinguishable technical effects"

Decisions cited:
T 0290/86, T 0254/93, T 0241/95

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: W 0023/03 and W 0018/03 - 3.3.2

International Application No. PCT/EP 01/11485

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 3 November 2004

Applicant: NOVIMMUNE S.A.
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Representative: Ernest Gutmann - Yves Plasseraud S.A.
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Decision under appeal: **Protest according to Rule 40.2(c) of the Patent Cooperation Treaty made by the applicants against the invitation (payment of additional fees) of the European Patent Office (International Searching Authority) dated 5 June 2002 / Protest according to Rule 68.3(c) of the Patent Cooperation Treaty made by the applicants against the invitation of the European Patent Office (International Preliminary Examining Authority) to restrict the claims or pay additional fees dated 13 February 2003.**

Composition of the Board:

Chairman: U. Oswald
Members: M. Ortega Plaza
B. Günzel

Summary of Facts and Submissions

I. The applicant filed an international patent application PCT/EP 01/11485 comprising a set of 93 claims. Claims 1 to 26, 31 to 46, 49 to 59, 68 to 84 and 86 to 92 have not been searched or examined in view of the fact that they relate to methods for treatment of the human or animal body by therapy (Rule 39.1 iv) PCT).

Moreover, the search report was incomplete since it has been carried out for those parts of the claims which appeared to the International Searching Authority (ISA) to be supported and disclosed (Articles 5 and 6 PCT), namely those parts relating to the diseases: type I diabetes, multiple sclerosis, rheumatoid arthritis, Chron's disease, lupus erythematosus, psoriasis, eczema, uveitis and those parts relating to the compounds structurally equivalent to statins.

The relevant claims for the unity assessment read as follows:

"27. A method for identifying molecules that inhibit IFN-γ induced CIITA expression, said inhibition being at least partially reversible by addition of L-mevalonate, comprising the steps of:

- contacting a cell which is IFN-γ responsive with a candidate inhibitory molecule and with IFN-γ;

- detecting the inhibition or absence of CIITA expression or MHC class II expression in the presence of the candidate molecule;

– further contacting the cell with L-mevalonate; and

– detecting a total or partial reversal of the inhibitory effect."

"28. A method for identifying molecules that inhibit IFN-γ induced CIITA expression, comprising the steps of:

– contacting a cell which is IFN-γ responsive with a statin, or a functional or structural equivalent thereof, and with IFN-γ;

– detecting the inhibition or absence of CIITA expression or MHC class II expression in the presence of the statin, or a functional or structural equivalent thereof."

"29. A method for identifying molecules that inhibit induced CD40 expression, said inhibition being at least partially reversible by addition of L-mevalonate, comprising the steps of:

– contacting a cell with a candidate inhibitory molecule and with the molecule inducing CD40 expression;

– detecting the inhibition of CD40 expression in the presence of the candidate molecule;

– further contacting the cell with L-mevalonate; and

– detecting a total or partial reversal of the inhibitory effect."

Claim 30 is a dependent claim of claim 29.

"47. Use of a statin , or a functional or structural equivalent molecule, for the preparation of a medicament for treating an autoimmune disease or an immuno-inflammatory disease, such statin being present in an amount effective modulate IFN-γ inducible MHC class II expression and/or CD40 expression, thereby alleviating at least partially the symptoms of said disease."

"48. Use according to claim 47 wherein the disease is rheumatoid arthritis."

"60. Use of a statin, or a functional or structural equivalent molecule, for the preparation of a medicament for reducing inflammation or for reducing tissue rejection, or both, such statin being present in an amount effective to inhibit IFN-γ inducible MHC Class II expression or CD40 expression such that inflammation or tissue rejection, or both is reduced, for administration to a subject before, during or after a tissue graft."

Claims 61 to 63 are dependent claims of claim 60.

"64. A kit comprising a tissue graft material and a statin, or a functional or structural equivalent molecule, either in the same or separate packaging."

Claims 65 to 67 are dependent claims to claim 64.

"85. Use of a statin , or a functional or structural equivalent molecule in the preparation of a medicament for reducing inflammation in an inflammatory skin disorder, such statin being present in an amount effective for reducing inflammation."

"93. Use of a statin , or a functional or structural equivalent molecule, in the preparation of a medicament for reducing inflammation in an inflammatory ocular disorder, such statin being present in an amount effective for reducing inflammation."

II. By the communication of 5 June 2002, the European Patent Office, acting as an International Searching Authority (ISA), invited the applicant pursuant to Article 17(3)(a) and Rule 40.1 PCT to restrict the claims or to pay nine additional search fees.

The ISA raised an objection of lack of unity a priori for the inventions of groups 1 and 2 since MHC Class II and CD40 were two distinguishable genes which had nothing in common which each other.

Referring to documents (9) WO-A-92 19105, (10) WO-A-99 26657 and (11) WO-A-00 48989 the ISA raised an objection of lack of unity a posteriori. The ISA considered that the common concept linking the inventions 3 to 10 (which was the use of statin for the treatment of autoimmune diseases or for the reduction of graft rejection) was known from the said documents since statins were used to treat the claimed pathologies (i.e. type I diabetes, multiple sclerosis, rheumatoid arthritis, Chron's disease, lupus erythematosus, psoriasis, eczema, uveitis, reduction of

graft rejection). The claimed inventions were further split up by the ISA since the remaining common concept related to two different modes of action (i.e. the regulation of MCH Class II and of CD40).

In view of these findings the ISA considered that the searchable claims covered ten different inventions or groups of inventions:

Group 1: claims 27 and 28 as far as they related to a method of identifying molecules that inhibit the expression of CIITA or MCH Class II.

Group 2: claims 29 and 30 as far as they related to a method for identifying molecules that inhibit the expression of CD40.

Group 3: claims 47 and 48 (partly) as far as they related to the use of a statin for the preparation of a medicament for the treatment of autoimmune diseases such as rheumatoid arthritis (RA) wherein the statin is present in an amount effective to modulate the expression of MHC Class II.

Group 4: claims 60 to 67 (partly) as far as they related to the use of a statin for the preparation of a medicament for the reduction of graft rejection wherein the statin is present in an amount effective to modulate the expression of MHC Class II.

Group 5: claim 85 (partly) as far as it related to the use of a statin for the preparation of a medicament for the treatment of skin disorders wherein the statin is

present in an amount effective to modulate expression of MHC Class II.

Group 6: claim 93 (partly) as far as it related to the use of a statin for the preparation of a medicament for the treatment of ocular disorders wherein the statin is present in an amount effective to modulate expression of MHC Class II.

Group 7: claims 47 and 48 (partly) as far as they related to the use of a statin for the preparation of a medicament for the treatment of autoimmune diseases such as rheumatoid arthritis (RA) wherein the statin is present in an amount effective to modulate the expression of CD40.

Group 8: claims 60 to 67 (partly) as far as they related to the use of a statin for the preparation of a medicament for the reduction of graft rejection wherein the statin is present in an amount effective to modulate the expression of CD40.

Group 9: claim 85 (partly) as far as it related to the use of a statin for the preparation of a medicament for the treatment of skin disorders wherein the statin is present in an amount effective to modulate expression of CD40.

Group 10: claim 93 (partly) as far as it related to the use of a statin for the preparation of a medicament for the treatment of ocular disorders wherein the statin is present in an amount effective to modulate expression of CD40.

III. By its reply dated 5 July 2002, the applicant paid nine additional search fees under protest pursuant to Rule 40.2(c) PCT.

In support of the protest the applicant argued that the application in suit contained, at the most, two distinct inventions. The applicant stated that the first group of inventions related to groups 1, 3, 4, 5 and 6 identified by the ISA and the technical relationship between them was the identification of the inhibitory effect of statins on IFN-γ induced MHC class II expression. This technical effect was reflected in a process claims of group 1 identified by the ISA and for treating auto-immune or immuno-inflammatory diseases, such as rheumatoid arthritis, rejection of graft transplant, skin disorders or ocular disorders (groups 3, 4, 5, 6 identified by the ISA). This common concept was neither disclosed nor suggested in the prior art before the effective date and could be acknowledged as the general inventive concept for the first group of inventions (groups 1, 3, 4, 5 and 6 identified by the ISA).

In analogy to the above the second group of inventions incorporated the groups 2, 7, 8, 9 and 10 identified by the ISA and the technical relationship between them was the identification of the inhibitory effect of statins on IFN-γ induced CD40 expression. The arguments put forward for the first group applied mutatis mutandis to the second group of inventions.

IV. In a prior review pursuant to Rule 40.2(e) PCT dated 9 October 2002, the review panel of the ISA found the invitation to pay additional fees to be partly

justified and on the one hand invited the applicant to pay the protest fee and on the other it refunded four search fees. In substance the review panel agreed with the lack of unity a priori for the groups of inventions 1 and 2 identified by the ISA. In its further opinion the review panel considered that the elucidation of the underlying mechanisms of the inhibitory effects of statin on IFN-γ induced MCH class II expression or IFN-γ induced CD40 expression, respectively, did not contribute to the achievement of a new therapeutic effect as far as the technical effect obtained remained the same (treating the same disease), since a new therapeutic window was not opened.

The review panel did not share the division of the following four groups of claims: claims 47-48, claims 60-67, claim 85 and claim 93 into eight groups of inventions due to the different mode of action. In the review panel's view to make a distinction in this respect, based on the mode of action, could only have been justified if the respective subject-matter involved a new technical effect in the claimed therapeutic application, whereby a new therapeutic window would have been opened. It would have been conceivable that treatment of a disease with different amounts of a medicament could have lead in certain cases to different therapeutic effects in relation to the same therapeutic application. However, the description of the application in suit did not provide any indication in this respect.

In summary, the review panel identified six inventions: the combined inventions 3 and 7 as identified by the ISA, the combined inventions 4 and 8 as identified by

the ISA, the combined inventions 5 and 9 as identified by the ISA, and the combined inventions 6 and 10 as identified by the ISA.

V. By a letter of 11 November 2002, received on 11 November 2002, the applicant paid the protest fee according to Rule 40.2(e) PCT and submitted a statement of grounds and detailed arguments why it disagreed with first the ISA's position and second with the panel's position.

The applicant submitted as in its letter of 5 July 2002 that the application in suit contained at most two inventions. The unifying concept being either the modulation by statins, or their functional equivalents, of the expression of MCH class II or the modulation by statins, or their functional equivalents, of the expression of CD40 respectively.

The applicant denied the correctness of identifying the unifying concept on the basis of groups of pathologies to be treated. The distinction between the groups should be made in the applicant's opinion on the basis of the immune pathway involved in the treatment, i.e. either the modulation of the expression of MCH class II, or the modulation of the expression of CD40.

The applicant argued (i) that the pathways defined in the application in suit were not merely an elucidation of the underlying mechanism, (ii) that the effects of statins on these pathways constituted novel therapeutic indications; and (iii) that the therapeutic effects thus formed novel unifying concepts providing a legally

valid basis for the grouping of the inventions disclosed in the application in suit.

With respect to (i) the applicant stated that the pathways disclosed in the application in suit were not the sole pathways which could come into play when statins were administered to a patient in the context of immune and inflammatory pathologies. The disorders involving the immune system (such as auto-immune diseases or graft rejection) were highly complex and involved many different immune pathways, mediators and effectors. A drug may act on one or more different aspects of the same disease and may exert one or more therapeutic effects in the context of the same disease.

With respect to (ii) the applicant referred to the case law of the boards of appeal and to decision T 290/86, OJ EPO, August 1992, 414-427.

It would not be concluded that the effects disclosed in the documents (9), (10) or (11) were the result of immunomodulation involving MHC class II or CD40 regulation by statins.

With regard to (iii) the applicant stated that it did not contest the lack of unity a priori because MHC class II and CD40 were two distinct unrelated genes. However, it was a contradiction not to allow the medical indications to be grouped according to the gene involved in the regulation by statins.

VI. By the communication of 13 February 2003, the European Patent Office, acting as an International Preliminary Examining Authority (IPEA), pursuant to Article 34(3)(a)

and Rule 68.2 PCT informed the applicant that the application did not comply with the requirements of unity of invention (Rule 13.1, 13.2 and 13.3 PCT) and invited the applicant to restrict the claims or to pay five additional preliminary examination fees.

The IPEA raised an objection of lack of unity a priori for the inventions of groups 1 and 2 since MHC Class II and CD40 were two distinguishable genes which had nothing in common which each other.

Referring to documents (9) WO-A-92 19105, (10) WO-A-99 26657 and (11) WO-A-00 48989 together with documents (12) to (17) and (19) (numbered in their order of appearance in the search report) the IPEA raised an objection of lack of unity a posteriori. The IPEA considered that the common concept linking the inventions 3 to 6 (which was the use of statin for the treatment of autoimmune diseases or for the reduction of graft rejection) was known from the said documents since statins were used to treat the claimed pathologies (i.e. type I diabetes, multiple sclerosis, rheumatoid arthritis, Chron's disease, lupus erythematosus, psoriasis, eczema, uveitis, reduction of graft rejection).

With respect to the wording "such statin being present in an amount effective to modulate IFN-γ inducible MHC class II expression and/or CD40 expression" appearing in claims 47 and 60 the IPEA considered that "even if this technical effect is not described in the prior art, this one is **implicit** because the administration of statins in the present application at the same dose as described in the prior art will **automatically** inhibit

the expression of IFN-gamma inducible MHC-Class II or CD40- even if the public was not aware of it. Therefore this technical effect is not considered as an effect which can confer novelty and inventive step to the common concept."

The IPEA also cited decisions T 254/93 (OJ EPO 1998, 285) and T 241/95 (OJ EPO 2001, 103).

In view of these findings the IPEA considered that the searchable claims covered six different inventions or groups of inventions:

Group 1: claims 27 and 28 as far as they related to a method of identifying molecules that inhibit the expression of CIITA or MCH Class II.

Group 2: claims 29 and 30 as far as they related to a method for identifying molecules that inhibit the expression of CD40.

Group 3: claims 47 and 48 as far as they related to the use of a statin for the preparation of a medicament for the treatment of autoimmune diseases such as rheumatoid arthritis (RA) wherein the statin is present in an amount effective to modulate the expression of MHC Class II or CD40.

Group 4: claims 60 to 67 as far as they related to the use of a statin for the preparation of a medicament for the reduction of graft rejection wherein the statin is present in an amount effective to modulate the expression of MHC Class II or CD40.

Group 5: claim 85 as far as it related to the use of a statin for the preparation of a medicament for the treatment of skin disorders wherein the statin is present in an amount effective to modulate expression of MHC Class II or CD40.

Group 6: claim 93 as far as it related to the use of a statin for the preparation of a medicament for the treatment of ocular disorders wherein the statin is present in an amount effective to modulate expression of MHC Class II or CD40.

VII. By its reply dated 13 March 2003, the applicant paid five additional preliminary examination fees under protest pursuant to Rule 68(3)(c) PCT.

In support of the protest the applicant argued that the application in suit contained, at the most, two distinct inventions. With respect to the reasons therefor the applicant made reference to its letters of 5 July 2002 and of 11 November 2002, received on 11 November 2002, sent for the same application with respect to the lack of unity of invention raised by the ISA and sent a copy of the second.

VIII. In a prior review pursuant to Rule 68.3 (e) PCT dated 3 June 2003, the IPEA found the invitation to pay additional fees to be justified.

In substance the review panel agreed with the finding of lack of unity a priori for the groups of inventions 1 and 2 identified by the IPEA. Furthermore the review panel considered that the elucidation of the underlying mechanisms of the inhibitory effects of statin on IFN-γ

induced MCH class II expression or IFN-γ induced CD40 expression, respectively, did not contribute to the achievement of a new therapeutic effect as far as the technical effect obtained remained the same (treating the same disease), since a new therapeutic window was not opened.

IX. By a letter of 2 July 2003, the applicant paid the protest fee according to Rule 68.3(e) PCT. With respect to the statement of grounds for the protest it referred to its letter of 11 November 2002 filed in the same application with respect to lack of unity objection raised by the ISA.

Reasons for the Decision

1. The protests comply with the requirements of Rules 40.2 and 68.3(c) and (e) PCT and are therefore admissible.

2. In the present application the ISA and the IPEA raised each an objection of lack of unity of the invention and invited the applicant to restrict the subject-matter claimed or to pay additional fees. The applicant paid in both cases under protest and it also paid the protest fee for both cases. The applicant has requested the consolidation of both protest cases with a letter of 2 July 2003. Its reasons are that both pending cases concern protest against the same non-unity objections for the same application.

In both cases the same set of claims is to be examined.

Moreover, the objection made by the ISA to divide the inventions of groups 3 to 10 from four into eight groups of inventions is not subject to review by the board since a refund of the search fees has already taken place insofar.

Accordingly, there are six groups of inventions left in both cases which ISA and IPEA have found not to be unitary for the same or analogous reasons.

Consequently, the board grants the applicant's request for consolidation.

3. The applicant did not contest the accurateness of the objection of lack of unity a priori and insofar did not ask for a refund of fees. Accordingly, the board sees no reason to comment it further irrespective of the fact whether the a priori objection was well founded or not.

The board agrees with the ISA and the IPEA in that the use of a statin or structural equivalent molecule for the preparation of a medicament for the treatment of autoimmune disease or immuno-inflammatory disease is known from documents (9), (10) and (11). The applicant has not denied this point.

In view of the fact that statins and structural equivalent molecules are known to be useful for the treatment of autoimmune diseases or immuno-inflammatory diseases the subject-matter claimed disintegrates into a multitude of uses relating to the different diseases to be treated.

As regards the applicant's arguments, even if the board agrees that the pathways disclosed in the application in suit are not merely explanations of previously described effects but are new pathways found with the application in suit, the fact is that when a medicament is administered for treating an autoimmune or immuno-inflammatory disease it cannot be distinguished which pathway it undergoes. Indeed both pathways, the known pathway and the newly discovered pathway will be involved when a statin is used in treating an autoimmune or immuno-inflammatory disease. The applicant has failed to demonstrate that different aspects of the same disease are targeted when a statin is administered according to the application in suit in comparison to the prior art. There is no disclosure in the application in suit that the amounts used of the medicament can regulate the choice of one pathway instead of another. On the contrary, in the passage bridging pages 22 and 23 of the application in suit it is said that: "As for every drug, the dosage is an important part of the success of the treatment and the health of the patient. The degree of efficiency as immunomodulator, immunosuppressor or anti-inflammatory agent depends on the statin or derivative used. An appropriate amount is comprised for example between about 1 and about 500 mg per day and more preferably 10 and 80 mg per day. Most preferably, when using a commercially available statin, between 20 and 40 mg per day for currently used statins." "In every case, in the specified range, the physician has to determine the best dosage for a given patient, according to his sex, age, weight, pathological state and other parameters."

Therefore the ISA correctly ignored the feature appearing in claims 47 and 60 "such statin being present in an amount effective to modulate IFN-γ inducible MHC class II expression and/or CD40 expression" for its considerations when identifying the common general concept since it does not make a distinction over the prior art.

The board is of the opinion that the immune pathway involved cannot be taken as a special technical feature within the meaning of Rule 13.1 PCT for the second medical use claims since it cannot be taken as contribution to the prior art.

The board agrees with the applicant in that the unifying concept does not require to be necessarily the diseases, but in the present case there is no other feature left since the substance, the medicament and the mode of administration are those previously disclosed in the prior art. As regards the decision T 290/86 (loc cit) it has to be noted that it relates to a case where two distinguishable effects were involved: to remove the plaque and/or stains from the teeth, and to depress the solubility of tooth enamel in organic acids. In the application in suit the different pathways are not reflected in distinguishable technical effects. In the light of the contents of the application in suit, the skilled person after knowledge of the new pathways would not do anything different when addressing a patient suffering from an autoimmune disease or an immuno-inflammatory disease nor would it be able to observe any difference when treating the patient.

Consequently, the board is of the opinion that the subject-matter of claims 47-48, 60-67, 85 and 93 relates to four different inventions.

Since the review panel of the ISA had already ordered the refund of four search fees it is no longer necessary to correct the ISA decision in that respect.

Finally, in claims 27 to 30 which relate to methods for identifying molecules the modulation of IFN-γ inducible MHC class II expression and/or CD40 expression is detected and hence the said modulation concerns a functional feature of the claim. In contrast thereto, the remaining claims relate to the so-called second medical use claims for which, as already mentioned, no distinguishable technical effect related to the modulation of IFN-γ inducible MHC class II expression and/or CD40 expression is detected. Moreover, it has to be noted that such feature is not even reflected by the wording of the claims (cf. claims 64, 85 and 93).

Order

For these reasons it is decided that:

1. Cases W 0023/03 and W 0018/03 are consolidated.

2. One protest fee is to be refunded.

3. The consolidated protest is rejected.

The Registrar: The Chairman:

C. Eickhoff U. Oswald