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**Datasheet for the decision
of 17 July 2007**

Case Number: T 1470/05 - 3.3.08

Application Number: 94931000.7

Publication Number: 0725824

IPC: C12N 15/40

Language of the proceedings: EN

Title of invention:

Immunodominant human T-cell epitopes of hepatitis C virus

Patentee:

Innogenetics N.V.

Opponents:

Intercell AG
Novartis Vaccines and Diagnostics, Inc.

Headword:

HCV T-cell epitopes/INNOGENETICS

Relevant legal provisions:

EPC Art. 54, 56, 123(3)

Keyword:

"Main and first auxiliary request: extension of the protection conferred (yes)"

"Second auxiliary request: novelty (no)"

"Third auxiliary request: inventive step (no)"

Decisions cited:

G 0001/03, T 0231/89

Catchword:

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Case Number: T 1470/05 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 17 July 2007

Appellant:
(Patent Proprietor)

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(Opponent 01)

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(Opponent 02)

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Decision under appeal:

Decision of the Opposition Division of the
European Patent Office posted 22 September 2005
revoking European patent No. 0725824 pursuant
to Article 102(1) EPC.

Composition of the Board:

Chairman: L. Galligani
Members: T. J. H. Mennessier
C. Rennie-Smith

Summary of Facts and Submissions

- I. The patentee (appellant) lodged an appeal against the decision of the opposition division dated 22 September 2005, whereby European patent 0 725 824 was revoked. The patent had been granted on European patent application No. 94 931 000.7 entitled "*Immunodominant human T-cell epitopes of hepatitis C virus*" and published under the international publication number WO 95/12677.

Claim 1 as granted read as follows:

"1. Use of a polypeptide of about 8 to about 20 amino acids for the preparation of an HCV immunogenic composition, with said polypeptide comprising or consisting of about 8 to about 20 contiguous amino acids selected from the region comprised between amino acid positions 157 to 176 of the core region of HCV: NH₂-X₃₀X₃₁X₃₂DGX₃₃NX₃₄X₃₅TGNX₃₆PGCSFI-COOH (SEQ ID NO 51), and with said contiguous amino acids containing a T-cell stimulating epitope, **and wherein said polypeptide mimics the T-cell immunological stimulation properties of the polypeptide as represented in SEQ ID NO 13**, and wherein X₃₀ represents V or A or L, X₃₁ represents L or V or I, X₃₂ represents E or G, X₃₃ represents V or I, and X₃₄ represents F or Y, X₃₅ represents A or P, X₃₆ represents L or I."

(emphasis added by the Board)

- II. The patent was revoked on the basis of a main request filed with the letter of 31 March 2005 and four auxiliary requests all filed at the oral proceedings

held on 31 May 2005. Reasons for the revocation were (a) as regards the main request and auxiliary request 1, lack of clarity (Article 84 EPC) and non-compliance with the requirements of Articles 123(2) and 123(3) EPC, and (b) as regards auxiliary requests 3 and 4, lack of inventive step (Article 56 EPC). Auxiliary request 2 had not been admitted into the proceedings.

III. The patent had been opposed on the grounds as set forth in Articles 100(a), (b) and (c) EPC that (i) the invention was neither new (Article 54 EPC) nor inventive (Article 56 EPC), (ii) the invention was not sufficiently disclosed (Article 83 EPC) and (iii) the patent contained subject-matter which extended beyond the content of the application as filed (Article 123(2) EPC).

IV. A statement setting out the grounds of appeal was filed on 20 January 2006. It was accompanied by a main request (claims as granted) and five auxiliary requests (referred to as auxiliary requests I to V).

V. Each of opponent 01 (respondent I) and opponent 02 (respondent II) filed on 12 June 2006 a reply to the statement setting out the grounds of appeal.

VI. The Board issued a communication under Article 11(1) of the Rules of Procedure of the Boards of Appeal (RPBA) expressing a provisional, non-binding opinion on some of the pending issues.

VII. On 8 June 2007, the appellant filed additional submissions as well as 25 auxiliary requests (1 to 25) to replace the previous auxiliary requests.

VIII. Oral proceedings took place on 17 July 2007, at which the appellant withdrew its main request (claims as granted) and all the auxiliary requests of 8 June 2007 except auxiliary requests 2, 8 and 5 designated as, respectively, the main request, the first auxiliary request and the second auxiliary request. A further auxiliary request numbered 5b filed during the oral proceedings constituted the third auxiliary request.

IX. Claim 1 of the respective requests read as follows:

Main request (auxiliary request 2 of 8 June 2007):

"1. Use of a polypeptide of 8 to 20 amino acids for the preparation of an HCV immunogenic composition, with said polypeptide comprising or consisting of 8 to 20 contiguous amino acids selected from the region comprised between amino acid positions 157 to 176 of the core region of HCV:

NH₂-X₃₀X₃₁X₃₂DGX₃₃NX₃₄X₃₅TGNX₃₆PGCSFI-COOH (SEQ ID NO 51), and with said contiguous amino acids containing a T-cell stimulating epitope, and wherein X₃₀ represents V or A or L, X₃₁ represents L or V or I, X₃₂ represents E or G, X₃₃ represents V or I, and X₃₄ represents F or Y, X₃₅ represents A or P, X₃₆ represents L or I."

First auxiliary request (auxiliary request 8 of 8 June 2007):

"1. Use of a polypeptide of 8 to 20 amino acids for the preparation of an HCV immunogenic composition, with said polypeptide consisting of 8 to 20 contiguous amino

acids selected from the region comprised between amino acid positions 157 to 176 of the core region of HCV: NH₂-X₃₀X₃₁X₃₂DGX₃₃NX₃₄X₃₅TGNX₃₆PGCSFI-COOH (SEQ ID NO 51), and with said contiguous amino acids containing a T-cell stimulating epitope, **and wherein said polypeptide induces a lymphoproliferative response**, and wherein X₃₀ represents V or A or L, X₃₁ represents L or V or I, X₃₂ represents E or G, X₃₃ represents V or I, and X₃₄ represents F or Y, X₃₅ represents A or P, X₃₆ represents L or I."

(emphasis added by the Board)

X. **Claim 18 of the second auxiliary request** (auxiliary request 5 of 8 June 2006) reads:

"18. A peptide consisting of the sequence of any of the following peptides, with said peptides containing a T-cell epitope:

- a) VLEDGVNYATGNLPGCSFSI (SEQ ID NO 13 = peptide CORE 27),
VLEDIVNYATGNLPGCSFSI (SEQ ID NO 73),
GVNYATGNL (SEQ ID NO 78), or
NLPGCSFSI (SEQ ID NO 80),
LPGCSFSI (SEQ ID NO 81);

- b) **GGAARALAHGVRVLEDGVNY** (SEQ ID NO 12 = peptide CORE 25),
ALAHGVRVL (SEQ ID NO 88),
LAHGVRVL (SEQ ID NO 89),
VRVLEDGV (SEQ ID NO 90),
VLEDGVNY (SEQ ID NO 92);

- c) LMGYIPLVGAPLGGGAARALA (SEQ ID NO 11 = peptide CORE 23)
LMGYIPLV (SEQ ID NO 69),
YIPLVGAPL (SEQ ID NO 71),
IPLVGAPL (SEQ ID NO 72), or
LVGAPLGGGA (SEQ ID NO 94),
VGAPLGGGA (SEQ ID NO 95);
- d) PTDPRRRSRNLGKVIDTLTC (SEQ ID NO 9 = peptide CORE 19),
or
NLGKVIDTL (SEQ ID NO 98),
LGKVIDTL (SEQ ID NO 117);
- e) **GRTWAQPGYPWPLYGNEGCG (SEQ ID NO 6 = peptide CORE 13),**
or
TWAQPGYPW (SEQ ID NO 102),
WAQPGYPW (SEQ ID NO 103)."

(emphasis added by the Board)

Claim 18 of the third auxiliary request (auxiliary request 5b filed during the oral proceedings) differs from claim 18 of the second auxiliary request only in that the references to peptides SEQ ID NO 88 and SEQ ID NO 98 have been deleted.

XI. The following documents are referred to in the present decision:

(D1) Hsiang Ju Lin et al., Virus Research, Vol. 30,
October 1993, Pages 27 to 41

(D2) C. Alvarado Esquivel et al., Gastroenterology,
Vol. 104, No. 4, Part 2, April 1993, Page A660

(D5) WO 94/20127 (published on 15 September 1994)

(D9) WO 93/18054 (published on 16 September 1993)

XII. The submissions made by the appellant, insofar as they are relevant to the present decision, may be summarised as follows:

Main request (Article 123(3) EPC)

As is apparent from page 25, lines 12 to 20 in the application, "mimicking" in the context of the invention was no more than providing for immunological stimulation after which the T-cells were reactive with a HCV strain. Therefore, the feature "**wherein said polypeptide mimics the T-cell immunological stimulation properties of the polypeptide as represented in SEQ ID NO 13**" in claim 1 as granted added nothing to the other requirement that the contiguous amino acids should contain a T-cell stimulating epitope. Consequently, its removal could not have had any impact on the scope of protection of claim 1 of the main request compared to the scope of protection of claim 1 as granted. Therefore, claim 1 of the main request satisfied Article 123(3) EPC.

First auxiliary request (Article 123(3) EPC)

As they were equivalent, replacement of the feature "**wherein said polypeptide mimics the T-cell immunological stimulation properties of the polypeptide as represented in SEQ ID NO 13**" by the feature "**wherein said polypeptide induces a lymphoproliferative response**", was neutral in terms of scope of protection.

Therefore, claim 1 of the first auxiliary request did not violate Article 123(3) EPC.

Second auxiliary request (Article 54 EPC)

Document D5 did not show that the 9-mer peptides 1.0094 on page 102 and 1.0091 on page 104 contained a T-cell epitope. It only indicated that peptides having a binding of at least 0.01 were capable of inducing CTL (see page 76, lines 31 to 35). The said peptides had a binding of less than 0.01 (see Appendix 1, pages 102 and 104) and were not immunogenic. Claim 1 was thus novel.

Document D9 disclosed only biotinylated peptides. Therefore, it was not relevant when assessing whether the individual peptides of claim 18 were new.

Third auxiliary request (Article 56 EPC)

The immunodominant regions identified in the present patent were not restricted to a certain HVC genotype or even HCV type, while, in contrast, the candidate T-cell epitopes identified in D1 were derived from absolutely conserved regions of HCV gene products. As a result the immunodominant peptides of claim 18 were capable of stimulating the T-cell lymphoproliferative response in chronic HCV patients, regardless of the type of HCV infection. In any case, document D1 was not a relevant basis for the assessment of inventive step because, relying on a theoretical computer-assisted analysis, it did not show that any of the candidate sequences actually contained a T-cell epitope.

Document D9 did not teach the presence of a T-cell stimulating epitope in the modified peptides it disclosed. Therefore, it was not relevant too when assessing whether the individual peptides of claim 18 were inventive.

XIII. The submissions made by respondent I, insofar as they are relevant to the present decision, may be summarised as follows:

Main request (Article 123(3) EPC)

The removal of the ambiguous but essential technical feature "**wherein said polypeptide mimics the T-cell immunological stimulation properties of the polypeptide as represented in SEQ ID NO 13**" from granted claim 1, had inevitably resulted in an extension of the protection conferred.

First auxiliary request (Article 123(3) EPC)

The proposed replacement in claim 1 as granted of the technical feature "**wherein said polypeptide mimics the T-cell immunological stimulation properties of the polypeptide as represented in SEQ ID NO 13**" by the broader technical feature "**wherein said polypeptide induces a lymphoproliferative response**" was bound to fail as it resulted in an extension of the protection conferred.

Second auxiliary request (Article 54 EPC)

Document D5 disclosed two peptides which had sequences identical to SEQ ID NO 88 and SEQ ID 98 which were part

of the subject-matter of claim 18. Thus, there was lack of novelty.

Third auxiliary request (Article 56 EPC)

This was a very late filed request being filed during oral proceedings when the 25 auxiliary requests filed on 8 June 2007 had already put an excessive burden on the respondents and the Board. Therefore, it should not be admitted into the present proceedings.

Removal of references to peptides SEQ ID NO 88 and SEQ ID NO 98 in claim 18 had the same effect of a non-allowable disclaimer.

Insofar as the T-cell epitope RALAHGVRVLEDG was known from document D1, selecting a longer peptide including the same, such as peptide CORE 25 (SEQ ID NO 12), could be done by the skilled person without the exercise of inventive step. Claim 18 was not inventive.

- XIV. The submissions made by respondent II, insofar as they are relevant to the present decision, may be summarised as follows:

Main request (Article 123(3) EPC)

The wording "**wherein said polypeptide mimics the T-cell immunological stimulation properties of the polypeptide as represented in SEQ ID NO 13**" was not clear but it had a technical meaning which implied a limitation. With the removal of the feature, claim 1 covered also peptides which "did not mimic". Therefore, the protection conferred had been extended.

First auxiliary request (Article 123(3) EPC)

Replacing in claim 1 as granted the technical feature **"wherein said polypeptide mimics the T-cell immunological stimulation properties of the polypeptide as represented in SEQ ID NO 13"** by the broader technical feature **"wherein said polypeptide induces a lymphoproliferative response"** had also resulted in an extension of the protection conferred.

Second auxiliary request (Article 54 EPC)

Two peptides with sequences identical to SEQ ID NO 88 and SEQ ID 98 were disclosed in the state of the art, namely in document D5, while peptide CORE 13 (SEQ ID NO 6) represented by the sequence GRTWAQPGYPWPLYGNEGCG which was part of the subject-matter of claim 18 was disclosed in document D9 (see peptide VII on page 13).

Third auxiliary request (Article 56 EPC)

As this request was filed very late after a great number of previous requests, it should not be admitted into the proceedings.

There were patentability problems with peptide CORE 13 (SEQ ID NO 6) in view of document D9. It was neither new for the reason given with respect to the second auxiliary request nor inventive. In this last respect, in view of Table 9 (see page 78) which indicated the precise location of the core epitope RTWAQP in peptide CORE 13, it would have been obvious to use that peptide in a vaccine.

XV. The appellant (patentee) requested that the decision under appeal be set aside and the patent be maintained on the basis of one of auxiliary requests 2, 8, and 5 filed on 8 June 2007, or auxiliary request 5b filed during the oral proceedings (being now, respectively, the main request and auxiliary requests 1 to 3).

XVI. The respondents (opponents) requested that the appeal be dismissed.

Reasons for the Decision

Main request

1. Claim 1 of the main request differs from claim 1 as granted essentially in that a technical feature **"wherein the polypeptide mimics the T-cell immunological stimulation properties of the polypeptide as represented in SEQ ID NO 13"** has been removed.
2. The removal of one individual feature from a patent claim is not admissible, since it leads to an extension of the scope of protection and, therefore, violates Article 123(3) EPC, unless it is of no technical relevance (T 231/89, OJ EPO 1993, 013; cf. point 3.5 of the Reasons).
3. In the present case, the removed feature, even if not clearly formulated due to the use of the ambiguous term "mimics", implies that the polypeptides referred to in claim 1 should immunologically react to some extent in the same way as a definite peptide, namely peptide

SEQ ID NO 13. Therefore, it has an undisputable technical meaning, and its removal results in the extension of the scope of protection conferred in comparison with granted claim 1.

4. Therefore, the main request violates Article 123(3) EPC.

First auxiliary request

5. Claim 1 of the first auxiliary request differs from claim 1 of the main request as granted in particular in that the technical feature reading "**wherein the polypeptide mimics the T-cell immunological stimulation properties of the polypeptide as represented in SEQ ID NO 13**" has been replaced by the feature "**wherein said polypeptide induces a lymphoproliferative response**".

6. The appellant's argument that the replacement feature would be equivalent to the removed feature is not tenable as the latter feature was in relation to a specific polypeptide, whatever its immunological stimulation properties as a whole might be, while the replacement feature is in relation to the capability of inducing a lymphoproliferative response which is possibly one of the immunological stimulation properties.

7. Therefore, the first auxiliary request also violates Article 123(3) EPC.

Second auxiliary request

8. Claim 18 relates to a list of 22 peptides, each being defined independently of the others, in particular

peptide CORE 13 (SEQ ID NO 6), CORE 25 (SEQ ID NO 12), ALAHGVRVL (SEQ ID NO 88) and NLGKVIDTL (SEQ ID NO 98).

9. As accepted by the appellant, of the listed peptides only peptides CORE 19 (SEQ ID NO 9), CORE 23 (SEQ ID NO 11), CORE 25 (SEQ ID NO 12) and CORE 27 (SEQ ID NO 13) are disclosed in the priority document. Therefore, the remaining embodiments of claim 18, especially, peptide CORE 13 (SEQ ID NO 6), ALAHGVRVL (SEQ ID NO 88) and NLGKVIDTL (SEQ ID NO 98), do not enjoy the claimed priority date of 4 November 1993 and are only entitled as to the filing date of the international application, namely 28 October 1994. As a result any document published before this date belongs to the state of the art available for the assessment of both novelty and inventive step as regards those remaining embodiments. This is in particular the case with documents D5 and D9, published on 15 September 1994 and 16 September 1993, respectively.
10. The peptides of claim 18 are defined in terms of their sequence. The feature that the peptides contain a T-cell epitope is not to be regarded here as an additional feature but as an inherent feature associated with the specific primary sequence of amino acids.
11. Three peptides of claim 18 have been considered by the respondents to be anticipated by the state of the art, namely peptide CORE 13 (SEQ ID NO 6) in view of document D9 as well as peptides SEQ ID NO 88 and SEQ ID 98, both in view of document D5.

11.1 Document D9 discloses peptide VII/core 13 (see page 13) which has the formula: (A)-(B)-(X)-Y-Gly-Arg-Thr-Trp-Ala-Gln-Pro-Gly-Tyr-Pro-Trp-Pro-Leu-Tyr-Gly-Asn-Glu-Gly-Cys-Gly-Y-(X)-Z, in which Y is a covalent bond or one or more particular chemical entities, and A, B and X are optional, with the proviso that either B which represents biotin or X which represents a biotinylated compound be present (see page 7). As it is not biotinylated, peptide CORE 13 (SEQ ID NO 6) of claim 18 is new.

11.2 Document D5 reports that in order to assess the immunogenicity of a panel of 161 9-mer-peptides of potential target molecules of viral and tumour origin with varying HLA-A2-1 binding affinity, the peptides were individually used to immunize transgenic mice to evaluate the T-cell response to potential epitopes contained therein (see page 76, from line 18 onwards). These peptides are represented in Appendix I. Two of them are ALAHGVRVL (see peptide 1.0094 on page 102) and NLGKVIDTL (see peptide 1.0091 on page 104). These sequences are identical to SEQ ID NO 88 and SEQ ID NO 98, respectively. Notwithstanding the fact that both peptides in the context of the reported experiment have been considered not to be immunogenic, it remains that their respective sequences are identical to those of peptides SEQ ID NO 88 and SEQ ID NO 98 of claim 18. Therefore, in view of the consideration in point 10 supra, both peptides are not new.

12. In view of the afore-mentioned remarks, it is concluded that two peptides of claim 18, namely peptides SEQ ID NO 88 and SEQ ID NO 98, are known from the prior

art. Thus, claim 18 lacks novelty and, thereby, does not comply with Article 54 EPC.

Third auxiliary request

13. Both respondents have requested that the third auxiliary request filed during the oral proceedings not be admitted into the present proceedings. In view of the amendment carried out starting from the second auxiliary request, i.e. the removal of references to peptides SEQ ID NO 88 and SEQ ID NO 98, analysis of the third auxiliary request does not require any special effort by the respondents and the Board. It can also be considered that the respondents were not taken by surprise, as in order to overcome the underlying objection of lack of novelty, the same amendments had already been proposed in auxiliary requests 16 to 18 and 20 to 22 of 8 June 2007. Therefore, the Board, exercising its discretion, has decided to admit the present third auxiliary request into the appeal proceedings.
14. Claim 18 of the third auxiliary request differs from claim 18 of the second auxiliary request in that the references to peptides SEQ ID NO 88 and SEQ ID NO 98 have been deleted.
15. Respondent I argued that this deletion had the effect of a non-allowable disclaimer. That position is not tenable as a disclaimer is *"an amendment to a claim resulting in the incorporation therein of a "negative" technical feature, typically excluding from a **general** feature specific embodiments or areas"* (G 1/03, OJ EPO 2004, 413; cf. point 2 of the Reasons - emphasis added

by the Board). Indeed, in the present case, as the subject-matter is rather a compilation of individual peptides, each being regarded as a separate invention for which protection is individually sought, the exclusion of one of them does not affect the patentability of the others.

16. As peptides SEQ ID NO 88 and SEQ ID 98 were the only peptides listed in claim 18 of the second auxiliary request to be known from the prior art (see point 12 supra), claim 18 of the third auxiliary request is new.
17. Each of the peptides of claim 18 should be non-obvious. If one of them fails then the claim as a whole lacks inventive step.
18. The claimed peptide CORE 25 (SEQ ID NO 12) has the amino acid sequence: GGAARALAHGVRVLEDGVNY which corresponds to positions 145 to 164 of the type 1a sequence HC-J1 as referred to in the patent (see paragraph 0109 on page 15 of the patent specification).
19. Document D2 which was published in April 1993, i.e. before the priority date enjoyed by peptide CORE 25. and of which the authors are the inventors, provides a brief overview of the experiments, as reported in the description of the patent, in which recognition of peptides representing proteins of HCV type 1a by peripheral blood mononuclear cells from 39 patients with chronic hepatitis C has been tested. The precise sequence of the peptides is not specified. The conclusions are reached that the structural proteins of HCV contain multiple T-cell epitopes and that the core

protein is the most immunogenic at the T-cell level, because it is the most conserved region.

20. Starting from document D2 chosen as the closest state of the art, the technical problem faced by the skilled person may be regarded as the provision of HCV type 1a core peptides containing an immunodominant T-cell epitope and, thereby, most likely to be found among different HCV strains.
21. The skilled person would have been aware of document D1, the authors of which, using the TSites software program which carries out searches using four computer algorithms, identified T-cell epitopes most likely to be found among different HCV strains (see pages 29 and 34). One of those T-cell epitopes listed in Table 3 (see page 35) has the amino acid sequence:
RALAHGVRVLEDG which corresponds to positions 149 to 161 within the core of the HCV type 1a sequence HC-J1 (see footnote (e) in Table 3 which refers to Okamoto et al., 1990b, which is the same citation referred to at paragraph 0109 on page 15 of the patent specification).
22. The skilled person looking for HCV type 1a core peptides containing an immunodominant T-cell epitope would have been prompted to select peptides consisting of a sequence of the HCV type 1a core protein containing the T-cell epitope RALAHGVRVLEDG of document D1. Such a peptide is in fact peptide CORE 25.
23. The argument made by the appellant that document D1 is essentially theoretical can be rejected in view of the experimental strategy which guided the authors. As the large numbers of potential T-cell epitopes revealed by

the computer search were narrowed down by imposing the criterion of absolute conservation of amino acid sequences within the existing data bases, sequence conservation being an important factor in identifying candidate epitopes (see section entitled "Candidate T-cell epitopes" on page 33), the skilled person would have regarded the candidate T-cell epitope RALAHGVRLEDG as highly credible and would have been willing to test it. Therefore, peptide CORE 25 (SEQ ID NO 12) lacks an inventive step.

24. In view of the afore-mentioned remarks (see points 17 to 23 supra), it is concluded that claim 18 does not satisfy Article 56 EPC.

25. As each of the four requests on file for different reasons fails to satisfy the EPC, none of them can form a basis for the maintenance of the patent in an amended form.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar

The Chairman

A. Wolinski

L. Galligani