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**Datasheet for the decision
of 13 July 2006**

Case Number: T 0021/05 - 3.3.04

Application Number: 95914048.4

Publication Number: 0759937

IPC: C07K 14/18

Language of the proceedings: EN

Title of invention:

Peptides for inducing cytotoxic T lymphocyte responses to hepatitis C virus

Patentee:

THE SCRIPPS RESEARCH INSTITUTE

Opponent:

Innogenetics NV

Headword:

CTL responses to HCV/SCRIPPS

Relevant legal provisions:

EPC Art. 54, 56, 83, 84, 123

Keyword:

"New main request - added subject-matter (no)"

"Novelty, inventive step, sufficiency, clarity (yes)"

Decisions cited:

T 0019/90, G 0005/83

Catchword:

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Case Number: T 0021/05 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 13 July 2006

Appellant I: THE SCRIPPS RESEARCH INSTITUTE
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Appellant II: Innogenetics NV
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Representative: Kraft, Henricus Johannes
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Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted
15 October 2004 concerning maintenance of the
European Patent No. 0759937 in amended form.

Composition of the Board:

Chair: U. Kinkeldey
Members: M. Wieser
G. Weiss

Summary of Facts and Submissions

- I. Appeals were lodged by the Patent Proprietor (Appellant I) and by the Opponent (Appellant II) against the decision of the Opposition Division whereby European Patent No. 0 759 937 was maintained in amended form pursuant to Article 102(3) EPC.
- II. The patent had been opposed under Article 100(a) EPC for lack of novelty (Article 54 EPC), lack of inventive step (Article 56 EPC) and lack of industrial applicability (Articles 52(4) and 57 EPC), under Article 100(b) EPC on the ground of lack of sufficient disclosure (Article 83 EPC) and under Article 100(c) EPC on the ground of added subject-matter (Article 123(2) EPC).
- III. The Opposition Division had decided that the claims of the main request and of auxiliary request I before them violated Article 123(2) EPC, but that the claims of auxiliary request II met all requirements of the EPC.
- IV. The Board expressed its preliminary opinion in a communication dated 8 February 2006.

On 12 May 2006 the Board received observations by a third party according to Article 115 EPC.

Oral proceedings were held on 13 July 2006.
- V. Appellant I requested to set aside the decision under appeal and to maintain the patent on the basis of claims 1 to 7 of the new main request filed at oral proceedings.

Appellant II requested to set aside the decision under appeal and to revoke the patent.

VI. Independent claims 1, 2, 4, 6 and 7 of Appellant's I new main request read as follows:

"1. A pharmaceutical composition for inducing hepatitis C virus (HCV) specific response in CTLs, the composition comprising a polypeptide having from 8 to less than 25 amino acids and having at least 80% of the same amino acid residues in the same or analogous position as in a CTL epitope which is ADLMGYIPLV (Core₁₃₁₋₁₄₀; SEQ ID NO:1), LLCPAGHAV (NS3₁₁₆₉₋₁₁₇₇; SEQ ID NO:26), KLVALGINAV (NS3₁₄₀₆₋₁₄₁₅; SEQ ID NO:28), SLMAFTA AV (NS4₁₇₈₉₋₁₇₉₇; SEQ ID NO:34, or ILDSFDPLV (NS5₂₂₅₂₋₂₂₆₀; SEQ ID NO:42), wherein the polypeptide is capable of inducing an HLA-A2 restricted cytotoxic T lymphocyte response against HCV.

2. A conjugate comprising:

(a) a polypeptide having from 8 to less than 25 amino acids and having at least 80% of the same amino acid residues in the same or analogous position as in a CTL epitope which is ADLMGYIPLV (Core₁₃₁₋₁₄₀; SEQ ID NO:1), LLCPAGHAV (NS3₁₁₆₉₋₁₁₇₇; SEQ ID NO:26), KLVALGINAV (NS3₁₄₀₆₋₁₄₁₅; SEQ ID NO:28) or SLMAFTA AV (NS4₁₇₈₉₋₁₇₉₇; SEQ ID NO:34, wherein the polypeptide is capable of inducing an HLA-A2 restricted cytotoxic T lymphocyte response against HCV; and

(b) a substance selected from the group consisting of a radiolabel, an enzyme, a fluorescent label, a solid matrix, a carrier and an additional polypeptide of (a).

4. A conjugate comprising two polypeptides, each having from 8 to less than 25 amino acids and having at least 80% of the same amino acid residues in the same or analogous position as in a CTL epitope which is ADLMGYIPLV (Core₁₃₁₋₁₄₀; SEQ ID NO:1), LLCPAGHAV (NS3₁₁₆₉₋₁₁₇₇; SEQ ID NO:26), KLVALGINAV (NS3₁₄₀₆₋₁₄₁₅; SEQ ID NO:28), SLMAFTA AV (NS4₁₇₈₉₋₁₇₉₇; SEQ ID NO:34, or ILDSFDPLV (NS5₂₂₅₂₋₂₂₆₀; SEQ ID NO:42), wherein each of the polypeptides is capable of inducing an HLA-A2 restricted cytotoxic T lymphocyte response against HCV.

6. An in vitro method of detecting in lymphocytes of a mammal cytotoxic T cells that respond to a T cell epitope of hepatitis C virus, comprising the steps of:

(a) contacting target cells with a polypeptide comprising at least one of the peptides selected from the group consisting of ADLMGYIPLV (Core₁₃₁₋₁₄₀; SEQ ID NO:1), LLCPAGHAV (NS3₁₁₆₉₋₁₁₇₇; SEQ ID NO:26), KLVALGINAV (NS3₁₄₀₆₋₁₄₁₅; SEQ ID NO:28), SLMAFTA AV (NS4₁₇₈₉₋₁₇₉₇; SEQ ID NO:34, ILDSFDPLV (NS5₂₂₅₂₋₂₂₆₀; SEQ ID NO:42), and peptides that have at least 80% of the same amino acid residues at the same or analogous position thereto and which are capable of inducing an HLA-A2 restricted cytotoxic T lymphocyte response against HCV, wherein said target cells are of the same HLA class as the lymphocytes to be tested for said cytotoxic T cells;

(b) contacting said lymphocytes to be tested for said cytotoxic T cells with a polypeptide comprising at

least one of the peptides selected from the group consisting of ADLMGYIPLV (Core₁₃₁₋₁₄₀; SEQ ID NO:1), LLCPAGHAV (NS3₁₁₆₉₋₁₁₇₇; SEQ ID NO:26), KLVALGINAV (NS3₁₄₀₆₋₁₄₁₅; SEQ ID NO:28), SLMAFTA AV (NS4₁₇₈₉₋₁₇₉₇; SEQ ID NO:34, and ILDSFDPLV (NS5₂₂₅₂₋₂₂₆₀; SEQ ID NO:42), and peptides that have at least 80% of the same amino acid residues in the same or analogous position thereto and which are capable of inducing an HLA-A2 restricted cytotoxic T lymphocyte response against HCV; and

(c) determining whether said lymphocytes exert a cytotoxic effect on said target cells.

7. In vitro use of a polypeptide selected from the group consisting of ADLMGYIPLV (Core₁₃₁₋₁₄₀; SEQ ID NO:1), LLCPAGHAV (NS3₁₁₆₉₋₁₁₇₇; SEQ ID NO:26), KLVALGINAV (NS3₁₄₀₆₋₁₄₁₅; SEQ ID NO:28), SLMAFTA AV (NS4₁₇₈₉₋₁₇₉₇; SEQ ID NO:34, ILDSFDPLV (NS5₂₂₅₂₋₂₂₆₀; SEQ ID NO:42), and peptides that have at least 80% of the same amino acid residues at the same or analogous position thereto and which are capable of inducing an HLA-A2 restricted cytotoxic T lymphocyte response against HCV in the preparation of an immune response provoking vaccine in the event of HCV infection, said vaccine being prepared by contacting said polypeptide in an immune response provoking amount with a specific CTL."

VII. The following documents are referred to in this decision:

(3) J. Cell. Biochemistry; vol.Sup17D, no.308, 1993, page 64A

(4) WO-94/20 127

(5) WO-93/18 054

(6) WO-95/22 317

(8) Seminars in Immunology; vol.5, 1993, pages 81-94

(16) WO-95/00 670

(17) Nature; vol.351, 1991, pages 290-296

VIII. The submissions made by Appellant I as far as they are relevant to the present decision may be summarised as follows:

Claims 1 to 7 were based on the application as originally filed (Article 123(2) EPC). The term "from 8 to less than 25 amino acids" had a basis on page 9 of the original application. The assay for testing the desired physiological activity was explicitly disclosed in the patent. Thus, the claims were clear and supported by the description (Article 84 EPC). All claims were novel over the prior art on file and could not be derived therefrom in an obvious way (Articles 54 and 56 EPC). Screening of a large number of proteins for a certain activity by using a well known and precisely described test did not amount to undue burden. A mere allegation without being substantiated by verifiable facts was not a ground to consider an invention as not being sufficiently disclosed (Article 83 EPC).

IX. The submissions made by Appellant II as far as they are relevant to the present decision may be summarised as follows:

The application as originally filed did not contain a basis for polypeptides having from 8 to less than 25 amino acids. The term "less than about 25" on page 9 of the original application included the value 25. The claims encompassed peptides not having the anchor amino acid sequences on positions 2 and 9, for which there was no basis in the original application (Article 123(2) EPC).

A claim referring to substances defined by a functional feature, not containing the indication of the exact method for determining this functional feature, lacked clarity within the meaning of Article 84 EPC.

Starting from the disclosure in the closest prior art, document (3), it would have been a routine task to screen the published nucleotide sequence of HCV-1 virus and to find sequences encoding peptides having the well known HLA-A2 binding motif. Testing these peptides for the ability to induce the desired activity was also a pure routine task not requiring any inventive activity, contrary to the requirements of Article 56 EPC.

Due to the wording of the claims they encompassed an immense number of polypeptides. Testing all of them for the desired activity amounted to undue burden. Certain peptides falling within the scope of the claim, namely all octapeptides, were known not to have the desired activity. Therefore, the invention was not sufficiently disclosed (Article 83 EPC).

Reasons for the decision

Amendments - Articles 123(2) and 123(3) EPC

1. Claim 1 is based on claim 21, page 6, lines 27 to 34, page 14, lines 1 to 5 and page 16, lines 22 to 26 of the application as originally filed.

The feature "having from 8 to less than 25 amino acids" is based on page 9, lines 24 to 26 of the original application. The word "having" in front of the numerical range of "8 to less than 25" means that the claimed composition does not contain any additional amino acid residues.

2. Appellant II argues that the term "less than **about** twenty-five amino acids" (emphasis added by the Board) as used on page 9 of the application as filed, which in their opinion includes the figure 25, cannot form a basis for "less than 25 amino acids" as used in the claim. The Board takes the view that the term "less than **about** twenty-five" forms a basis for "less than 25". The reason for this is that the term "about 25" implies a range of figures around 25 and includes 25, for example 24, 25 and 26. Thus, the phrase "less than about 25" includes "less than 24", "less than 25" and "less than 26".

3. Appellant II further argues that the claim, due to the wording "and having at least 80% of the same amino acid residues in the same or analogous position as in a CTL epitope" included compositions comprising a polypeptide not containing the so-called "anchor-amino-acid-

residues", namely Leucine at position 2 and Valine at position 9, for which polypeptides there was no basis in the application as filed.

The polypeptides contained in the pharmaceutical compositions and conjugates claimed are functionally defined as being "capable of inducing an HLA-A2 restricted T lymphocyte response against HCV". As the presence of the two anchor-amino-acid-residues is a necessary requirement for this specific response (see page 44, lines 9 to 14 of the application as filed) the claim does not encompass subject-matter not disclosed in the application as filed.

4. In addition to the basis given for claim 1 above, claim 2 is based on claims 1 and 5, claim 3 on claim 8, claim 4 on claim 6 and claim 5 on claim 7, all as originally filed. Present claim 6 is additionally based on claim 19 as originally filed. Claim 7, taking the form of a claim referring to a second or further medical use of a substance, as acknowledged by the Enlarged Board of Appeal in decision G 5/83 (OJ EPO 1985, 64) is additionally based on original claims 12, 15 and 16.

5. The scope of protection of present independent claims 1, 2, 4, 6 and 7 is narrower than the scope of protection of claims 3, 4, 6, 11 and 12 as granted, because the number of CTL epitopes has been reduced. Therefore, the claims have not been amended during opposition proceedings in such a way as to extend the protection conferred.

6. Claims 1 to 7 of Appellant's I new main request meet the requirements of Articles 123(2) and 123(3) EPC.

Clarity - Article 84 EPC

7. The polypeptides contained in the pharmaceutical compositions and conjugates of claims 1 to 5 and used in the methods of claims 6 and 7, are functionally defined by being "capable of inducing an HLA-A2 restricted cytotoxic T lymphocyte response against HCV".

Appellant II argues that the claims are not clear as they did not contain the exact method for determining this functional feature.

8. The patent in suit describes in example 2, on page 20, lines 2 to 12 in detail the used cytotoxicity test. This test, "a standard 4 hour ⁵¹Cr-release assay", is known in the art and is referred to, for instance, in document (3) (abstract). The fact that other cytotoxicity tests may be known to the skilled worker does not mean that the present claims lack clarity. The claims are supported by the description, which explicitly describes a well known test for determining the functional feature in question.
9. Therefore, the claims are clear and meet the requirements of Article 84 EPC.

Sufficiency of disclosure - Article 83 EPC

10. Due to the wording "a polypeptide having from 8 to less than 25 amino acids and having at least 80% of the same amino acid residues in the same or analogous position

as in a CTL epitope", which is one of the five epitopes defined in the claims by their respective SEQ. ID. NOs., a large number of substances fall within the scope of the claims. Appellant II argues that it amounts to undue burden to identify those which show the desired functional activity, namely induction of an HLA-A2 restricted cytotoxic T Lymphocyte response against HCV.

11. As already stated in point (8) above, the patent in suit describes in example 2, on page 20, lines 2 to 12 in detail the used cytotoxicity test.

Screening a large number of peptides for a certain physiological activity may be a laborious undertaking. However, the Board is convinced that the exact disclosure of the assay to be carried out enables a skilled person to reproduce the present invention, possibly in a time-consuming and cumbersome way, but in the given circumstances, without undue burden of experimentation and without needing inventive skill.

12. The claims refer to compositions, conjugates and methods which comprise or use polypeptides having from 8 to less than 25 amino acids. Thus, peptides with eight amino acids are encompassed.

Appellant II, by referring to document (17), page 293, left column, argues that epitopes with eight amino acids only do not have the physiological activity required by the claims. The cited passage reads as follows:

"Position 10 showed no increase for any residue, indicating A-2 restricted epitopes to be nonapeptides.

Anchors appear to Leu or Met at position 2 and Val or Leu at position 9."

13. This statement discloses that the peptides naturally occupying the HLA-A2 groove are nonapeptides. It is not a disclosure proving that octapeptides don't work, in the sense that they are not capable of inducing an HLA-A2 restricted T lymphocyte response against HCV.
14. An objection based on lack of sufficient disclosure presupposes that there are serious doubts, substantiated by verifiable facts (cf decision T 19/90, OJ EPO 1990, 476, point (3.3) of the reasons). The mere fact that a claim is broad (points (14) to (15) above), or an unproven allegation (points (16) to (17) above) are not in itself grounds for considering a patent as not complying with the requirements of sufficient disclosure.

As no such verifiable facts leading to serious doubts are seen by the Board in the present case, the requirements of Article 83 EPC are met.

Novelty - Article 54 EPC

15. Appellant II did not object to the novelty of the subject-matter of claims 1 to 7 of the new main request filed at the oral proceedings.
16. Documents (4) and (6), which both belong to the state of the art under Article 54(3) EPC, disclose a nonapeptide which is 90% homologous to SEQ. ID. NO: 1 (document (4) on page 90, table 26 and document (6) on pages 24 and 25).

Document (16), which also belongs to the state of the art under Article 54(3) EPC, discloses on page 23 (example 2) peptide "T8" which has 25 amino acids and comprises SEQ. ID. NO: 28.

Document (5) discloses in figure (7c), second column, a polypeptide corresponding to present SEQ. ID. NO: 42. However, the document does not refer to pharmaceutical compositions and conjugates containing this peptide.

17. Thus, none of documents (4), (5), (6) or (16) discloses the pharmaceutical compositions and conjugates according to claims 1 to 4, or the methods according to claims 6 and 7 of the new main request.
18. The subject-matter of claims 1 to 7 is novel within the meaning of Article 54 EPC.

Inventive step - Article 56 EPC

19. The claims refer to pharmaceutical compositions and conjugates comprising polypeptides defined by their length, by their (partial) amino acid sequence, and by their ability to induce an HLA-A2 restricted cytotoxic T lymphocyte response against HCV. They also refer to the use of these polypeptides in an in vitro method to detect cytotoxic T cells that respond to a T cell epitope of HCV, and in the preparation of an immune response provoking vaccine in the event of HCV infection.
20. Document (3) is considered to represent the closest state of the art. It discloses that CTL's are a major

defence mechanism in viral infections. CTL mediated lysis of virus infected cells may lead to clearance of the virus, or if incomplete to viral persistence and chronic hepatitis after infection with HCV. Chronic HCV patients having the HLA-A2 allele were stimulated with HCV derived peptides containing the HLA-A2 binding motif xLxxxxxxV. Effector cells thus obtained were tested for their capacity to lyse HLA-A2 matched peptide sensitized target cells in a 4-hour ⁵¹Chromium release assay. These tests showed that HLA-A2 restricted CTL responses could be detected in the peripheral blood of chronic HCV patients. These responses were directed to peptides derived from structural as well as from non-structural regions of HCV. Some patients had no detectable CTL activity against the HCV peptides used.

Document (3) concludes:

"Current efforts are directed to correlate the clinical status and the evolution of liver disease with the presence or absence of HCV specific CTL in the peripheral blood of patients during the natural course of disease and in response to antiviral therapy. Information derived from such an approach may be useful as a predictor for clinical evolution, as a means to monitor antiviral and immunomodulatory treatment and as a basis for a rational design of a HCV vaccine."

21. The problem to be solved in the light of this disclosure is the provision of pharmaceutical compositions and conjugates for the diagnosis and therapy of HCV.

This problem has been solved by the provision of the compositions and conjugates according to claims 1 to 5 and by their use according to claims 6 and 7 (see especially examples 5 and 6 of the patent in suit).

22. It is known from the prior art that CTL's are a major defence mechanism in viral infections and that xLxxxxxxV is a HLA-A2 binding motif (see documents (3), (8) and (17)). As the HCV-1 amino acid sequence has been published in 1991, before the priority date of the patent in suit, Appellant II considers it as an obvious task for a skilled person trying to solve the posed problem in the light of the disclosure in document (3) to screen the HCV genome for the HLA-A2 binding motif and to arrive at the claimed subject-matter in an obvious way and with a reasonable expectation of success.

23. However, document (3) does not contain any information concerning the actual length and the amino acid sequence of the used polypeptides. It closes with an invitation to the skilled reader to undertake further efforts to correlate the clinical status and the evolution of liver disease with the presence or absence of HCV specific response in CTLs which is understood to be a summons to perform further investigations and experiments.

The skilled person when following this invitation, having in mind that some patients had no detectable CTL activity against the peptides used (document (3), last paragraph, point (4)) and learning from document (8) (see table on pages 82 and 83) that xLxxxxxxV is not the only HLA-A2 binding motif, will be confronted with

a plethora of possibilities to perform these further investigations which are necessary to solve the underlying problem.

In the light of this situation the Board is convinced that the disclosure in the closest prior art (document (3)), either if taken alone or in combination with any document on file, does not contain information that would enable a skilled person, trying to solve the problem underlying the present invention, to arrive at the compositions and conjugates according to claims 1 to 5, comprising the polypeptides which are precisely defined as described in point (9) above, and to their use according to claims 6 and 7.

24. The subject-matter of claims 1 to 7 involves an inventive step and meets the requirements of Article 56 EPC.

Order

For these reasons it is decided:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent in amended form on the basis of claims 1 to 7 filed at the oral proceedings according to the new main request and a description yet to be adapted thereto.

Registrar:

Chair:

P. Cremona

U. Kinkeldey