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D E C I S I O N
of 13 January 2005

Case Number: T 0451/99 - 3.3.4

Application Number: 86902998.3

Publication Number: 0220273

IPC: C12Q 1/70

Language of the proceedings: EN

Title of invention:

Synthetic antigens for the detection of AIDS-related disease

Patentee:

Bio-Rad Laboratories, Inc.

Opponents:

Roche Diagnostics GmbH
Dade Behring Marburg GmbH

Headword:

AIDS-related disease/BIO-RAD LABS.

Relevant legal provisions:

EPC Art. 54, 56

Keyword:

"Main, first and second auxiliary requests - novelty - no"
"Third auxiliary request - inventive step - yes"

Decisions cited:

G 0002/03, T 0666/89

Catchword:

-



Case Number: T 0451/99 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 13 January 2005

Appellant I: Bio-Rad Laboratories, Inc.
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Decision under appeal: **Interlocutory decision of the Opposition
Division of the European Patent Office posted
9 February 1999 concerning maintenance of
European patent No. 0220273 in amended form.**

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: F. L. Davison-Brunel
R. A. M. Moufang

Summary of Facts and Submissions

- I. European patent No. 0 220 273 with the title "Synthetic antigens for the detection of AIDS-related disease" was granted with 43 claims for all designated Contracting States on the basis of European patent application No. 86 902 998.3 filed on 21 April 1986 and published as WO 86/06414. Priorities were claimed from 29 April 1985 (US 728052), 19 August 1985 (US 767303) and 26 March 1986 (US 844485).

Granted claim 1 read as follows:

"1. A method of detecting the presence of LAV/HTLV-III virus or antibody to LAV/HTLV-III virus where a sample is combined with a composition having epitopic sites immunologically competitive with LAV/HTLV-III epitopic sites, whereby antibodies bind to such protein composition to form a specific binding pair complex and the amount of complex formation is determined, characterized by

employing in the assay medium as a reagent a composition containing at least one peptide which has at least six amino acids and fewer than 50 amino acids, at least six of those amino acids are contiguous and encoded for by part of the coding region of LAV/HTLV-III from bp 450 to bp 731 from the gag region or bp 900 to bp 1421 (from the gag region) or bp 7210 to bp 7815 (from the env region)."

- II. Two oppositions were filed pursuant to Article 100(a) to (c) EPC for lack of novelty and inventive step, lack of sufficient disclosure, added subject-matter. The Opposition Division decided to maintain the patent in

amended form pursuant to Article 102(3) EPC on the basis of the third subsidiary request then on file.

III. The Patent Proprietor (Appellant I) and Opponent 2 (Appellant II) filed appeals and submitted statements of grounds of appeal. The appeal by Appellant I was accompanied by one main request and two subsidiary requests.

Claim 1 of the main request read as follows:

"1. A method of detecting the presence of LAV/HTLV-III virus or antibody to LAV/HTLV-III virus where a sample is combined with a composition having epitopic sites immunologically competitive with LAV/HTLV-III epitopic sites, whereby antibodies bind to such protein composition to form a specific binding pair complex and the amount of complex formation is determined, characterized by:

employing in the assay medium as a reagent a composition containing at least one peptide which has at least six amino acids and fewer than 50 amino acids, at least six of those amino acids are contiguous and encoded for by part of the coding region of LAV/HTLV-III from bp 450 to bp 731 (from the gag region) or bp 900 to bp 1421 (from the gag region) or bp 7210 to bp 7815 (from the env region), except the following peptides:

a) peptides from the gag region defined starting from amino acid 1 = Met coded by the ATG in position 336-338 in the LAV DNA sequence:

(here follow the sequences of seven peptides from the above-mentioned gag regions)

b) peptides from the env region defined starting from aminoacid 1 = Lysine coded by the AAA at position 5746-5748 in the LAV DNA sequence:

(here follow the sequences of six peptides from the above-mentioned env region)

- IV. A first oral proceeding took place on 28 May 2002. It was then decided that the proceedings would be continued in writing, a two months term being given to the parties to propose question(s) to be referred to the Enlarged Board of Appeal regarding the admissibility of disclaimers of the kind found in claim 1 of the main request.
- V. On 14 March 2003, the Board issued a decision referring questions to the Enlarged Board of Appeal (EBA) on this issue (cf the referral decision T 451/99, OJ EPO 2003, 334). The EBA answered these questions with decision G 2/03 (OJ EPO 2004, 448).
- VI. A second oral proceeding was summoned for 12 and 13 January 2005.
- VII. Appellants I and II filed further submissions, Appellant I also filed subsidiary requests II to VIII in replacement of subsidiary request II then on file.
- VIII. On 10 January 2005, a main request and five subsidiary requests destined to replace all requests on file were faxed to the European Patent Office by Appellant I.

IX. At oral proceedings, subsidiary requests III to V were replaced by a new subsidiary request III.

The claims of relevance for this decision are as follows:

Main request, claims 1 and 2

"1. A method of detecting the presence of LAV/HTLV-III virus or antibody to LAV/HTLV-III virus where a sample is combined with a composition having epitopic sites immunologically competitive with LAV/HTLV-III epitopic sites, whereby antibodies bind to such protein composition to form a specific binding pair complex and the amount of complex formation is determined, characterized by:

employing in the assay medium as a reagent a composition containing at least one peptide which has at least six amino acids and fewer than 50 amino acids, at least six of those amino acids are contiguous and encoded for by part of the coding region of LAV/HTLV-III from bp 900 to bp 1421 (from the gag region) or bp 7210 to bp 7815 (from the env region), except the following peptides:

a) peptides from the gag region defined starting from amino acid 1 = Met coded by the ATG in position 336-338 in the LAV DNA sequence:

(here follow the sequences of four peptides from the above-mentioned gag region)

b) peptides from the env region defined starting from aminoacid 1 = Lysine coded by the AAA at position 5746-5748 in the LAV DNA sequence:

(here follow the sequences of six peptides from the above-mentioned env region) "

"2. A method of detecting the presence of LAV/HTLV-III virus or antibody to LAV/HTLV-III virus where a sample is combined with a composition having epitopic sites immunologically competitive with LAV/HTLV-III epitopic sites, whereby antibodies bind to such protein composition to form a specific binding pair complex and the amount of complex formation is determined, characterized by:

employing in the assay medium as a reagent a composition containing at least one peptide which is a variant, by conservative or non-conservative substitution, of a peptide as specified in claim 1, the variant being immunologically competitive with a native LAV/HTLV-III virus protein."

Subsidiary request I; claim 1

"1. A method of detecting the presence of LAV/HTLV-III virus or antibody to LAV/HTLV-III virus where a sample is combined with a composition having epitopic sites immunologically competitive with LAV/HTLV-III epitopic sites, whereby antibodies bind to such protein composition to form a specific binding pair complex and the amount of complex formation is determined, characterized by:

employing in the assay medium as a reagent a composition containing at least one peptide synthesized

in solution or on a solid support, said peptide having at least six amino acids and fewer than 50 amino acids, at least six of those amino acids are contiguous and encoded for by part of the coding region of LAV/HTLV-III from bp 900 to bp 1421 (from the gag region) or bp 7210 to bp 7815 (from the env region)."

Subsidiary request II; claims 9, 19 and 20

"9. A peptide of the formula:

(X) (39)

Arg-Ile-Leu-Ala-Val-Glu-Arg-Tyr-Leu-Lys-
Asp-Gln-Gln-Leu-Leu-Gly-Ile-Trp-Gly-Cys-
Ser-Gly-Lys-Leu-Ile-Cys-X (from the env gp41
protein sequence)

where X is OH or NH₂, N-terminal acetylated X, or X linked to a peptide or protein of at least 5,000 molecular weight, which peptide or protein does not normally bind to antibodies present in a human host."

"19. A peptide immunoreactive with antibodies to LAV/HTLV-III virus which has at least twelve and fewer than 50 amino acids, at least twelve of those amino acids are contiguous and within the sequence of one of the peptides as specified in claims 8 and 9."

"20. A peptide immunoreactive with antibodies to LAV/HTLV-III virus which has at least twelve and fewer than 50 amino acids, which peptide is a variant, by conservative or non-conservative substitution, of a peptide as specified in claim 19, the variant being

immunologically competitive with a native LAV/HLTV-III virus protein."

New subsidiary request III

This request comprised 12 claims, each of them being directed to a specific peptide from the gag or env protein sequences. They read as follows:

"1. A peptide of the formula:

(I) (15)

Y-Asp-Cys-Lys-Thr-Ile-Leu-Lys-Ala-Leu-
Gly-Pro-Ala-Ala-Thr-Leu-Glu-Glu-Met-Met-
Thr-Ala-Cys-X (from the gag p25 protein sequence)

where X is OH or NH₂, and Y, if present, is an amino acid added to facilitate coupling, N-terminal acetylated I, or I linked to a peptide or protein of at least 5,000 molecular weight, which peptide or protein does not normally bind to antibodies present in a human host.

2. A peptide of the formula:

(III) (92)

Y-Asp-Arg-Val-His-Pro-Val-His-Ala-Gly-Pro-
Ile-Ala-Pro-Gly-Gln-X (from the gag p25 protein
sequence)

where X is OH or NH₂, and Y, if present, is an amino acid added to facilitate coupling, N-terminal acetylated III, or III linked to a peptide or protein of at least 5,000 molecular weight, which peptide or

protein does not normally bind to antibodies present in a human host

3. A peptide of the formula:

(IV) (90)

Y-Tyr-Ser-Pro-Thr-Ser-Ile-Leu-Asp-Ile-Arg
Gln-Gly-Pro-Lys-Glu-Pro-Phe-Arg-Asp-Tyr-Val-
Asp-Arg-Phe-Tyr-Lys-Thr-Leu-Arg-Z-X (from the gag
p25 protein sequence)

where X is OH or NH₂, and Y and Z, if present, are amino acids added to facilitate coupling, N-terminal acetylated IV, or IV linked to a peptide or protein of at least 5,000 molecular weight, which peptide or protein does not normally bind to antibodies present in a human host.

4. A peptide of the formula:

(V) (88)

Y-Asn-Trp-Nor-Thr-Glu-Thr-Leu-Leu-Val-Gln-
Asn-Ala-Asn-Pro-Asp-Cys-Lys-Thr-Ile-Leu-Lys-
Ala-Leu-Gly-Pro-Ala-Ala-Thr-Leu-Glu-Glu-Nor-
Nor-Thr-Ala-Cys-X (from the gag p25 protein
sequence)

where X is OH or NH₂, and Y, if present, is an amino acid added to facilitate coupling, N-terminal acetylated V, or V linked to a peptide or protein of at least 5,000 molecular weight, which peptide or protein does not normally bind to antibodies present in a human host.

5. A peptide of the formula:

(VI) (97)

Y-Arg-Glu-Leu-Glu-Arg-Phe-Ala-Val-Asn-Pro-Gly-
Leu-Leu-Glu-Thr-Ser-Glu-Gly-Cys-Arg-Gln-Ile-
Leu-Gly-Gln-Leu-Gln-Pro-Ser-Leu-Gln-Thr-X
(from the gag p18 protein sequence)

where X is OH or NH₂, and Y, if present, is an amino acid added to facilitate coupling, N-terminal acetylated VI, or VI linked to a peptide or protein of at least 5,000 molecular weight, which peptide or protein does not normally bind to antibodies present in a human host.

6. A peptide of the formula:

(VII) (71)

Y-Asp-Thr-Gly-His-Ser-Ser-Gln-Val-Ser-Gln-
Asn-Tyr (from the gag p18 protein sequence)

where Y, if present, is an amino acid added to coupling, N-terminal acetylated VII, or VII linked to a peptide or protein of at least 5,000 weight, which peptide or protein does not normally bind to antibodies present in a human host.

7. A peptide of the formula:

(VIII) (36)

Val-Lys-Ile-Glu-Pro-Leu-Gly-Val-Ala-Pro-
Thr-Lys-Ala-Lys-Arg-Arg-Val-Val-Gln-Arg-
Glu-Lys-Arg-Ala-Z-X
(from the env gp110 protein sequence)

where X is OH or NH₂, and Z, if present, is an amino acid added to facilitate coupling, N-terminal acetylated VIII, or VIII linked to a peptide or protein of at least 5,000 molecular weight, which peptide or protein does not normally bind to antibodies present in a human host.

8. A peptide of the formula:

(IX) (56)

Ile-Lys-Gln-Leu-Gln-Ala-Arg-Ile-Leu-
Ala-Val-Glu-Arg-Tyr-Leu-Lys-Asp-Gln-Gln-Z-X
(from the env gp41 protein sequence)

where X is OH or NH₂, and Z, if present, is an amino acid added to facilitate coupling, N-terminal acetylated IX, or IX linked to a peptide or protein of at least 5,000 molecular weight, which peptide or protein does not normally bind to antibodies present in a human host.

9. A peptide of the formula:

(X) (39)

Arg-Ile-Leu-Ala-Val-Glu-Arg-Tyr-Leu-Lys-
Asp-Gln-Gln-Leu-Leu-Gly-Ile-Trp-Gly-Cys-
Ser-Gly-Lys-Leu-Ile-Cys-X (from the env gp41
protein sequence)

where X is OH or NH₂, N-terminal acetylated X, or X linked to a peptide or protein of at least 5,000 molecular weight, which peptide or protein does not normally bind to antibodies present in a human host.

10. A peptide of the formula:

(XI) (40)

Y-Lys-Ser-Leu-Glu-Gln-Ile-Trp-Asn-Asn-
Met-Thr-Trp-Met-Glu-Trp-Asp-Arg-Glu-
Ile-Asn-Z-X (from the env gp41 protein sequence)

where X is OH or NH₂, and each of Y and Z, if present, is an amino acid added to facilitate coupling, N-terminal acetylated XI, and XI linked to a peptide or protein of at least 5,000 molecular weight, which peptide or protein does not normally bind to antibodies present in a human host.

11. A peptide of the formula:

(XII) (23)

Y-His-Ser-Leu-Ile-Glu-Glu-Ser-Gln-Asn-
Gln-Gln-Glu-Lys-Asn-Glu-Gln-Glu-Leu-Leu-
Glu-Leu-Asp-Lys-Trp-Z-X (from the env gp41 protein sequence)

where X is OH or NH₂, and each of Y and Z, if present, is an amino acid added to facilitate coupling, N-terminal acetylated XII, or XII linked to a peptide or protein of at least 5,000 molecular weight, which peptide or protein does not normally bind to antibodies present in a human host.

12. A peptide of the formula:

(XIII) (79)

Y-Lys-Asp-Gln-Gln-Leu-Leu-Gly-Ile-Trp-Gly-
Cys-Ser-Gly-Lys-Leu-Ile-Cys-X (from the env gp41
protein sequence)

where X is OH or NH₂, and Y, if present, is an amino acid added to facilitate coupling, N-terminal acetylated XIII, or XIII linked to a peptide or protein of at least 5,000 molecular weight, which peptide or protein does not normally bind to antibodies present in a human host."

X. The following documents are mentioned in the present decision:

- (1): WO 86/02383 filed on 18 October 1985 and published on 24 April 1986 claiming priority from 18 October 1984 (FR 84/16013), 16 November 1984 (GB 8429099) and 21 January 1985 (GB 8501473);
- (2): Chang, N.T. et al., Science, Vol. 228, 5 April 1985, pages 93 to 96;
- (3): Cowl, R. et al., Cell, Vol.41, July 1985, pages 979 to 986;
- (5): Cabradilla, C.D. et al., Bio/Technology, Vol. 4, February 1986, pages 128 to 133;
- (7): Hopp, T.P., Molecular Immunology, Vol. 18, No. 9 1981, pages 869 to 872;

- (8): Prince, A.M. et al., Proc.Natl.Acad.Sci.USA
Vol. 79, January 1982, pages 579 to 582;
- (9): Hopp, T.P., Molecular Immunology, Vol. 21, No. 1
1984, pages 13 to 16;
- (11): Hopp, T.P. and K.R., Woods, Molecular Immunology,
Vol. 19, No. 11, 1982, pages 1453 to 1463.

XI. Appellant I's submissions in writing and during oral proceedings insofar as they are relevant to the present decision may be summarized as follows:

Article 123(2) EPC; admissibility of disclaimers

Main request

Claims 1 and 6 contained disclaimers of specific peptides which had been introduced for the purpose of delimiting the claimed subject-matter against the teachings of document (1) which was relevant for novelty purposes pursuant to Article 54(3)(4) EPC. There was no clearer way to disclaim these peptides than to identify them by their sequences. The number of disclaimed peptides (11 in claim 1 and 5 in claim 6) was entirely compatible with the requirement of clarity. The disclaimers were, thus, allowable.

Article 54(3)(4) EPC; novelty

Main request: claim 2; subsidiary request II: claim 20

- Claim 2 of the main request related to a method to be carried out with at least one peptide which was a

variant by conservative or non conservative substitution of a peptide specified in earlier claim 1 (ie which, in particular, was of the same size as the peptide disclosed in claim 1) and which was immunologically competitive with a LAV/HTLV-III protein. The patent specification (page 4, lines 14 to 17 and 43 to 45) made clear what kind of primary structure a variant peptide would be expected to have: it was produced to accommodate strain-to-strain variations and usually fewer than 20%, more usually fewer than 10% of its amino acids were exchanged. Indeed, four of the variant peptides described in the patent in suit were respectively 7.7%, 8.3%, 12.5% and 5.9% substituted. It would also be obvious for the skilled person that a variant had to come from the same genomic region as the peptide, it was derived from.

Thus, specific peptides disclosed in document (1) which happened:

- (a) to be of a size of at least 6 amino acids and smaller than 50 amino acids (as in claim 1, section IX supra), and
- (b) to be immunologically competitive with a LAV/HTLV-III protein and
- (c) to have a sequence **completely** different from any peptide originating from the regions mentioned in claim 1,

did not answer the definition of a variant peptide as was derivable from the technical information disclosed in the patent specification. Thus, the method disclosed

in document (1) did not destroy the novelty of the subject-matter of claim 2 of the main request.

- Claim 20 of subsidiary request II was directed to peptide variants by conservative or non conservative substitution of, in particular, the specific 19 and 26 amino acids long peptides disclosed in claims 8 and 9. For the same reasons as given in relation to claim 2 of the main request, specific, immunologically competitive, 19 or 26 amino acids long peptides disclosed in document (1) which had a **completely** different sequence from that of the specific peptides claimed in claims 8 or 9 were not detrimental to the novelty of the subject-matter of claim 20.

Subsidiary request I; claim 1

The claimed method required the use of peptides characterized by a combination of three specific features: their region of origin, their size and the way they were produced (synthesized in solution or on a solid support). This combination was not disclosed in document (1). Furthermore, it had to be kept in mind that the conformation of proteins was complex, involving a primary structure (the succession of specific amino acids), a secondary structure (for example, helical), a tertiary structure (folding upon itself) and, possibly, a quaternary structure (dimerisation). For this reason, it could equally be expected that synthetic peptides would have a different conformation from that of recombinantly synthesized peptides. In addition, synthetic peptides generally were of a smaller size (less than 49 amino acids instead of more than 50 amino acids). Thus, they would

not necessarily mimic or expose the same epitope in the same manner. Moreover, as a consequence of their greater length, recombinant peptides could contain additional epitopes. Accordingly, as the claimed method and that described in document (1) were carried out with different reagents, they could not be the same. Thus, the method described in document (1) was not detrimental to the novelty of the subject-matter of claim 1.

Article 56 EPC; inventive step

New subsidiary request III

The closest prior art document was document (2) which was a study of which HTLV-III encoded peptides immunologically reacted with antibodies in sera from AIDS patients. It was determined that some gag or env peptides of a length of at least 75 amino acids had that property. It was also suggested that these peptides could ultimately be useful reagents in particular to diagnose AIDS.

Starting from these teachings and aware of other scientific publications (eg. documents (3) or (4)) which taught to use large recombinant proteins for their antigenic properties, the skilled person would have been deterred from using short peptides for the same purpose as disclosed in document (2). Indeed, it was known that in general these peptides did not retain the 3-dimensional conformational epitopes and, so, might lose a significant degree of immune reactivity. It would also have been felt that with a small peptide there was a great risk of missing antibodies directed

to several retroviral strains i.e. a risk of not accommodating strain-to-strain variations. For these reasons, the skilled person would not have embarked on the project of obtaining small, immunologically competitive peptides such as claimed. Alternatively, he/she would not have had a reasonable expectation of success that small peptides could be used for the purpose they were intended to. The subject-matter of subsidiary request III as a whole was inventive.

- XII. Appellant II's submissions in writing and during oral proceedings insofar as they are relevant to the present decision may be summarized as follows:

Article 123(2) EPC; admissibility of disclaimers

Main request

Claim 1 contained as many as 11 disclaimers. This number of disclaimers clearly went against the principle stated in the Enlarged Board decision G 2/03 (OJ EPO 2004, 448) that a disclaimer is not allowable if the necessary limitation can be expressed in simpler terms, or if the disclaimers are so numerous that it would put an unreasonable burden on the public to find out what is protected and what is not protected.

Article 54(3)(4) EPC; novelty

Main request: claim 2; subsidiary request II: claim 20

- Claim 2 of the main request was drafted in very wide terms: the peptide variants were neither qualitatively nor quantitatively defined. The argument to the avail

that the skilled person would narrowly construe the "concept" of variants as defined in the claim (by conservative or non conservative substitution) on the basis of the technical information in the patent specification that the number of substituted amino acid residues in the variant would usually not exceed 20%, more usually not exceed 10% of the total amino acid residues was not convincing. Indeed, any feature following the term "usually" had to be understood not as a compulsory feature but as a preferred embodiment. Furthermore on page 4, lines 49 to 50, it was mentioned that the sequence of the polypeptides employed in the subject invention needed not be identical to that of any particular LAV/HLTV-III peptide. This last characteristic, of course, also implied that a variant needed not be recognizable as originating from the same region of the LAV protein as a putative corresponding native peptide. Thus, as the claimed variants could have any sequences, they were in fact solely characterized by their length and their ability to be immunologically competitive with a LAV/HTLV-III protein.

Document (1) (eg. page 14, lines 23 to 26) disclosed polypeptides comprising antigenic determinants included in the proteins encoded and expressed by the LAV genome, as well as the use of said polypeptides in an in vitro process of diagnosis for the detection of anti-LAV antibodies in sera of AIDS patients (page 44, lines 6 to 12). Many specific peptides were described which had a length of between 7 and 50 amino acids, for example, the peptides identified as "amino acids 780-803" (claim 8 and page 30) or as "amino acids 239-264" (claim 9 and page 24). These immunogenic peptides

respectively comprised 24 and 26 amino acids and, thus, were peptide variants in accordance with claim 2 of the main request or in accordance with claim 20 of subsidiary request II (dependent on claim 9). Thus, document (1) disclosed a method/a product which happened to fall within the scope of method claim 2 of the main request or within the scope of product claim 20 of the subsidiary request II. These requests were not allowable under Article 54(3)(4) EPC.

Subsidiary request I; claim 1

Appellant I had not provided any evidence to show that a synthetic peptide would be in any way different from the same peptide but recombinantly produced. It was impossible to conceive which step in either of the methods would bring a difference. This was all the more true since the peptides in question were of a small size, thus it would be most unlikely that they adopted a tertiary conformation. In this respect, it had to be noted that in the patent itself (page 8, lines 38 to 42 and 49 to 50), either method of peptide synthesis was proposed without any suggestion that it made any difference to the peptide structure. For these reasons, the feature "synthesized in solution or on a solid support" did not have any bearing on the claimed process which was not novel in view of the teaching in document (1) of a method using specific immunogenic peptides of the same length and originating from the same regions as now claimed.

Article 56 EPC; inventive step

New subsidiary request III

The closest prior art was document (2). The purpose of the study described therein was to identify regions of HTLV-III proteins which could ultimately be used for detecting anti-HTLV-III antibodies in the sera of AIDS patients. One peptide which had been recombinantly produced was described as particularly efficient: it was derived in part from the env region and was 81 amino acids in length (ORF clone 121 containing a portion of the env-lor region; page 96).

Starting from the closest prior art, the problem to be solved could be defined as isolating further peptides which would be better diagnostic reagents.

The solution given in claims 7 to 12 was specific peptides originating from the same env region as the DNA contained in clone 121, these peptides having a length from 17 to 26 amino acids.

Taking into account that the region was already identified in document (2), it needed no inventive step to look for further immunogenic peptides in this region. Moreover, the skilled person would have been perfectly aware that in order to obtain a good diagnostic reagent, one had to strike a balance between sensitivity and specificity. Thus, it would have been obvious to choose, in the specific env region, peptides of smaller size than 81 amino acids and test them for having retained sensitivity.

The entire sequence of the HTLV-III proteins was known and in accordance with the patent itself isolating the peptides was only a matter of routine work (page 8,

lines 38 to 50). Consequently, no inventive step could be seen in producing them.

Appellant I's argument that the skilled person would have been deterred from producing small peptides as diagnostic reagents for fear that they may have lost sensitivity was not convincing because the state of the art provided numerous examples of the use of short peptides in diagnosis (eg in document (11)). In the same manner, as it was known from document (7) to (9) that a short peptide (11 amino acids) could bind significantly to antibodies of different subtypes of hepatitis causing viruses, the skilled person would not have regarded the intrinsic, strain-to-strain variability of the HLTIV-III proteins as an obstacle to using a small peptide as diagnostic reagent.

For these reasons, inventive step was to be denied.

XIII. Appellant I requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or the first or second subsidiary request (all filed with fax of 10 January 2005) or the new third subsidiary request filed at the oral proceedings (consisting of claims 1 to 12 and an adapted description thereto).

Appellant II requested that the decision under appeal be set aside and the patent be revoked.

The other party (opponent 1) requested that the decision under appeal be set aside and that the patent be revoked.

Reasons for the Decision

Main request

Article 123(2) (3) EPC and 84 EPC

1. 11 and 5 disclaimers were added to granted claims 1 and 6 respectively to delimit the claimed subject-matter against the method as disclosed in document (1), a prior art document pursuant to Article 54(3) (4) EPC (see point 7 below). Each of these disclaimers is directed to a specific peptide identified by its sequence (or parts thereof).

2. In the Enlarged Board decision G 2/03 (supra, Order, point 2.1), it is stated that "a disclaimer may be allowable in order to restore novelty by delimiting a claim against state of the art under Article 54(3) and (4) EPC" and further that "a disclaimer is not allowable if the necessary limitation can be expressed in simpler terms in positive, originally disclosed features in accordance with Rule 29(1), 1st sentence EPC. In addition, a plurality of disclaimers may lead to a claim drafting which puts an unreasonable burden on the public to find out what is protected and what is not protected." (Reasons, point 3)

3. In the Board's opinion, there can be no clearer way to refrain from claiming specific peptides falling within regions of a protein which are themselves claimed than to disclaim these specific peptides. The presentation of at most eleven small peptide sequences does not create confusion which would cause lack of clarity as

to what is protected and what is not protected. For these reasons, the disclaimers in claims 1 and 6 are admissible (Article 123(2) EPC and 84 EPC).

4. The subject-matter of claims 1 and 6 is, by nature, of a narrower scope than the subject-matter of granted claim 1 because of the disclaimers. The method of claim 1 is also of a narrower scope than that of granted claim 1 because it is to be carried out with peptides originating from a restricted number of regions (Article 123(3) EPC).
5. Claims 2 to 5, 7 to 42 essentially correspond to granted claims 2 to 5, 7 to 21, 23 to 43 (granted claim 22 being deleted as well as the reference to peptide No. II in all claims previously containing it).
6. Thus, the requirements of Articles 123(2)(3) and 84 EPC are fulfilled by the claims of the main request.

Article 54(3)(4) EPC; novelty of claim 2

7. Document (1) is the publication of a Euro PCT application which claims priority from three priority documents having earlier filing dates (18 October 1984, 16 November 1984 and 21 January 1985) than the earliest priority date of the patent in suit (29 April 1985). Insofar as the disclosure of the Euro PCT application enjoys priority rights, its content is state of the art pursuant to Article 54(3)(4) EPC and, therefore, is to be taken into account when assessing novelty.
8. Of particular relevance is the teaching in the second priority document. In the passage bridging pages 1

and 2, the invention is described as follows: "*The present invention further aims at providing polypeptides containing sequences in common with polypeptides encoded by the LAV genomic RNA. It relates even more particularly to polypeptides comprising antigenic determinants included in the proteins encoded and expressed by the LAV genome occurring in nature. An additional object of the invention is to further provide means for the detection of ... antibodies against the LAV virus or proteins related therewith, particularly in patients afflicted with AIDS or pre-AIDS....*", and on page 15: "*These polypeptides can be used as diagnostic tools, particularly for the detection of antibodies in biological media, ...*".

Figures 4 to 12 show the complete sequence of the LAV genome including the gene encoding the gag protein. Figures 13 to 18 show the sequence of part of the LAV genome containing the gene coding for the envelope protein. The beginning and end of the gag open-reading frame, and specific gag peptides are taught on page 9, lines 8 to 12, 21 to 36 whereas the beginning and end of the env open-reading frame and specific env peptides are respectively taught on page 10, lines 14 to 17 and on page 11, lines 33 to 36 and on page 12, lines 1 to 26. These gag or env peptides which, for the majority of them, consist of between 6 and 50 amino acids are the same as those disclosed in the Euro PCT application itself (document (1), pages 23, 24, 28 to 30).

9. Claim 2 of the main request is directed to a method for detecting anti-LAV/HTLV-III antibodies in a sample whereby the sample is combined with a composition which, in its simplest formulation, comprises a peptide which is immunologically competitive with a LAV/HTLV-III

- protein, contains at least 6 and fewer than 50 amino acids and is further characterised as being a variant by conservative or non-conservative substitution of a peptide encoded for by the gag or env region.
10. It is, thus, immediately apparent that the claimed method and that disclosed in document (1) have in common the use of peptides within the same size range and having the same functional property. What remains to be assessed for reaching a conclusion on novelty is whether or not any of the specific peptides disclosed in document (1) can be considered as a variant by conservative or non-conservative substitution of a peptide originating in the gag or env regions, because, if one of them can, then an embodiment of the method of the prior art falls within the scope of claim 2 and there will be lack of novelty.
11. The expression "by conservative or non-conservative substitution" gives the "qualitative" information as regards the variants that any amino acid may be found at any position in the peptide. Indeed, it is an expression which covers the replacement of an amino acid by any other of the amino acids without restriction.
12. As for the term "variant", definitions thereof may be found in dictionaries (to be regarded as common general knowledge), for example as: "something which is slightly different from other similar things" (Cambridge Advanced Learner's Dictionary) or as "one or two more persons or things exhibiting usually slight differences" (Webster On Line). However, the term "variant" as found in claim 2 is not used for the sole

purpose of defining the peptide in the absence of considerations other than finding out its proper, absolute meaning (as is done in dictionaries); it is used in the framework of establishing the extent of protection which the patent proprietor deems commensurate with his technical achievement.

13. Indeed, Article 69(1) EPC states that: "The extent of protection conferred by a European patent or a European patent application shall be determined by the terms of the claims. Nevertheless the description and drawings shall be used to interpret the claims.". This statement is reflected many a time in the case law which establishes that in order to make an objective assessment of the content of a claim for the purpose of judging whether its subject-matter is novel and non-obvious, it is allowable to interpret the claim in the light of the description and drawings (cf. Case law of the Boards of Appeal of the European Patent Office; 4th Edition, 2001, page 169).

14. Turning now to the description in the patent in suit, one finds on page 4 the following three statements regarding the variant peptides:

"To accommodate strain-to-strain variations among different isolates, adjustments for conservative substitutions and selection among the alternatives where non conservative substitutions are involved, may be made."

"The peptides may be modified by introducing conservative or non-conservative substitutions in the peptides, usually fewer than 20 number per cent, more

usually fewer than 10 number per cent of the peptides being exchanged."

"It should be understood that the polypeptides employed in the subject invention need not be identical to any particular LAV/HTLV-III polypeptide sequence, so long as the subject compounds are able to provide for immunological competition with proteins of at least one of the strains of the LAV/HTLV-III retrovirus".

15. The first of these three statements could *prima facie* be understood as implying that the variant peptides will only contain a few changes reflecting the well-known genomic variability. Yet, the third of these statements definitely deprives the first one of its relevance: if a peptide variant need not be identical to any particular LAV/HTLV-III peptide, then it does not need to be produced to accommodate strain-to-strain variations. Otherwise stated, whichever limitation in the number of envisaged changes could have been inferred from the earlier passage is no more a limitation in the light of the latter. As for the second statement, it is written in such a way as to make any limitation to the number of changes a preferred embodiment rather than an unavoidable feature: this is the consequence of using the terms "usually" or "more than usually". On the basis of the description, it is, thus, not possible to give the expression "variant by conservative or non conservative substitution" any meaning other than the widest: ie a peptide having any amino acid sequence.

16. As counter-arguments to this finding, Appellant I pointed out that four examples in the patent in suit

were carried out with peptides comprising less than 10% substitution, and also expressed the view that the skilled person would, as a matter of fact, consider that a variant would be originating from the same viral region as the peptide, it is derived from. In the Board's judgment, the exemplified peptides serve to illustrate the invention in its most preferred embodiment but they may not assist an evaluation of the scope of the claim as discussed above. As for the further argument that it should be possible to "trace" a variant, it is remarked that such a property is not disclosed in the patent in suit, all to the contrary since, as already mentioned above (see point 15) and in accordance with the third paragraph mentioned in point 4, the variant need not be identical to any peptide from a viral isolate.

17. On page 30 of document (1), a peptide originating from the env region and being 24 amino acids in length is identified as "amino acids 780-803". Being a specific embodiment of the then disclosed invention, it is immunologically competitive with a native LAV/HTLV-III viral protein. It is not disclaimed in present claim 1 and therefore, cannot be considered as disclaimed in claim 2 by virtue of this claim being dependent on claim 1. The peptide "amino acids 780-803" falls within the definition of a variant in the claimed method.
18. In conclusion, the Board holds the view that it does not in general make sense to regard every peptide as a variant of every other peptide but that it makes sense to construe claim 2 in accordance with the claim itself and the disclosure in the patent. This leads to the finding that a peptide which is a variant by

conservative or non-conservative substitution need only have the required length and functionality. Thus, document (1) which teaches a method for detecting the presence of anti-LAV/HTLV-III antibodies in a sample employing in the assay medium, in particular, the peptide "amino acids 780-803" which falls within the definition of a peptide variant, destroys the novelty of the subject-matter of claim 2 under Article 54(3)(4) EPC.

19. One last remark may be made in relation to the main request. In the course of the written and oral proceedings, the novelty of the subject-matter of claim 1 (Section IX, supra) was also discussed at length. Arguments were brought forward as to how the generic disclosure - in particular but not exclusively in document (1) - of LAV/HTLV-III specific immunogenic regions could be damaging to novelty insofar as the peptides in claim 1 were also identified by their regions of origin and all of these regions were encoded by fragments of the same portion of the viral genome. Reference was made in this respect to the prevailing case law on overlapping ranges according to which novelty had to be denied when the skilled person would seriously contemplate applying the teaching of the prior art document in the range of overlap (T 666/89, OJ EPO 1993, 495). Also this approach seems to have some merits, but in view of the findings in point 18, supra, no reasoning will be developed on this point.

Subsidiary request I

Formal requirements

20. No objections were raised against this request on the grounds of Articles 123(2)(3) and 84 EPC and the Board is of the opinion that these requirements are fulfilled. With regard to claim 1 in particular, the following is noticed: the feature that the claimed method is to be carried out with a peptide synthesized in solution or on a solid support is found on page 16, lines 35 to 38 of the application as filed (Article 123(2) EPC). The peptides to be used in the claimed method are derived from a restricted number of regions when compared to those in granted claim 1 (Article 123(3) EPC). The claim wording is clear and supported by the description (Article 84 EPC).

Article 54(3)(4) EPC; novelty of the subject-matter of claim 1

21. According to Appellant I, the novelty of the method of claim 1 over the method disclosed in document (1) is ensured by the fact that the peptides to be used are produced in solution or on a solid support rather than recombinantly. Seen scientifically, there is *prima facie* no reason to assume that the different methods to produce the peptides would result in different entities. Had Appellant I produced any **evidence** to the contrary that small peptides - one such peptide disclosed in document (1) is 9 amino acids long: "amino acids 226-234" - such as are disclosed in the prior art and are also contemplated for use in the presently claimed method, would have a different structure depending on the way they were isolated, the case would be different

but no such evidence is on file. Instead, it was only **arguments** which were presented by Appellant I to the avail that chemically synthesized peptides would generally be of a smaller size than recombinantly produced peptides (less than 49 amino acids rather than more than 50 amino acids) and to the avail that the tertiary structure of proteins could be different depending on the way they were synthesized.

22. The Board does not see the relevance of these arguments to novelty. While it is true that on page 8 of the patent in suit, it is mentioned that the peptides, because of their relatively short size, may be synthesized in solution or on a solid support, it is also mentioned on that same page that the region of the viral genome coding for the peptide may be cloned by conventional DNA techniques and expressed. Thus, whereas the skilled person may have preferences as to which methods he/she will use, there is no absolute requirement that one is used and not the other, depending on the length of the peptide to be produced. Otherwise stated, both methods are available to prepare anyone of the peptides to be used in the claimed method. As for proteins which are, by definition, of bigger size than peptides, it is true that they may have for example, a different tertiary structure (eg. folding) depending, in particular but not exclusively, on the way they are synthesized. What is missing, however, is the rationale as to why such an observation would equally apply to such peptides as are comprised within the claim and are disclosed in document (1) which may be as small as 9 amino acids.

23. The above position is further supported by the fact that neither the patent itself nor any of the prior art documents caution against the fact that a given peptide may have a different structure depending on its mode of production, although differences in structure may well have consequences on antigenicity.
24. Thus, the method of document (1) which makes use of recombinantly produced peptides (such as peptide "amino acids 226-234") deprives the now claimed method of novelty. Subsidiary request I is thus rejected for failing to comply with the requirements of Article 54 EPC.

Subsidiary request II

Article 54(3)(4) EPC; novelty of the subject-matter of claim 20

25. Claim 20 of this request (section IX, supra) relates to a peptide which is a variant by conservative or non-conservative substitution of the specific 26 amino acids long peptide of claim 9. An interpretation of the expression "variant by conservative or non conservative substitution" was given in points 11 to 16 supra and the conclusion was reached that, in this specific case, the sequence of the variant did not help in defining said variant, the only two properties to be taken into account being its length and its functionality. Document (1) describes a 26 amino acids long peptide identified on page 24 as "amino acids 239-264". Being a specific embodiment of the there disclosed invention, it is immunologically competitive with a native LAV/HTLV-III viral protein. This peptide falls within

the definition of a variant as claimed in claim 20. The subject-matter of claim 20 is, thus, not novel and subsidiary request II is rejected for failing to fulfil the requirements of Article 54 EPC.

New subsidiary request III

26. This request relates to 12 specific peptides originating from either the gag or env regions. No objections were raised against any of the claims on formal grounds nor under Article 54 or 83 EPC. It is also the Board's opinion that the requirements of Articles 123(2)(3), 84, 54 and 83 EPC are fulfilled. The issue which remains to be decided is that of inventive step.
27. All parties and the Board agree that the closest prior art to the claimed specific peptides encoded by parts of the LAV/HTLV-III gag or env region is document (2). In this study, a combined cloning and expression system is used to identify HTLV-III encoded peptides which immunologically react with antibodies in sera from AIDS patients. DNA analysis indicates that HTLV-III DNA fragments encoding such peptides are derived from the open-reading frames corresponding to the gag, pol and env-lor regions. Two clones containing DNA fragments spanning the gag region from bp 1202 to bp 1690 express antigenic peptides with a size of respectively 156 and 75 amino acids. Three clones containing DNA fragments spanning the env region from bp 7077 to bp 7722 express antigenic peptides with a size of respectively 213, 81 and 108 amino acids (see Table 1, page 95).

28. Starting from the closest prior art, the problem to be solved can be defined as isolating further antigenic peptides which are immunoreactive with the sera of AIDS patients.

29. The provided solutions are six specific peptides encoded by DNA fragments spanning the gag region from bp 696 to bp 1385, having a size of between 12 amino acids (claim 6) and 36 amino acids (claim 4) and six specific peptides encoded by DNA fragments spanning the env region from bp 7498 to bp 7779, having a size of between 17 amino acids (claim 12) and 26 amino acids (claim 9) (see section IX, supra).

30. It is readily apparent that the claimed antigenic peptides and those disclosed in document (2) stem from neighbouring or even overlapping regions of the viral genome, yet that there is an important difference between them: the claimed ones are of significantly smaller size. In fact, they are of a smaller size than any of the antigenic immunoreactive HTLV-III gene products disclosed before the third priority date (26 March 1986) which is the valid priority date for all of the claimed peptides (some of them even enjoying earlier priority dates, 29 April 1985 or 19 August 1985). Thus, document (3) published in July 1985 discloses a 165 amino acids long protein (residues 475-640) which is characterized on page 985 as containing "a highly conserved epitope that may provide the best possibility as a wide-range diagnostic reagent.". Document (5) (abstract; published in February 1986) describes a 102 amino acids long immunoreactive protein as highly specific and sensitive.

31. *Prima facie*, it is the Board's opinion that the skilled person aware of these data had no reason to turn to smaller peptides. However, it was argued by Appellant II on the basis of further prior art that he/she would have had a reasonable expectation of success when attempting to isolate small antigenic peptides which, because of their intended use, should at the same time be highly antigenic (ie comprise more than one epitope or, at least, a very good epitope such as a conformational one) and be able to recognize antibodies raised against different strains of AIDS virus, as these are known for the sequence variability of their proteins.
32. Documents (7) to (9) and (11) were cited in this respect. The first three documents are all concerned with an 11 amino acids long peptide stemming from the Hepatitis B surface antigen. This antigen exhibits mutually exclusive strain-specific subtype antigenic determinants and the peptide contains epitopes of two of these determinants (HBsAg/a and HBsAg/d) but not of the third one (document (8), page 579, right-hand column, first full par.). It is also said on page 580, right-hand column, that the peptide has a limited antibody binding capacity. Document (11) is a study of the antigenic reactivity of small peptic fragments of α -lactalbumin. They are found to be antigenic when bound to each other by disulphide bridges ie when adopting a tri-dimensional configuration (abstract and Figure 4). It is mentioned on page 1463 (left-hand column, first full par.) that when no such configuration is formed, loss of antigenic reactivity ensues.

33. In the Board's judgment, the skilled person reading documents (7) to (9) or (11) would draw the conclusion that small peptides may indeed be antigenic yet not provide a solution to the problem to be solved: their size may hinder antibody binding, they may not be suitable to care for strain-to-strain variation and their antigenicity is best secured by the fact that they are able to form a tri-dimensional structure by interacting with each other. Otherwise stated, it would not have been obvious, especially in the light of the prior art teaching that larger molecules were very suitable, to make use of small peptides when setting up a method for detecting anti-LAV/HTLV-III antibodies in the sera of AIDS patients using such peptides, nor would it be done with a reasonable expectation of success. Accordingly, it is concluded that the claimed peptides are inventive.
34. Subsidiary request III fulfils the requirements for patentability.
35. At oral proceedings, the description was adapted by Appellant I: some objections raised by Appellant II were taken into account; others did not convince the Board.

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 maintain the patent on the basis of:
 - claims 1 to 12 of the New Third Subsidiary Request
 - pages 3 to 20 of the Adapted Description filed at the oral proceedings.

The Registrar:

The Chairwoman:

P. Cremona

U. Kinkeldey