BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS | BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE | CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

1164

Internal distribution code:
(A) [ ] Publication in OJ
(B) [X] To Chairmen and Members
(C) [ ] To Chairmen
(D) [ ] No distribution

D E C I S I O N
of 15 January 2002

Case Number: T 0351/98 - 3.3.4

Application Number: 85307860.8

Publication Number: 0181150

IPC: C12N 15/48

Language of the proceedings: EN

Title of invention:
Recombinant proteins of viruses associated with lymphadenopathy syndrome and/or acquired immune deficiency syndrome

Patentee:
CHIRON CORPORATION

Opponents:
Biotest AG
F. HOFFMANN-LA ROCHE & CO. Aktiengesellschaft
British Bio-technology Limited
Murex Biotech Limited
Akzo Pharma B.V.
Dade Behring Marburg GmbH
IMMUNO Aktiengesellschaft

Headword:
HIV-I/CHIRON CORPORATION

Relevant legal provisions:
EPC Art. 123(2) (3), 87, 54, 56, 83

Keyword:
"Main request: added subject-matter (no), broadening of scope (no)"
"sufficiency of disclosure (yes), right to priority (yes)"
"Novelty (yes), Inventive step (yes)"

Decisions cited:
G 0002/98, G 0001/93, T 0576/91, T 0939/92, T 0982/94, T 0824/94, T 0996/92, T 0323/91

Catchword:
Disclaimer based solely on Article 54(3) EPC prior art document held allowable (see point 45), contrary to view expressed in decision T 323/97.

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0351/98 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 15 January 2002

Appellant I: (Proprietor of the patent)
CHIRON CORPORATION
4560 Horton Street
Emeryville
California 94608 (US)

Representative:
Hallybone, Huw George
CARPMAELS AND RANSFORD
43 Bloomsbury Square
London WC1A 2RA (GB)

Appellant II: (Opponent 02)
Biotest AG
Landsteinerstrasse 5
D-63303 Dreieich (DE)

Representative:
Keller, Günter, Dr
Lederer, Keller & Riederer
Patentanwälte
Prinzregentenstrasse 16
D-80538 München (DE)

Appellant III: (Opponent 03)
F. HOFFMANN-LA ROCHE & CO
Aktiengesellschaft
Grenzacherstrasse 124
CH-4002 Basel (CH)

Representative:
Keller, Günter, Dr
Lederer, Keller & Riederer
Patentanwälte
Prinzregentenstrasse 16
D-80538 München (DE)

Other party: (Opponent 04)
British Bio-technology Limited
Watlington Road Cowley
Oxford OX4 5LY (GB)

Representative:
Walls, Alan J.
British Biotech Pharmaceutical Ltd
Watlington Road
Oxford OX4 5LY (GB)

1166

Other party:
(Opponent 05)

Murex Biotech Limited
Central Road
Temple Hill
Dartford, Kent DA1 5LR (GB)

Representative:

Silveston, Judith
ABEL & IMRAY
20 Red Lion Street
London, WC1R 4PQ (GB)

Appellant VI:
(Opponent 06)

Akzo Pharma B.V.
Weth. van Eschstraat 1
P.O. Box 20
NL-5340 BH Oss (NL)

Representative:

Armitage, Ian Michael
MEWBURN ELLIS
York House
23 Kingsway
London WC2B 6HP (GB)

Other party:
(Opponent 08)

Dade Behring Marburg GmbH
Postfach 1149
D-35001 Marburg (DE)

Representative:

Buck, Dr.
Dade Behring Marburg GmbH
P.O. Box 1149
D-35001 Marburg (DE)

Other party:
(Opponent 09)

IMMUNO Aktiengesellschaft
Industriestrasse 67
A-1221 Wien (AT)

Representative:

Kolb, Helga, Dr. Dipl.-Chem.
Hoffmann Eitle
Patent- und Rechtsanwälte
Arabellastrasse 4
D-81925 München (DE)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 10 March 1998 concerning maintenance of European patent No. 0 181 150 in amended form.**

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: R. E. Gramaglia
S. C. Perryman

Summary of Facts and Submissions

I. European Patent No. 0 181 150 (application No. 85 307 860.8) claiming priorities from US 667501 of 31 October 1984 (P1), US 696534 of 30 January 1985 (P2) and US 773447 of 6 September 1985 (P3) was filed on 30 October 1985. The patent relates to recombinant proteins of viruses associated with lymphadenopathy syndrome and/or acquired immune deficiency syndrome and was granted on the basis of 36 claims. Claims 1, 11, 15, 18, 21, 22, 31, 34, 35 and 36 as granted read as follows:

"1. A recombinant DNA construct useful for the expression of a recombinant polypeptide in a cell containing the construct, the construct comprising control sequences which regulate transcription and translation of the recombinant polypeptide in the cell and a coding sequence regulated by the control sequences, wherein the coding sequence comprises a DNA sequence of at least about 21 bp in reading frame characterised in that the DNA sequence encodes an antigenic HIV-I amino acid sequence of Figure 2 which sequence is immunologically non-cross-reactive with HTLV-I and HTLV-II and is reactive with HIV-I.

11. A cell comprising a recombinant DNA construct according to anyone of claims 1 to 10, wherein the cell expresses the antigenic HIV-I amino acid sequence and is free from other cells which do not express the antigenic HIV-I amino acid sequence.

15. A method of producing a recombinant polypeptide comprising an antigenic HIV-I amino acid sequence wherein a population of cells according to claim 11 is

cultured under conditions whereby the recombinant polypeptide is expressed.

18. An immunoassay for detecting antibodies to HIV-I in a sample suspected of containing the antibodies, characterised in that at least one recombinant polypeptide is used to bind the antibodies and the recombinant polypeptide comprises an antigenic env, gag or pol HIV-I amino acid sequence contained in the sequence shown in Figure 2, which polypeptide is immunologically non-cross-reactive with HTLV-I and HTVL-II.

19. An immunoassay according to claim 18 wherein at least one env amino acid sequence and one gag amino acid sequence are used to bind the antibodies.

21. A diagnostic reagent, immunogen or vaccine capable of binding an anti-HIV-I antibody in human serum characterised in that said reagent, immunogen or vaccine consists of an antigen comprising an immunogenic fragment of at least seven amino acids of an HIV-I env, gag or pol polypeptide, which fragment is immunologically non-cross-reactive with HTLV-I and HTVL-II and which has a sequence contained in the sequence shown in Figure 2.

22. A recombinant polypeptide characterised in that it is produced by a cell transformed by a recombinant construct according to claim 5.

31. An article of manufacture for use in an immunoassay for HIV-I antibodies characterised in that it comprises a solid support having bound thereto a recombinant polypeptide according to claim 22.

34. A DNA sequence encoding a HIV-I polypeptide derived from a phage selected from ARV-2(7D) (ATCC No. 40143), ARV-2(8A) (ATCC No. 40144), and ARV-2(9B) (ATCC No. 40158).

35. A recombinant DNA construct capable of expressing an antigenic HIV-I polypeptide derived from an organism selected from ATCC No. 53246, ATCC No. 20769 and ATCC No. 20768.

36. An isolated polynucleotide comprising the ARV-2 sequence of Figure 2 or a fragment of at least 21 bp thereof, provided that said fragment of at least 21 bp is not

i) a 3.5 kb viral insert from HTLV-III recombinant clone BH5,
ii) a 5.5 kb viral insert from HTLV-III recombinant clone BH8, or
iii) a 9.0 kb viral insert from HTLV-III recombinant clone BH10

disclosed in published European patent application EP-A1-0173529

further provided that said fragment of at least 21 bp is not

a) a 0.6 kbp viral insert from LAV designated LAV75,
b) a 0.8 kbp viral insert from LAV designated LAV82,
c) a 2.5 kbp viral insert from LAV designated LAV13,
d) a 9.1 to 9.2 kbp viral insert from phage ëJ19,
e) a DNA fragment extending from KpnI (6100) to approximately BamHI (8150) of ëJ19,
f) a DNA fragment extending from approximately

KpnI(3500) to approximately BglIII (6500) of ëJ19, or

g) a DNA fragment extending from approximately Pst (800) to approximately KpnI (3500) of ëJ19

disclosed in published European patent application EP-A1-0178978

further provided that said fragment of at least 21 bp is not

I a 2.3 kbp KpnI-KpnI fragment,
II a 1.0 kbp EcoRI-EcoRI fragment, or
III a 2.4 kbp EcoRI-HindIII fragment

disclosed in published European patent application EP-A2-0185444."

II. Notices of opposition were filed by nine opponents (O1) to (O9) all requesting the revocation of the European patent on the grounds of Article 100(a), (b) and (c) EPC. Opponents (O1) and (O7) withdrew the opposition when the case was still pending before the opposition division. By a decision notified on 10 March 1998, the latter held that the claims of the third auxiliary request filed during the oral proceedings held from 2 to 5 February 1997 satisfied the requirements of the EPC.

III. Appellant I (patentee) and appellants II, III and VI (opponents (O2), (O3) and (O6); hereinafter: appellants/opponents) filed appeals against the decision of the opposition division. Appellants II, VI and the other party (opponent (O5)) withdrew the appeal or opposition, respectively.

IV. The following documents are cited in the present decision:

(D1) EP-A-0185444;

(D1.1) USSN 659,339;

(D4) Sanchez-Pescador R. et al., Science, Vol. 227, pages 484-492 (February 1985);

(D6) Ratner L. et al., Nature, Vol. 313, pages 277-284 (24 January 1985);

(D7) EP-A-0178978;

(D7.1) GB 8423659;

(D9) Sarngadharan M. G. et al., Science, Vol. 224, pages 506-508 (4 May 1984);

(D10) Schüpbach J. et al., Science, Vol. 224, pages 503-505 (4 May 1984);

(D12) Wain-Hobson S. et a., Cell, Vol. 40, pages 9-17 (1985);

(D13) Kalyanaraman V.S. et al., Science, Vol. 225, pages 321-323 (20 July 1984);

(D22) Arya S.K. et al., Science, Vol. 225, pages 927-930 (31 August 1984);

(D30) Gnann J.W. et al., J. Virology, Vol. 61, No. 8, pages 2639-2641 (1987);

(D34) Levy J.A. et al., Science, Vol. 225, pages 840-842 (24 August 1984);

(D35) EP-A-0173529;

(D35.1) USSN 643,306;

(D42) Popovic M. et al., Science, Vol. 224, pages 497-500 (4 May 1984);

(D43) Gallo R.C. et al., Science, Vol. 224, pages 500-503 (4 May 1984);

(D49) Montagnier L. et al., Science, Vol. 225, pages 63-66 (6 July 1984);

(D60) Seiki M. et al., Proc. Natl. Acad. Sci. USA, Vol. 80, pages 3618-3622 (1983);

(D82) Gallo R.C. et al. in "Acquired Immune Deficiency Syndrome", M.S. Gottlieb and J.E. Groopman Editors, Alan R. Liss Inc. New York, pages 47-58 (1984);

(D88) San Francisco Chronicle of 10 September 1984;

(D120) Meyerhans A. et al., Cell, Vol. 58, pages 901-910 (1989);

(D122) Wain-Hobson S., AIDS, Vol. 3 (suppl. 1), pages S13-S18 (1989);

(D123) Marx J.L., Research News, pages 450-454 (22 March 1985);

(D124) Hopp T.P. et al., Proc. Natl. Acad. Sci. USA, Vol. 78, pages 3824-3828 (1981);

(D125) Kyte J. et al., J. Mol. Biol., Vol. 157, pages 105-132 (1982);

(D129) Geysen H.M. et al., Proc. Natl. Acad. Sci. USA, Vol. 81, pages 3998-4002 (1984);

(D162) US-A-4,716,102;

(A5) Comparison of the cell culture conditions according to documents (D34), (D48) and (D43) (appellant III);

(A7) Mann D.L. et al., AIDS Research and Human Retroviruses, Vol. 5, No. 3, pages 253-255 (1989);

(A8) American Type Culture Collection, Catalogue of Strains II, Fourth Edition 1983, pages 212 and 437;

(A9) Test report from Dr E. Faatz dated 6 July 1998 (appellant III);

(A11) Sell K.W. et al., The New England Journal of Medicine, Vol. 309, No. 17, pages 1064-1065 (1983);

(A12) Kelly A.T., Medical Hypothesis, Vol. 14, pages 347-351 (1984);

(A13) Executive Summary by the Subcommittee on Oversight and Investigation on the HIV Blood

Test Patent Dispute, 5 March 1997 (Gallo investigation);

(A15) Boucher C.A.B. et al., Journal of Clinical Laboratory Analysis, Vol. 4, pages 43-47 (1990);

(A18) Goudsmit J. et al., AIDS, Vol. 2, pages 157-164 (1988);

(A19) Goudsmit J. et al., Intervirology, Vol. 31, pages 327-338 (1990);

(A21) Janvier B. et al., AIDS Research and Human Retroviruses, Vol. 12, No. 6, pages 519-525 (1996);

(A30) Declaration of Prof. J.A.T. Young dated 15 March 1999 (appellant/patentee);

(A31) Comparison of the restriction maps shown in documents (D12) and (D7) (appellant/patentee);

(A32) Seligman S.J., AIDS Research and Human Retroviruses, Vol. 10, No. 2, pages 149-156 (1994);

(A33) Haaheim L.R. et al., Scand. J. Immunol., Vol 34, pages 341-350 (1991);

(A34) Papsidero L.D. et al., J. Virol., Vol. 63, No. 1, pages 267-272 (1989);

(A41) Declaration of Dr M. G. Sarngadharan dated 2 August 1999 (appellant VI);

(A46) Evans L.A. et al., J. Immunol., Vol. 138, No. 10, pages 3415-3418 (1987);

(A53) Di Marzio Veronese F. et al., AIDS Research and Human Retroviruses, Vol. 3, No. 3, pages 253-264 (1987);

(A54) Henderson L.E. et al., J. Virol., Vol. 66, No. 4, pages 1856-1865 (1992);

(A56) Declaration of Prof. G. Hobom and Prof. J.A. Richt dated 14 March and 3 March 2000, respectively (other party (opponent (O8));

(A59) Expert Report of Dr Cecilia Cheng-Meyer submitted on 19 May 1995 before the US District Court, Nothern District of California;

(A61) Kuiken C. et al. in "Human Retroviruses and AIDS 1999", Los Alamos National Laboratory, pages 300-301 and 332-341 (1999);

(A62) Declaration of Prof. J.A.T. Young dated 16 October 2000 (appellant/patentee);

(A63) Comparison of the restriction maps shown in documents (D35.1), (D7.1) and (D1.1) (appellant III);

(A70) Declaration of Prof. Robin Weiss dated 26 October 1999 (appellant VI);

(A71) Material Transfer Agreement between Dr R. Gallo and Prof. G. Hunsmann dated 14 August 1984 (appellant III);

(A72) Test report on the expression of HIV-I env according to Example 9 of priority document (P1)(other party (opponent (O8)).

V. On 24 September 1999 and 14 January 2000, the board issued two communications pursuant to Article 11(2) EPC of the rules of procedure of the Boards of Appeal with preliminary observations and comments on the case.

VI. The first three days of oral proceedings were held from 2 to 4 November 1999. These were resumed from 24 to 26 January 2001, during which appellant I (hereinafter: appellant/patentee) submitted a new main request (claims 1 to 29) in replacement of any previous claim request. Claims 1, 7, 9, 13, 16-19, 21-25, and 27-29 read as follows:

"1. A recombinant DNA construct useful for the expression of a recombinant polypeptide in a cell containing the construct, the construct comprising control sequences which regulate transcription and translation of the recombinant polypeptide in the cell and a coding sequence regulated by the control sequences, wherein the coding sequence comprises a DNA sequence of at least about 21 bp in reading frame characterised in that the DNA sequence encodes an antigenic HIV-I gag or env amino acid sequence of Figure 2 which sequence is immunologically non-cross-reactive with HTLV-I and HTLV-II and is reactive with HIV-I.

7. A recombinant DNA construct according to any one of claims 1 to 4, characterised in that the DNA sequence encodes an amino acid sequence from a gag polypeptide of HIV-I.

9. A cell comprising a recombinant DNA construct according to any one of claims 1 to 8, wherein the cell expresses the antigenic HIV-I amino acid sequence and is free from other cells which do not express the antigenic HIV-I amino acid sequence.

13. A method of producing a recombinant polypeptide comprising an antigenic HIV-I amino acid sequence wherein a population of cells according to claim 9 is cultured under conditions whereby the recombinant polypeptide is expressed.

16. An immunoassay for detecting antibodies to HIV-I in a sample suspected of containing the antibodies, characterised in that at least one recombinant polypeptide is used to bind the antibodies and the recombinant polypeptide comprises an antigenic env or gag HIV-I amino acid sequence contained in the sequence shown in Figure 2, which polypeptide is immunologically non-cross-reactive with HTLV-I and HTLV-II.

17. An immunoassay according to claim 16 wherein at least one env amino acid sequence and one gag amino acid sequence are used to bind the antibodies.

18. A diagnostic reagent or immunogen capable of binding an anti-HIV-I antibody in human serum characterised in that said reagent or immunogen consists of an antigen comprising an immunogenic fragment of at least seven amino acids of an HIV-I env or gag polypeptide, which fragment is immunologically non-cross-reactive with HTLV-I and HTLV-II and which has a sequence contained in the sequence shown in Figure 2.

19. A recombinant polypeptide characterised in that it is produced by a cell transformed by a recombinant construct according to claim 5.

21. A recombinant polypeptide characterised in that it is produced by a cell transformed by a recombinant DNA construct according to claim 7.

22. A recombinant polypeptide according to claim 21, wherein the gag amino acid sequence comprises p16 gag.

23. A recombinant polypeptide according to claim 21, wherein the gag amino acid sequence comprises p25 gag.

24. A recombinant polypeptide according to claim 21, wherein the gag amino acid sequence comprises a fusion protein of p16 gag and p25 gag amino acid sequences.

25. An article of manufacture for use in an immunoassay for HIV-I antibodies characterised in that it comprises a solid support having bound thereto a recombinant polypeptide according to claim 19.

27. A DNA sequence encoding an HIV-I polypeptide derived from a phage selected from ARV-2(7D) (ATCC No. 40143) and ARV-2(8A) (ATCC No. 40144).

28. A recombinant DNA construct capable of expressing an antigenic recombinant HIV-I polypeptide derived from organism ATCC No. 53246.

29. An isolated polynucleotide comprising a fragment of at least 21 bp from the gag or env region of the ARV-2 sequence of Figure 2, wherein said polynucleotide is not greater than 180 bp."

Claims 2 to 6 and 8 related to specific embodiments of the recombinant DNA construct of claim 1. Claims 10 to 12 related to specific embodiments of the cell of claim 9. Claims 14 to 15 related to specific embodiments of the method of claim 13. Claim 20 related to a specific embodiment of the recombinant polypeptide of claim 19. Claim 26 was addressed to a specific embodiment of the article of manufacture of claim 25.

VII. At the end of the resumed oral proceedings of 24 to 26 January 2001, the Chairwoman announced the following decision:

1. The debate on the claims is closed.

2. The appellant (patentee) is given two months from today in which to file an amended description adapted to the claims of the main request filed on 26 January 2001.

VIII. The appellant/patentee submitted on 14 March 2001 an amended description, which the appellants/opponents disapproved. On 27 July 2001, the board sent a communication expressing its provisional opinion on this issue. Oral proceedings were resumed on 15 January 2002 for the only purpose of adaptation of the description to the claims.

IX. The submissions by the appellants/opponents and the other party (opponent (O8)) in writing and during oral proceedings, insofar as they are relevant to the present decision, can be summarized as follows:

(A) *Article 123(2) EPC*

Claim 1

(a) In the application as filed, the DNA was defined by its being "substantially complementary" to a viral DNA sequence (see page 2, lines 27-29 and claim 1). In claim 1, however, this essential feature had been omitted and the DNA was defined by its encoding an amino acid sequence of env and gag of Figure 2. This meant that the subject-matter of claim 1 as filed had been extended to also cover DNA sequences degenerate to the sequence of Figure 2, which still encoded the same amino acid sequence.

Claim 1 in its present version comprised the wording "in reading frame", which was a feature disclosed in the application as filed only in connection with adaptors (page 6, lines 21-23). The claim, unlike the application as filed, thus covered DNA sequences of the env or gag regions which did not lie in the reading frame of env or gag but lay in "shifted" ORF's encoding proteins other than env or gag such as pol or "3'-ORF" (see the overlapping DNA sequences in Figure 2 on page 280 of document (D6)).

Claims 1, 5, 7, 9, 13, 16, 18 and 25-28

(b) The feature "HIV-I" in these claims found no basis in the application as filed, relating to the ARV-2 virus (see page 13, under the heading "Experimental").

Claim 9

(c) The feature "free from other cells which do not express the antigenic HIV-I amino acid sequence" found no basis in the application as filed.

Claim 18

(d) The term "immunogen" found no basis in the application as filed.

The claimed reagent or immunogen was not limited to recombinant proteins or fragments as in the application as filed but also covered natural or synthetic viral proteins and fragments thereof to be used as reagents or immunogens.

The feature "seven amino acids" found no basis in the application as filed.

Claim 29

(e) The feature "not greater than 180 bp" found no basis in the application as filed.

The term "region" found no basis in the application as filed.

(B) *Article 123(3) EPC*

Claims 25 and 26

(a) These claims had no counterpart in the granted claims so that a broadening of the scope of protection took place.

Claim 29

(b) Since claim 29 no longer comprised the disclaimers present in granted claim 36, a broadening of the scope of protection took place.

(C) *Article 84 EPC*

Claims 1, 16 and 18

(a) The expression "HIV-I gag or env" and "gag or env HIV-I" were not clear because of lack of sufficient definition.

Claim 29

(b) It was not clear whether the term "gag or env region" meant the open reading frame (ORF) or the DNA sequences coding for the viral proteins.

(D) *Sufficiency of disclosure (Article 83 EPC)*

Claims 1 and 16

(a) These claims were not enabled because the patent in suit did not teach how to select antigenic polypeptides having the required immunological activity, especially in the case of heptapeptides, which were too short to be antigenic. A test report from Dr Faatz (A9) demonstrated that no 25-mer immunogenic fragment could be identified by applying the "PepScan" method to the HIV-I p24 gag protein. Furthermore, document (D30) showed that no computer program had been successful in the prediction of antigenic determinant "598-609 of gp41" described in that report.

Claim 18

(b) Given the high mutation rate of the virus, it was impossible for the skilled person to identify HIV-I conserved antigenic determinants (epitopes) and to determine whether a specific peptide was clinically useful in diagnosis. Indeed, most of the antigenic sequences of Figure 2 were merely characteristic of that particular HIV-I isolate ("snapshot"), not of mutated HIV-I isolates. Therefore this particular antigen could turn out to be useless in recognizing antibodies in sera infected by a different isolate.

Claims 1, 6, 8, 16, 18 and 22 to 24

(c) Putative epitopes might not be representative of those actually recognised by antibodies during infection because of their merely linear rather than conformational nature. There was also uncertainty as to whether the proteins encoded by the DNA sequences of Figure 2 of the patent in suit would have actually been exposed on the virion, bearing in mind that cellular viral precursor proteins, upon processing by the host cell machinery, might not turn up in the virion. For instance, the patent in suit failed to identify the processed "complete" env or gag proteins (claims 6 and 8) or the p16 and p24 proteins (claims 22 to 24) as they finally appeared in the virion. In other words, the patent in suit failed to identify the **viral** (ie, as found in the virus particle) proteins and thus did not provide a basis for identifying the epitopes. As a consequence, these claims were not enabled. On the

same grounds, claims 1 and 16 ("antigenic...gag or env amino acid sequence") were also not enabled across their scope. Since immunodiagnostic methods using these putative epitopes could not work, claim 18 ("an immunogenic fragment... of an...env or gag polypeptide") was also not enabled across its scope.

(E) *Right to priority*

Claims 1-29

(a) The "same invention" was not described in the patent in suit and in the priority documents (P1) to (P3) because the definitions of gag and env covered longer chain sequences in the former. There were discrepancies between Figure 2 of the patent in suit and Figure 4 of priority documents (P1) to (P3): in Figure 2, env comprised an additional Glu-Lys-Lys-Gln-Lys-Thr-Val-Ala- (8 codons) sequence before the first Met, while in Figure 4, env started at Met. As regarded gag, Figure 2 of the patent exhibited 4 additional codons (Lys-Glu-Arg-Glu-), whereas in Figure 4, it started at Met.

There was moreover a discrepancy in documents (P1) to (P3) ((P1): page 9; (P2): page 10; (P3): page 14) that gag started at nucleotide (nt) 838, while it should have been nt 792 according to Figure 4 of these documents.

In conclusion, the "same invention" was not described in priority documents (P1) to (P3) and in the patent in suit insofar as the above claims

related to gag and env.

Claims 1, 6, 8, 16, 18, 22 to 24

(b) The env, gag, p24/25 and p16/18 proteins and antigenic fragments thereof were not clearly and unambiguously defined in priority documents (P1) to (P3). The N- and/or C- terminus of these proteins could not be derived therefrom. For instance, it was stated in (P1), page 9, line 29 that "the initiation codon for the [env] protein may not be the first codon for methionine, but may be the second or the third methionine, so that employing the sequence indicated above may result in an extended protein". As regarded proteins p24/25 and p16/18, even if the N-terminal amino acid started at the indicated places in Figure 4 of the priority documents, the C-terminal was not known because there was uncertainty as to whether proteins p24/25 and p16/18 were viral proteins or viral precursors of HIV-infected cell, susceptible of further processing by the cell's machinery. Therefore, these claims relating to antigenic/immunogenic env or gag polypeptides/ sequences (1, 16 and 18), complete env or gag sequences (6 and 8) or the p16 and p25 (fusion)proteins (22 to 24) could not rely on documents (P1) to (P3) for priority because the latter did not unambiguously identify the sequences which after processing by the HIV-I-infected-cell, actually appeared in the viral particles and provided the characteristic epitopes.

Claims 1, 16 and 18

(c) In priority document (P1), all the immunological features such as "antigenic", "reactivity with HIV-I", "immunologically non-cross reactive with HTLV-I and HTLV-II", "diagnostic" or "immunogen" related to an amino acid sequence encoded by a "27 bp" oligonucleotide, not by a "21 bp" one as in the claims at issue. It was true that the figure "21 bp" could be found in claim 15 of priority document (P1), however, it was only in the context of the preparation of an "expression product" ("A method for producing an expression product...an hTLR oligonucleotide sequence of at least 21 bp having an open reading frame"). Therefore Claims 1, 16 and 18 were not entitled to the priority date of document (P1).

Claims 1, 4 and 15

(d) The expression in bacteria or yeasts was not exemplified in priority documents (P1) and (P2), which failed to teach the specific manipulations required at the 5'- and 3'-ends of the coding sequences for expression in bacteria or yeasts. These claims could not rely on priority documents (P1) and (P2) insofar as they covered HIV-I proteins expressed in bacteria and yeasts. Furthermore, the information that bacterially expressed, and hence unglycosylated env would have been antigenic, could not be derived from priority documents (P1) to (P3). Expression of fused HIV-I proteins was also insufficiently disclosed in priority document (P1).

Claims 22 to 24

(e) Example 8 of priority documents (P1) to (P3) was not workable because the starting material from which the "p25 and p16 coded proteins" had been isolated was the **viral extract** as opposed to the **HIV-infected cellular extract** as in the corresponding example of the patent in suit (compare page 15, lines 14-20 of priority document (P1): the pellet containing the virus had been recovered after three centrifugations of **supernatants** at 2 krpm/10 min, 7 krpm/15 min and 25 krpm/1 hr and the viral proteins were electrophoresed on an acrylamide gel and the band corresponding to a 24,000 daltons or 18,000 dalton was excised from the gel (page 22, lines 25-28) with page 6, lines 50-51 of the patent in suit: the pellet containing the virus had been recovered from a low speed (2 krpm/1 hr) **centrifugate**, i.e. as HIV-infected cellular material). However, later documents (A53) and (A54) taken as experts' opinion, showed that the protein composition of a viral extract differed from that of a HIV-infected cellular extract: while a p15 gag (precursor) protein could be found in the latter, the former comprised merely a degradation product thereof (p6 gag). As a consequence, priority documents (P1) to (P3) were not enabling for obtaining what was claimed.

Claims 1, 5, 7, 9, 13, 16, 18 and 25-28

(f) These claims and the patent in suit (page 3, lines 18-26) related to HIV-I, while priority documents (P1) to (P3) related to ARV-2 (see page 15, under the heading "Experimental"), ie a different invention. The expressions of HIV-I gag

and env were also not disclosed in the priority documents.

Claim 29

(g) In an attempt to delimit the claim over documents (D1), (D7) and (D35), the disclaimer "wherein said polynucleotide is not greater than 180 bp" had been introduced. However the figure "180 bp" in claim 29 was to be found nowhere in priority documents (P1), (P2) or (P3). Therefore, the claim was not entitled to the filing date of documents (P1) to (P3) for claiming priority.

Claims 1-6, 9-21, 24-27 and 29

(h) Example 9 of priority documents (P1) and (P2) was not workable to the extent that it had been deleted from the patent in suit. According to Example 9 of priority documents (P1) and (P2), plasmid pSV-7c/7D, wherein transcription was controlled by the SV40 early promoter and polyadenylation signal, was used to transfect COS cells. The plasmid comprised a 3,300 bp EcoRI-KpnI (bp 5750 to bp 9037) ARV-2 (ë7D) insert coding for the env region. However, the presence in this insert of other start codons (inter alia, the tat and rev regions) upstream of the env coding region precluded expression of any env protein. The few activity (5%) reported in this example had to be ascribed to antibodies against the tat or rev protein (see document (A56)). An attempt by appellants/opponents' experts to reproduce Example 9 of priority documents (P1) and (P2) failed, while a similar experiment involving a

shorter insert of 3,200 bp devoid of the tat and rev start codons led to env protein expression (see document (A72)). In the successive publication of the present invention (see document (D4), legend to Figure 8), the expedient of using a shorter SstI-KpnI insert of 3,200 bp devoid of the tat and rev start codons (yielding plasmid pSV7c/env) also led to success. Priority documents (P1) and (P2) were thus not enabling for the expression of env and fragments thereof. The above claims, insofar as they related to env proteins, could not enjoy the priority dates of documents (P1) and (P2).

Claim 1

(i) The claim was not entitled to the filing date of documents (P1) to (P3) for priority, owing to the discrepancy between the expressions "21 bp in reading frame" (claim 1), covering the three possible reading frames and "having an open reading frame" (claim 15 of documents (P1) to (P3)) relating to one reading frame only.

Claim 9

(j) The expression "free from other cells" was not derivable from priority documents (P1) and (P2)

Claim 17

(k) The embodiment of this claim, relating to an immunoassay involving one env **and** one gag polypeptides to bind the antibodies, found no basis in the priority documents (P1) and (P2).

Claim 29

(l) The term "gag or env region" found no basis in priority documents (P1) to (P3).

Claim 18

(m) The claim could not enjoy the filing date of document (P1) for the purpose of the right to priority because the claimed reagent or immunogen was not limited to recombinant proteins or fragments as in the priority document (P1) but also covered natural or synthetic viral proteins and fragments thereof to be used as immunogens or reagents.

(F) *Novelty*

Claims 1-29

(a) Figure 3 of document (D1.1), on which document (D1) relied for the purpose of entitlement to priority, disclosed a 3,112 bp long DNA sequence. It was stated on page 5, lines 1-2 of the description that "Fig. 3 shows nucleotide sequences for HTLV-III DNA which encompasses the env region" a DNA sequence of more than 3,000 bases. The preparation of fragments of the sequence of Figure 3 was implicitly disclosed in priority document (D1.1). The skilled person could thus have synthesized specific probes in the light of Figure 3 and screened a gene library by means of colony hybridization in order to isolate the HIV-I gene, as done in Example 4 of document (D1.1). The so-obtained HIV-I DNA could be have

been "shot-gunned" in an expression vector according to Example 2 or page 7, lines 12-28 of document (D1.1) in order to obtain by expression polypeptides reactive with sera of AIDS-infected patients. Therefore, the above claims lacked novelty over document (D1)

It had already been established in decision T 824/94 of 18 November 1999 that document (D7) could rely on document (D7.1) for the purpose of the right to priority of the clone ë-J19, which had been deposited in connection with priority document (D7.1) on 11 September 1984. The paragraph bridging page 4 and 5 of this document located the env and gag regions. Figure 2 of document (D7.1) showed the restriction map of the LAV virus. On page 13 thereof, it was suggested to "shot-gun" the proviral DNA in expression vectors to get fusion proteins. Therefore, document (D7.1) made available to the skilled person the HIV-I genome, fragments thereof and means for arriving at the claimed subject-matter.

The three clones deposited in connection with documents (D35)/(D35.1) contained sequence information from HIV-I. Figure 2 of these documents showed a restriction map. Therefore, arbitrary fragments as well as the entire sequence were made available to the skilled person. The claims thus lacked novelty.

Claim 18

(b) This claim was not limited to recombinant proteins. Since documents (D9) and (D13) disclosed immunoassays involving HIV-I natural proteins, the claim lacked novelty.

(G) *Inventive step*

(a) An article in the San Francisco Chronicle (document (D88)) announced the successful cloning by Chiron of the AIDS-related virus (ARV) responsible for AIDS. The reader would have easily retrieved document (D34) referred to in this document. Document (D34) related to the isolation of the HIV-I virus (ARV) and to the HIV-I high producer cell line HUT-78.

(b) The skilled person would have followed the teaching of this document and isolated peripheral mononuclear cells (PMC) from infected patients and established an ARV-producing cell culture. The cell line referred to in document (D34) was available from the ATCC as HUT-78 TIB 161 (see document (A8)). This was equal to the HUT-78 H9 cell referred to in document (D34) used to isolate HIV-I (see document (A7), page 254, last 2 lines). Also the conditions for cultivating the cells were common general knowledge (see Table (A5)).

(c) The HIV-I high producer cell line referred to in document (D42) was freely distributed by Dr R. Gallo to several outside laboratories for research before the priority date of the patent in suit (see declaration from Dr M. G. Sarngadharan

(Document (A41)). Dr R. Gallo may have refused to release the cell to some scientists but this was not always true. With some of them the agreements were less restrictive (see document (A13), page 2 of 11: "Collaboration at will for Dr Weiss. O.K. R. Gallo" instead of "work performed will be on a collaborative basis" and Declaration of Prof Robin Weiss (document (A70); see also the Material Transfer Agreement between Dr R. Gallo and Prof. G. Hunsmann (document (A71)).

(d) The stably-infected cell line was not necessary, provided enough virus could be obtained. Document (D60) showed that adult T-cell leukemia virus (ATLV) could be cloned without such a stably-infected cell line. The skilled person would have established a PMC culture from infected patients and purified the virus from which the RNA could have been isolated, reverse translated in the presence of ^{32}P and the 9800 nt (cf. document (D88)) labelled cDNA used as a probe for screening a DNA library containing proviral DNA, and arrived.

(H) *Adaptation of the description*

Main request

(a) Adaptation of the description was fundamental for interpreting the scope of the claims by national patent judges, who might lack the necessary technical knowledge. No pol coding region, vaccines or labelled DNA probes fell within the scope of the claims presently on file. Doubts therefore arose as to whether these products were

within the scope thereof or not. Hence, the following passages had to be deleted from the description:

(i) Example 14 on page 20 referring to SOD-p31. This example also failed to illustrate the embodiment of claim 17 because it disclosed an immunoassay involving three components (p25 gag, env and SOD-p31) rather than two (claim 17). Protein p31 also did not belong to the prior art.

(ii) The reference to "p31" on page 5, last line.

(iii) The expression "as vaccines" (page 4, line 52); the sentence on page 4, lines 54-55 ending with "to be used for vaccination"; the passage on page 5, lines 1 to 9 relating to vaccines.

(iv) The reference to labelled DNA probes on page 6, lines 41-43.

Auxiliary request

(b) The objections raised under point 8.1 above against the amended description according to the main request still applied to the one according to the auxiliary request, merely differing therefrom by the deletion on page 20, line 36, of the reference "see EP-A-0181150".

XI. The submissions by appellant I (appellant/patentee) in writing and during oral proceedings insofar as they are relevant to the present decision can be summarized as

follows:

(A) *Article 123(2) EPC*

Claim 1

(a) The application as filed disclosed coding sequences in general with no limitation to DNA sequences "substantially complementary" to viral DNA and thus also contemplated degenerate coding sequences (see Example 12, page 31; page 6, lines 15-18). Therefore, no added subject-matter could be seen in omitting in claim 1 the wording "substantially complementary".

DNA sequences which did not lie in the reading frame encoding env or gag, although they belonged to the env or gag regions, could not "encode antigenic HIV-I polypeptide" as required by claim 1. Therefore, claim 1 did not cover said DNA sequences.

Claims 1, 5, 7, 9, 13, 16, 18 and 25-28

(b) The name "HIV-I" given to a virus was an arbitrary rather than a critical feature. In any case all the claims directly or indirectly related to the DNA sequence of Figure 2.

Claim 9

(c) No objection against the expression "free from other cells which do not express the antigenic HIV-I amino acid sequence" in claim 11 as granted (corresponding to present claim 9) had been raised

previously under Article 123(2) EPC by the appellants/opponents. Therefore consent was not given to the introduction of this new objection into the proceedings.

Claim 18

(d) The term "immunogen" in claim 18 found a basis on page 7, lines 25-26, page 8, lines 1-12, page 10, lines 30-32 and page 13, lines 6-7 of the application as filed.

The wording in the claim "consists of an antigen" (rather than "comprises") related to a single antigen (see page 3 of the minutes of the oral proceedings of 24 to 26 January 2001), ie a defined molecular species rather than to naturally-occurring polymorphic protein mixtures to be found in wild-type viral sources and which the application as filed did not relate to.

A claim to a polypeptide encompassed that polypeptide, whether obtained by synthetic chemical or biological means. Page 4, line 51 of the patent in suit did not relate to recombinant polypeptides or fragments thereof. The term "fragment" did not impart any "historical" feature on the product: a fragment of a recombinant protein could have been produced by chemical synthesis.

The feature "seven amino acids" found a basis on page 5, line 13 ("21 bp") of the application as filed.

Claim 29

(c) The figure "180" found a basis in the excluded subject-matter from document (D7), namely the shortest possible LAV BamHI-HpaI digest (181bp) obtainable by following the technical teaching of this document.

The term "region" found a basis in claim 1 as filed.

(B) *Article 123(3) EPC*

Claims 25 and 26

(a) These claims corresponded to claim 31 as granted.

Claim 29

(b) The claim was more restricted than claim 36 as granted because it related to coding fragments only and it excluded **all** the coding fragments of the prior art under Article 54(3) EPC. The appellants/opponents were not in a position to identify any fragment among the 13 DNA fragments excluded by the disclaimers in granted claim 36, which were covered by claim 29 (see paragraph VI supra).

(C) *Article 84 EPC*

Claims 1, 16 and 18

(a) The expression "HIV-I" given to a virus was

arbitrary. The patent in suit provided the genomic organisation of any strain of HIV-I, whose gag or env regions were fundamentally similar to that of HIV-I (see documents (A61) and (A62)).

Claim 29

(b) The term "gag or env region" was clear because it meant "gag or env coding region".

(C) *Sufficiency of disclosure (Article 83)*

Claims 1, 16 and 18

(a) Claims 1, 16 and 18 were enabled because the information provided by Figure 2 of the patent in suit gave enough information for the skilled person to identify short or long polypeptides which would be expected to be antigenic.

The patent in suit exemplified a very simple testing of the polypeptides against the serum of HIV-I-positive patients: a positive reaction indicated that the polypeptide contained the epitope looked for.

Methods for making theoretical predictions about whether a given sequence would contain an epitope were available from documents (D124) and (D125) disclosing the Hopp & Wood protocol. The "PepScan" method was already known before the priority date of the patent at issue and was particularly suited for identifying immunoreactive short peptides (see document (D129)). That the application of this technique to env peptides was possible, was

illustrated in later documents (A15), (A18) and (A19).

Dr Faatz's test report (A9) was contradicted by later documents (A21) and (A32) to (A34) showing that a great many antigenic peptides could be obtained from the p24-gag protein region by applying the Pepscan technique.

Since antigenic polypeptides cross-reacted with HIV-I patient sera, they were inherently suitable for use in immunoassays. It was not necessary to find a "golden" epitope as long as a mixture of epitopes could be recognised by most or by a substantial portion of AIDS patient antisera.

The claim did not cover putative epitopes which could not be detected in sera of HIV-I-infected patients. Speculating about what post-translational modifications might occur to the HIV-I proteins was not relevant as long as the patent in suit provided the necessary sequence information for obtaining the complete env or gag proteins or the p16 or p25 gag proteins.

(E) *Right to priority*

Claims 1-29

(a) Because the first amino acid to be translated was always a methionine (ATG codon), the skilled person would have known that the first four amino acids for gag and the first eight amino acids for env in Figure 2 of the patent in suit would not be translated. Therefore, the definitions of the env

and gag amino acid sequences were identical in both Figure 2 of the patent in suit and in Figure 4 of priority documents (P1) to (P3).

Claims 1, 6, 8, 16, 18, 22 to 24

(b) The statement on page 9, lines 29-30 of priority document (P1) and on page 4, lines 24-25 of the application as filed: "The initiation codon for the protein may not be the first codon for methionine but may be the second or the third methionine" was a cautious statement that in rare instances translation might begin with a methionine downstream of the first methionine. Whether the initiation codon was the first, the second or the third env ATG or which was the C-terminal of p25/24 or p18/16 was irrelevant to the issue of the right to priority since all the corresponding passages were the same in both priority document (P1) and in the patent in suit, ie they disclosed the "same invention" in this respect. As for the C-terminal of env or gag, Figure 4 of priority document (P1) gave the necessary information. Further claim 15 as originally filed referred to transforming a a unicellular microorganism host with an hTLR oligonucleotide sequence of at least 21bp. The skilled person would thus be aware from the priority document that 21bp was a possibility.

Claim 1 with its lower limit of "21 bp" was thus still directed to the same invention as disclosed in the priority document.

Claims 1, 4 and 15

(c) The priority documents gave the necessary information for the expression of HIV-I proteins in bacteria and yeasts and the expression of fusion proteins.

Speculation about what post-translational modifications might occur in the virus were not relevant.

Claims 1, 5, 7, 9, 13, 16, 18 and 25-28

(d) The name "HIV-I" given to a virus was an arbitrary rather than a critical feature. In any case all the claims directly or indirectly related to the DNA sequence of Figure 2.

Claim 29

(e) The introduction of a disclaimer in a claim in order to delimit this claim over the prior art was no matter of Article 88(1) but rather of Article 54 EPC.

Claims 1-6, 9-21, 24-27 and 29

(f) As for the workability of Example 9 of priority documents (P1) and (P2), the experiment carried out by the appellants/opponents (see document (A72)) differed from the protocol of Example 9 (see comparison list (A63)). The repeatability of the example had already been verified by an independent scientist who repeated Example 9 using the actual genetic construct described in detail in priority document (P1) (see document (A59)). Even if Example 9 could not be put into effect,

the teaching of priority document (P1) as a whole was sufficient to enable the skilled person to express the HIV-I env gene. The appellants/opponents had not been in a position to provide evidence that P1 was deficient in respect of some relevant technical information.

Claim 1

(g) Either of the expressions "in reading frame" (claim 1) or "having an open reading frame" (claim 15 of priority documents (P1) to (P3)) required that a HIV-I polypeptide be expressed. Therefore, only one reading frame was relevant to any particular construct in both claim 1 of the patent in suit and in claim 15 of priority documents (P1) to (P3).

Claim 9

(h) No objection against the expression "free from other cells which do not express the antigenic HIV-I amino acid sequence" in claim 11 as granted (corresponding to present claim 9) had been raised previously by the appellants/opponents. Therefore consent was not given to the introduction of this new objection into the proceedings.

Claim 17

(i) The claim was based on page 9, line 15-7 and page 14, line 17 of priority document (P1).

Claim 29

(j) The term "region" found a basis on claim 5, 6 7 and 8 of P1,

The feature "immunologically non cross-reactive with HTLV-I and HTLV-II" found a basis in claims 6 and 13 of document (P1).

(F) *Novelty*

Claims 1-17 and 19-29

(a) Document (D1.1) did not represent an enabling disclosure from which document (D1) could claim priority. No deposit of the clone containing the HIV-I DNA had been made and no suitable library was publicly available. The skilled person had thus to repeat the complete task of cloning the HIV-I genome. Since no deposit of the clone had been made, one had to rely on the document (D1.1). But Figure 3 thereof not only lacked legibility (C could be mistaken for G and vice-versa) but also comprised an "A" insertion at position 2437 which resulted in a translational frame shift in the partial env gene, so that only 63 triplets of the env region were correct (see document (A30)).

There was also no information as to the correct genomic organisation of the virus. The fragment of Figure 3 comprised no gag since the fragment contained only pol, sor and only 883 bases belonging to env. Document (D1.1) failed to identify the correct ORF for env.

Document (D7) could not rely on the deposit, as the sequence disclosed in Figures 4 to 11 of

document (D7) was not the clone that has been deposited in connection with the priority document (D7.1) on 11 September 1984 as ë-J19.

Document (D7.1) failed to disclose any DNA sequence, let alone the env and gag coding regions. The mere deposit of the ë-J19 clone was not a disclosure of the env and gag coding regions. The technical information which would have been necessary for the skilled person to be able to select a DNA molecule falling within the env or gag region of the HIV-I genome was missing.

At worst document (D7.1) could have been enabling for "shot-gunning" of unrepeatable random fragments: doing this did not make any information available to the public as to whether one actually got env, gag proteins or something else.

The deposit of BH clones did not make fragments available to the public since the mere deposit of BH clones did not come close to being a disclosure of the env and gag coding regions, a technical information enabling the skilled person to select a DNA molecule falling within the env or gag region of the HIV-I genome.

Claim 18

(b) The wording in the claim "consists of an antigen" (rather than "comprises an antigen") related to a single antigen (see page 3 of the minutes of the oral proceedings of 24 to 26 January 2001), ie a defined molecular species, different from naturally-occurring polymorphic protein mixtures

to be found in wild-type viral sources.

(G) *Inventive step*

(a) At the priority date of the patent in suit, there was no clear identification of the agent responsible for AIDS. It was proposed that AIDS could be caused by a fungal infection (see document (A11)) or by a mutant hepatitis B virus or even a prion-like agent (see document (A12)). The group led by Gallo believed this agent (HTLV-III) to be related to the known human T-cell leukaemia viruses HTLV-I and HTLV-II (see document (D42)). The group headed by Montagnier termed LAV (lymphadenopathy associated virus) the agent causative for AIDS (see document (D49)), while the Levy group named it ARV (AIDS-associated retrovirus) (see document (D34)). Since no genomic nor DNA sequence information was available, it was not known that ARV, HTLV-III and LAV were the same virus (HIV-I). Because of this confused nature of the state of the art, there was no single closest prior art document. Taking as closest prior art eg, document (D88) (and document (D34) easily retrievable by cross-reference) was likely to point to the solution of the problem set out by the patent in suit.

The problem to be solved was to isolate and identify the agent (HIV-I) responsible for AIDS and the env and gag coding regions thereof in order to provide proteins and DNA suitable for diagnosis and therapy.

(b) HIV-I was a cytopathic virus which killed virus-

infected cells (see eg document (D42), page 497, r-h column). In order to clone the HIV-I genome, a decisive step was thus the identification and production of a special cell line capable of sustaining growth (propagation) upon infection by the virus, with no cythopathic effects, so as to recover substantial quantities of the virus.

None of documents (D88), (D34), (D42) and (D49) provided the skilled person with adequate information to arrive at this special cell line.

As for document (D34), even if the skilled person obtained a HUT-78 cell line from the ATCC, the document (page 842, l-h column) merely stated "we infected human T-cell lines in the presence of antiserum to interferon and Polybrene" without giving sufficient details for performing the transfection (no protocol, no virus and reagent levels, no timing, no temperature). Further, document (A7) showed that HUT-78 consisted of a mixture of clones with different "HIV-I productivities". The success rate with HUT-78 was very low, as not all the HIV-I isolates were able to infect cell lines HUT78, CEM, Jurkat or U937 (see document (A46), page 3415, r-h column). The HUT-78 infected cell was deposited on 9 August 1984 in connection with US patent No. 4,716,102 (document (D162)) and became available only at the grant and publication of the patent on 29 December 1987.

Dr R. Gallo refused to release the cell without confidentiality agreements (see document (A13))

As for Montagnier's group, the transfection of the FR8 cell line according to document (D49) was a highly random event which would not be reproducible by the skilled person.

(c) Other alternatives such as transient cell cultures, did not work (see document (D42), page 500, final paragraph and document (D49), paragraph bridging pages 65 and 66). The adult T-cell leukemia virus (ATLV) disclosed in document (D60) could be cloned without a stably-infected cell line because it was a transforming virus, not a cytopathic one as HIV-I. There was no evidence that HIV-I could be cloned from PMCs. No DNA library containing proviral DNA was available either.

Secondary indicators of inventive step

(d) Cloning alone did not provide the skilled person with the claimed subject-matter. Assignment of the correct virus genomic organisation was also not obvious. The evidence provided by documents (D1), (D7) and (D35) showed that those of more than ordinary skill in the art failed to identify the correct ORFs, despite the availability of sequence information. There was a considerable confusion due to incorrect taxonomy (see document (D10)).

(e) The patent in suit showed that the recombinant p25-gag proteins were as effective as the natural p25-gag protein in immunoassays. This finding was surprising by itself.

(H) *Adaptation of the description*

Main request

(a) Although none of the claims presently on file related to the pol coding region, to vaccines or to labelled DNA probes, the following passages (i) to (iv) need not be deleted from the description, for the reasons given below:

(i) Example 14 on page 20 related to an ELISA immunoassay involving the three proteins p25 gag, env and SOD-p31. It was true that the latter protein was a recombinant fusion protein of superoxide dismutase (SOD) with protein p31 of the HIV-I polymerase (pol) coding region, however, the example illustrated "an immunoassay wherein at least one env amino acid sequence and one gag amino acid sequence are use to bind the antibodies" according to claim 17.

(ii) At the last line of page 5, reference was made to "p31". This was one of the three components of an immunoassay also involving p25 gag and env. Therefore, it also illustrated the immunoassay of claim 17 (see point (i) supra).

(iii) The expression "as vaccines" (page 4, line 52), the sentence on page 4, lines 54-55 ending with "to be used for vaccination" and the passage on page 5, lines 1 to 9 relating to vaccines were neither in contradiction with the claims as maintained, nor obscured the scope thereof.

(iv) The reference to labelled DNA probes on page 6, lines 41-43 also satisfied the conditions put forward under point (iii) above.

Furthermore, a reference "see EP-A-0181150" had been introduced on page 20, line 36 after "0.1 % SDS, pH 7.2" in order to give the reader instructions as to how to produce SOD-p31 and to thus render Example 14 (see point (i) above) enabling. The published application EP-A-0181150 underlying the patent in suit indeed comprised technical information as to how SOD-p31 could be arrived at.

Auxiliary request

(b) The amended description according to this request differed from the one of the main request in that the former no longer comprised the reference "see EP-A-0181150" on page 20, line 36, after "0.1 % SDS, pH 7.2".

XII. The appellant I (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the claims submitted as main request at the oral proceedings on 26 January 2001, pages 6-15, and 21 and 22 of the description as granted and pages 3 to 5, 16 to 20 and 23 of the description submitted as main request or as auxiliary request at the oral proceedings on 15 January 2002, and Figures 1 to 7 of the Figures as granted.

The appellants III (opponent 03) and the other party (opponent 08) requested that the decision under appeal be set aside and the patent revoked.

Reason for the Decision

1. The appeals are admissible.

Article 123(2) EPC
Claim 1

2. It has been argued by the appellants/opponents that there was added subject matter in claim 1 with respect to the application as filed because the latter allowed only a single type of DNA sequence to be inserted into the construct, namely one which was "substantially complementary" to a sequence found in the gag or env region, whereas claim 1 at issue now defines this DNA sequence to be inserted in terms of the amino acid sequence to be coded, including degenerate coding sequences.

3. The board observes that on page 6, lines 17-18 of the application as filed it is stated that "codons may be changed". This embodiment is illustrated by Example 12 on page 31 of the application as filed disclosing the synthesis of a DNA sequence using yeast-preferred codons, ie a degenerate coding sequence. Therefore, it has to be concluded that the application as filed relates to coding sequences in general including degenerate coding sequences with no limitation to DNA sequences "substantially complementary" to the viral gag or env regions. With regard to Article 123(2) EPC, the underlying idea is to safeguard that the public

will not be taken by surprise by a claim reworded during examination and/or opposition/appeal proceedings. In the present situation, the public would have looked at the whole of the technical subject-matter described in the application as filed (see decision G 1/93, O.J. EPO, 1994, 541, point 9 of the "reasons"), and not just the originally filed claims. The omission in claim 1 as granted of the wording "substantially complementary" compared to the original claims, and the definition of the DNA sequence to be inserted in the construct in terms of amino acid sequence to be coded are thus fairly based on the application as originally filed taken as a whole, and thus allowable under Article 123(2) EPC.

4. The appellants/opponents further argue that claim 1 covers subject-matter not present in the application as filed because it encompasses DNA sequences which do not lie in the reading frame of env or gag, although they belong to the env or gag regions. However, since the claim requires that "the DNA sequence... in reading frame" has to "encode[s] an antigenic HIV-I gag or env amino acid sequence", this feature is exhibited only by DNA sequences belonging to the reading frame of env or gag being in phase with a translational initiation and termination codon, ie in operative association with the expression control sequences therefor (see page 3, lines 6-11 and page 9, lines 27-29 of the application as filed) and **not** by the "shifted" HIV-I DNA sequences the appellants/opponents consider being covered by claim 1. So there is no objection under Article 123(2) EPC made out on this basis.

Claims 1, 5, 7, 9, 13, 16, 18 and 25-28

5. The appellants/opponents object that the term "HIV-I" in these claims represents added subject-matter vis-à-vis the application as filed directed to ARV-2 (see page 17, line 6). Yet, in the board's judgement, renaming as "HIV-I" (human immunodeficiency virus I) in the claims at issue the virus termed "ARV-2" on page 13 of the application as filed in no way alters the technical subject matter, which is defined in the present claims and the application as filed by means of the DNA sequence of Figure 2, a technical feature which unambiguously identifies the virus, regardless of how it is named. This is merely a matter of assisting the reader by use of the now commonly accepted terminology.

Claim 9

6. It has been argued by the appellants/opponents that the feature in this claim "free from other cells which do not express the antigenic HIV-I amino acid sequence" has no basis in the application as filed. The board disagrees. This feature can be derived from page 9, lines 8-11 and 16-17 and page 24, line 1 ("single ampicillin resistant colonies") of the application as filed dealing with the selection of transformed prokaryotic or eukaryotic cells expressing HIV-I proteins by means of a marker.

Claim 18

7. Contrary to the appellants/opponents' view, the term "immunogen" in claim 18 finds a basis on page 7, lines 25-26, page 8, lines 1-12, page 10, lines 30-32 and page 13, lines 6-7 of the application as filed.

8. The appellants/opponents argue that the claimed reagent

or immunogen is not limited to recombinant proteins or fragments as in the application as filed, but also includes natural or synthetic viral proteins and fragments thereof to be used as immunogens or reagents, and thus added new subject-matter. In the board's view, however, the wording in the claim "consists of an antigen" (rather than "comprises") means that the claimed diagnostic reagent or immunogen must be a single antigen, as acknowledged by the appellant/patentee during oral proceedings (see page 3 of the minutes of the oral proceedings of 24 to 26 January 2001). The board sees here a contrast to something based on a number of different antigen molecules. Since the claim is directed to a single antigen only, natural viral proteins and their fragments are excluded from the claim in view of their polymorphic nature (see eg documents (D120) and (D122)).

9. Moreover, it has to be noted that the application as filed is directed inter alia to recombinant proteins/fragments expressed in prokaryotic cells (page 9, line 8) such as E. coli (page 23, line 28). These are normally indistinguishable from chemically synthesized proteins/fragments. As regards the protein fragments, it has to be noted that the application as filed is silent as to the way by which these fragments are to be obtained (see eg page 7, lines 13-14: "The polypeptides or immunologically active fragments thereof"). The skilled person reading the application as filed will assume that they can be obtained not only via direct recombinant expression, but also by digestion of recombinant proteins with enzymes or by chemical synthesis.

10. Finally, contrary to the appellants/opponents' contention, the feature "seven amino acids" finds a basis in the "21 bp" feature of claim 1 of the application as filed, corresponding to seven encoded amino acids.

Claim 29

11. The "disclaimer" in the claim "wherein said polynucleotide is not greater than 180 bp" is objected to by the appellants opponents as finding no basis in the application as filed. However, it is the board's view that this disclaimer fulfills the requirements for allowability of a disclaimer set out in quite a number of decisions on the allowability under Article 123(2) EPC of a limitation called "disclaimer", eg in decision T 982/94 of 16 September 1997, according to which the disclaimed subject-matter has inter alia to be adequately supported by the disclosure of the prior art document occasioning lack of novelty in order that it be allowable under Article 123(2) (ibidem, point 2.1). These requirements are fulfilled in the present case since the disclaimer excludes polynucleotides longer than 180 bp disclosed in document (D7), a document citable pursuant to Article 54(3) EPC as prior art only for the purpose of considering novelty, the shortest of which polynucleotides is the LAV BamHI-HpaI digest (181 bp).

12. It has been objected that the term "region" in the claim found no basis in the application as filed. The board disagrees since this term is to be found on page 2, line 28, on page 3, line 11 and in claim 1 thereof.

Article 123(3) EPC
Claims 25 and 26

13. It has been argued by the appellants/opponents that these claims have no counterpart in the granted claims. Yet, they correspond to claims 31 and 32 as granted, respectively.

Claim 29

14. According to the appellants/opponents, a broadening of the scope of protection occurs in view of the deletion of the disclaimers present in granted claim 36 to yield present claim 29. In the board's judgement, however, the scope of the claim is more restricted than that of claim 36 as granted because it relates now only to DNA fragments of the env and gag coding region and it excludes **all** the fragments of the prior art under Article 54(3) EPC, unlike the scope of claim 36 as granted, which excluded in fact only 13 DNA fragments described in documents (D1), (D7) and (D35) and there is no evidence before the board that any fragment(s) among the 13 DNA fragments then excluded by the disclaimers in granted claim 36, is/are now subject-matter of claim 29.

Article 84 EPC
Claims 1, 16 and 18

15. In the appellants/opponents' view, the expression "HIV-I gag or env" lacks clarity.

However, whatever name is given to a virus (see point 5 supra), there is no lack of clarity as long as the virus is unambiguously defined by technical means,

here, the DNA sequence of Figure 2.

Claim 29

16. It has been objected by the appellants/opponents that the expression "gag or env region" lacks clarity. Yet, in the board's view, this wording is clear and relates to a portion of the virus DNA sequence coding for the gag or env proteins and spanning an ATG start codon up to the next stop codon in reading frame downwards. This definition is in agreement with the one given by appellant III/opponent (03) himself (see submission of 14 March 2000, page 3, second paragraph). Since the claim further comprises a reference to Figure 2 of the patent in suit, the skilled person is able to establish whether or not a given DNA sequence of 21 nucleotides or longer belongs to the "gag or env region".

Sufficiency of disclosure (Article 83)
Claims 1 and 16

17. The appellants/opponents maintain that these claims are not enabled because the patent in suit fails to teach how to select antigenic polypeptides having the required biological activity, especially in the case of eg heptapeptides, which are too short to be antigenic.

The claims at issue require that the polypeptides be antigenic, namely that they have to exhibit the property of binding to HIV-I antibodies, while being immunologically non-cross-reactive with HTLV-I and HTLV-II. Owing to the presence of this feature in the claims, the present situation differs from that dealt with in the "Agrevo" decision T 939/92 (O.J. EPO 1996, 309), wherein a group of chemical compounds **per se** was

claimed, ie no technical effect to be achieved was part of the definition of the claimed compounds. Hence when considering inventive step under Article 56 EPC, the objection arose that the alleged problem could not be regarded as solved by all the compounds covered by the claim in question, as it was not credible that all the claimed compounds produced the desired technical effect. In the present case, the polypeptides which are not "capable of binding an anti-HIV-I antibody" do not fall under the terms of the claims, so that the objection at issue is one to be strictly dealt with under Article 83 EPC only.

Firstly, the board observes that the above peptides as such can be made. A second question is whether antigenic peptides having the required antigenic activity can be arrived at. As regards the latter issue, methods for making theoretical predictions about whether a given amino acid sequence would contain an epitope were available before the priority date of the patent in suit. In fact, prior art documents (D124) and (D125) teach how to predict epitopes from hydrophobicity plots of proteins (the Hopp & Wood protocol). Moreover, document (D129) discloses a procedure for rapid concurrent synthesis on solid supports of hundreds of peptides to be used in antibody detection without removing them from the support. This technique named "PepScan" (scanning for antibody-reactive peptides) is particularly suited for identifying immunoreactive short peptides since it enables the location of epitopes on a protein with a resolution of seven amino acids (see document (D129), Abstract).

18. As for the shortest polypeptide capable of being

recognized by an antibody, post-published document (A34), taken as expert's opinion, demonstrates that even hexapeptides share this property (see Figure 5). When adapting the "PepScan" technique to the identification of "antigenic HIV-I gag or env amino acid sequence of Figure 2" (claims 1 and 16), in the board's view, the skilled person is able to produce a very large number of HIV-I polypeptides and to test them against the serum of HIV-I-positive patients (see eg page 14, line 34 of the patent in suit: "in the ELISA of eight AIDS patient sera"): a positive reaction would indicate that the polypeptide contains an epitope looked for. The successful application of the "PepScan" technique to mapping HIV-I epitopes is further illustrated by post-published documents (A15), (A18) and (A19), taken as experts' opinions.

19. Appellant III/opponent (03) filed evidence in form of a test report carried out by Dr Faatz (document (A9)), according to which no antigenic peptides could be found by applying the "PepScan" method to the HIV-I p24-gag protein region. The board, however, firstly notes that Dr Faatz uses thirty 25-mers overlapping each with the previous one by 15 amino acids. The overall "scanned" sequence thus spans 315 (10 x 30 + 15) amino acid residues instead of the 230 of the complete HIV-I p24 gag sequence (see document (A21), Figure 2), which seems to be a contradiction. Furthermore, the data of document (A21) contradict Dr Faatz's experimental finding, since two antigenic peptides are in fact identified by applying the "PepScan" to the HIV-I p24-gag region (see Figure 1). Finally, Dr Faatz's results are also not in line with the successful reports in later documents (A15), (A18) and (A19) of "PepScan" analysis of other HIV-I proteins. Therefore,

the board cannot treat the experiments carried out by Dr Faatz as reported in document (A9) as typical of what the skilled person trying to put into the practice the invention in suit would be able or unable to do, and thus does not find that a case of insufficiency has been made out.

20. Appellant III/opponent (03) drew attention to document (D30), showing that computer programs had not been successful in the prediction of antigenic determinant "598-609 of gp41" described in that report. In the board's view, however, it cannot be deduced from the failure of a theoretical method such as the Hopp & Wood protocol that applying a practical one ("PepScan") would also fail. Rather, since the "golden" epitope "598-609 of gp41" disclosed in document (D30) has in fact been found by "synthesizing peptides representing potential antigenic domain of HIV-I proteins and analysing the binding of these peptides to antibodies from HIV-Infected patients" (see page 2639, l-h column, first paragraph of document (D30)), the board has to come to the opposite conclusion that empirical verification is the ultimate and decisive test.

21. In view of the above, the board is of the opinion that the patent in suit provides sufficient information for the skilled person to arrive at an "antigenic HIV-I gag or env amino acid sequence of Fig. 2" using techniques of the prior art. The board is prepared to accept that the task of preparing the fragments and examining their immunogenic capacity is time consuming but considers it nevertheless as routine work.

Claim 18

22. The appellants/opponents maintain that owing to the highly variable nature of the virus, it is impossible for the skilled person to identify HIV-I highly conserved antigenic determinants (epitopes) clinically useful in diagnosis, in the sense that they recognize antibodies from a substantial number of strain variants.

23. As regards HIV-I highly conserved antigenic epitopes, the board agrees to appellant VI/opponent (06)'s submissions provided in a different context (see pages 12 and 13 of the notice of opposition dated 9 March 1994), that HIV-I genetic variations would have no significant technical consequences since the random mutation process is self-selecting for those viral genomes which are still functional, ie the mutations not only result in functional viruses, but in viruses which are still recognisable as HIV-I. It is, thus, biologically reasonable to assume that the regions with the greatest genetic stability are those regions coding for viral proteins which are structurally and functionally and thus biologically essential. Therefore, different HIV-I strains would share highly conserved regions. This view is indeed supported by eg post-published documents (A19) (see page 331, end of r-h column: "Epitopes E1-E4, E6, E9 and E11 are highly conserved between HIV-I isolates"), document (A21) (see page 521, l-h column, lines 3-4: "This area of the capsid protein, which is highly conserved in HIV-2/SIV...") and document (A33) (see page 341, l-h column: "regions of p24 are highly conserved between HIV-I-1, HIV-I-2 and SIV").

24. In view of this, it must be concluded that the skilled person looking for "antigenic HIV-I gag or env amino

acid sequence of Fig. 2" by applying the "PepScan" technique followed by testing the polypeptides against the serum of HIV-I-positive patients, will inevitably also identify conserved antigenic determinants and portions thereof, which bind to a higher or substantial number of AIDS patient sera, and thus find something useful in diagnosis. This board's view is corroborated by eg later document (A21) dealing with the application of the "PepScan" to the HIV-I p24 capsid protein (see page 520, bottom of l-h column: "These two sequences corresponding to amino acids (aa) 178-192 and 288-302 of p55, were recognised by 8 and 9 of the 20 HIV-1 Ab-positive sera, respectively"). Therefore, whereas finding a "universal" or "golden" epitope binding to 100% or maybe 90% of the sera of HIV-I-infected patients may not easily be within the reach of the skilled person, no evidence is before the board that identifying HIV-I conserved epitopes in general presents more difficulties compared with identifying an "antigenic HIV-I gag or env amino acid sequence of Fig. 2", as dealt with under points 17 to 21 supra. This finding is the decisive one when considering the requirements of Article 83 EPC.

Claims 1, 6, 8, 16, 18, 22 to 24

25. It is argued by the appellants/opponents that putative epitopes might not be representative of those actually recognised by antibodies during infection owing to their possibly linear versus folded nature. An objection is also raised that the above claims are insufficient under Article 83 EPC because the patent in suit fails to identify the **viral** (ie, as found in the virus particle) env and gag proteins (claims 1, 16 and 18) or "complete" viral env or gag proteins (claims 6

and 8) as well as the viral p16 and p25 gag proteins (claims 22 to 24), and thus does not provide a basis for identifying the epitopes exposed on the virion's surface.

26. The board firstly notes that no claim at issue is directed to viral proteins as found in the virion but rather to recombinant proteins of the HIV-I gag or env amino acid sequence of Figure 2. Bearing this in mind, the board would accept that some putative epitopes may not correspond to those actually recognized by antibodies on the virion's surface during infection, owing to their possible linear rather than folded nature or to a possible further processing of the env, gag, p16 gag or p25 gag (precursor) proteins by the host cell machinery. For the purpose of sufficiency of disclosure, it is sufficient that the patent in suit provides enough information for the skilled person to identify and prepare a substantial number of epitopes useful as antigens or in diagnosis across the whole range claimed, using common general knowledge and without undue burden. As seen under points 21 and 24 supra, it is the case here, because Figure 2 of the patent in suit provides the necessary information as to the N-terminal and C-terminal ends of the putative gag, env, p16 and p25 proteins or of a fusion protein of p16 gag and p25 gag (claim 24) and the skilled person is in a position, by means of a simple empirical test, to discriminate between, on the one hand, epitopes which are actually recognized by antisera during natural human infection and, on the other hand, epitopes which are not.

Conclusion (Sufficiency of disclosure (Art 83 EPC))

27. In view of the above findings, the board concludes that no case has been made out that any of the objected claims of the new main request do not satisfy the requirements of Article 83 EPC.

Right to priority
Claims 1-29

28. One major appellants/opponents' argument is that the "same invention" is not described in priority documents (P1) to (P3) and the patent in suit insofar as the above claims relate to "gag and env" because the definitions of the gag and env amino acid sequence covered longer chain sequences in Figure 2 of the patent in suit as compared with Figure 4 of the priority documents. The region labelled "GAG" in Figure 2 of the patent in suit (see line "268") exhibits indeed an additional Lys-Glu-Arg-Glu- sequence (4 codons) before the first Met, whereas in Figure 4, the "GAG" definition starts at Met (see line "783"). When compared with the "ENV" label depicted in Figure 4 of the priority documents (see line "6181"), the "ENV" definition in Figure 2 (see line "5668") comprises an additional Glu-Lys-Lys-Gln-Lys-Thr-Val-Ala- (8 codons) sequence before the first Met.

29. However, in the board's opinion, the skilled person would realize that the first four codons encoding Lys-Glu-Arg-Glu- ("GAG") and the first eight codons encoding Glu-Lys-Lys-Gln-Lys-Thr-Val-Ala- ("ENV") in Figure 2 of the patent in suit cannot be translated and hence these amino acid sequences cannot exist in the actual translated protein because they are not immediately preceded by an ATG start codon encoding methionine, at which protein translation initiation

must always take place. The differences noted in the representation of "GAG" and "ENV" in Figure 4 compared with Figure 2 follow from the fact that the untranslated N-terminal codons upstream of the ATG start codons are shown in Figure 2 as belonging to an open reading frame (ORF), ie, a DNA portion having coding potential located between two stop codons in reading frame, separated by a predetermined number (multiple of three) of nucleotides. Whereas Figure 2 shows this complete ORF for "GAG" and "ENV", Figure 2 is silent as to the "coding potential" (ie, the information that the codons are in themselves "sense", regardless of their being actually translated into a protein) of the region of the ORF upstream of the first ATGs. This board's view is corroborated by Figure 1 (page 11) of document (D12), wherein seven additional "sense" triplet before the env ATG (Met) are also shown. In spite of that, the authors of document (D12) do not consider these codons as being part of the env coding region (see page 13, bottom of r-h column: "The env open reading frame has a possible **initiator methionine** near the beginning (eight triplets)" (emphasis added). In conclusion, the board considers that, despite the apparent differences, the technical information conveyed by Figure 2 as to the definition of gag and env is identical to the one derivable from Figure 4.

30. As for the wrong information in documents (P1) to (P3) that gag started at nucleotide (nt) "838", the skilled person will easily and inevitably derive from Figure 4 of these priority documents that "nt 838" should read "nt 792" .

31. In conclusion, the discrepancies emphasized by the

appellants/opponents are immaterial to the requirement of the "same invention" (Article 87 EPC) between priority documents (P1) to (P3) and the patent in suit insofar as the above claims relate to gag and env.

Claims 1, 6, 8, 16, 18, 22 to 24

32. In the appellants/opponents' view, priority documents (P1) to (P3) fail to clearly and unambiguously define and identify the **viral** (ie, as found in the virus particle) env and gag proteins (claims 1, 16 and 18) or "complete" viral env or gag proteins (claims 6 and 8) as well as the viral p16 and p25 gag proteins (claims 22 to 24) in terms of the N- and/or C- terminus of these proteins or in terms of the amino acid sequences which after processing by the cell machinery, are actually exposed in the viral particles and provide the epitopes looked for. Emphasis is placed on the passage in priority document (P1), beginning on page 9, line 29 "the initiation codon for the [env] protein may not be the first codon for methionine, but may be the second or the third methionine, so that employing the sequence indicated above may result in an extended protein".

33. In the board's view, this passage merely warns that the **viral** (ie, as actually found in the virion) env protein might be shorter than the putative env protein. However, **no** claim at issue is directed to viral proteins as found in the virion but rather to "recombinant proteins of the HIV-I gag or env amino acid sequence of Fig. 2". The board notes that the **putative** N- and C-termini of the env, gag, p24/25, p16/18 proteins as well as of the p16/p25 fusion protein (claim 24) which can be derived from Figure 4

of priority document (P1) are the same as in Figure 2 of the patent in suit. Moreover, the passage on page 9, line 29 of document (P1) pointed out by the appellants/opponents is also the same as the one starting on page 4, line 24 of the patent in suit. Therefore, it must be concluded that priority document (P1) and the patent in suit disclose the "same invention" (Article 87 EPC) in terms of technical information about the putative N- and C-termini of the env, gag, p24/25, p16/18 proteins and the p16/p25 fusion protein. It has to be noted that this technical information renders possible the production not only of "complete" proteins but also of N- and/or C-"truncated" forms thereof. Both the patent in suit (see page 4, line 24ff; page 4, lines 46-47; claim 19 (via claim 5) and claim 21 (via claim 7)) and priority document (P1) indeed relate to such "truncated" proteins (see page 9, line 29ff; page 10, last line to page 11, line 2; claims 5, 17 to 19, 22 and 23).

34. As for the p16/p25 fusion protein, it should be noted that claim 24 at issue is directed to "a recombinant polypeptide wherein the gag amino acid sequence **comprises** a fusion protein of p16 gag and p25 gag amino acid sequences" (emphasis added). The claim has to be seen as embracing any recombinant polypeptide including ("comprising") an amino acid sequence starting with Pro-Ile-Val- at position 139 and ending with -Ser-Ser-Gln at position 506 in Figure 2 of the patent in suit (see also the DNA insert of Figure 5, wherein the first Pro has been replaced with a Met to allow for translational initiation). The counterpart of this sequence in Figure 4 of priority document (P1) starts at line "1143" with Pro-Ile-Val- and ends with -Ser-Ser-Gln at line "2283". Priority document (P1) also

implicitly discloses such recombinant polypeptides falling under the term of claim 24 since by expression in eg E. coli of the SacI-EcoRV DNA fragment referred to on page 10, line 29 to page 11, line 2 of document (P1) (identical to page 4, lines 43-47 of the patent in suit) or of the DNA (encoding the complete gag) of claim 7 (document (P1)), one inevitably obtains a recombinant polypeptide including "a fusion protein of p16 gag and p25 gag amino acid sequences".

35. Therefore, it must be concluded that priority document (P1) and the patent in suit also disclose the "same invention" insofar as the p16/p25 fusion protein is concerned.

Claims 1, 16 and 18

36. The appellants/opponents maintain that any immunological feature in priority document (P1) ("antigenic", "reactivity with HIV-I", "immunologically non-cross reactive with HTLV-I and HTLV-II", "diagnostic" or "immunogen") relates to an amino acid sequence encoded by a "27 bp" oligonucleotide, not by a "21 bp" one as in the claims at issue, which are thus not entitled to the priority date of document (P1).

37. The board agrees that the figure "21 bp" in claim 15 of priority document (P1) relates to the preparation of an "expression product" ("a method for producing an expression product...an hTLR oligonucleotide sequence of at least 21 bp having an open reading frame"). However, priority document (P1) provides the further information that any expression product has to exhibit immunological properties that render it suitable for use in immunoassay (see page 11, lines 3-6: "The

polypeptides which are expressed by the above DNA sequences may find use in a variety of ways. The polypeptides or immunologically fragments thereof, may find use as diagnostic reagents"). Therefore, any amino acid sequence expressed from a "21 bp" has to share, by implication, the same immunological properties ("antigenic", "reactivity with HIV-I-1", "immunologically non-cross reactive with HTLV-I and HTLV-II", "diagnostic" or "immunogen") as those exhibited by a peptide expressed from a "27 bp" oligonucleotide. In conclusion, the lower limit "21 bp" does not affect the requirement of the "same invention" between the above claims and priority document (P1).

Claims 1, 4 and 15

38. These claims are not, in the appellants/opponents' view, entitled to the priority dates of documents (P1) to (P3), insofar as they cover HIV-I (fusion)proteins expressed in bacteria and yeasts. This objection is based on the following: (i) the expression in bacteria or yeasts is not exemplified in priority documents (P1) and (P2); (ii) these documents fail to teach the specific manipulations required at the 5' and 3' ends of the coding sequences for expression in bacteria or yeasts; (iii) the expression of fused HIV-I proteins is also insufficiently disclosed in priority document (P1); (iv) the information that bacterially expressed, and hence unglycosylated proteins would be antigenic, cannot be derived from priority documents (P1) to (P3).

39. In the board's judgement, while examples in a priority document may provide information whether or not the same invention in terms of validly claiming priority is disclosed, lack of examples does not automatically

allow the converse conclusion. The decisive question is rather whether the skilled person is able to put into practice the expression in bacteria or yeasts of HIV-I (fusion)proteins and fragments thereof in the light of the technical information provided by the priority documents as a whole, possibly supplemented by the common general knowledge. As regards the expression system, the teaching of eg priority document (P1) relates to an unicellular microorganism in general (see claims 6 and 16). On page 12, lines 30-32 thereof, E. coli and S. cerevisiae are mentioned among other microorganisms. The term "yeasts" is referred to on page 11, line 23. The coding regions of the gag and env polypeptides are specifically identified in Figure 4. On page 13 and 14, a general description of expression vectors (eg vector SV40 referred to on page 25, line 17) is to be found. Pages 9 and 10 disclose how to obtain fragments containing the desired coding region and how to modify DNA sequences by addition of linkers and by removal of superfluous nucleotides. Moreover, the skilled person is certainly aware that antigenicity is not confined to the case of glycosylation and that bacterially expressed (unglycosylated) proteins would be antigenic. Therefore, the conclusion cannot be drawn that the priority documents are deficient in respect of relevant technical information for achieving the expression in bacteria or yeasts of (possibly unglycosylated) antigenic HIV-I (fusion)proteins and fragments thereof.

Claims 22 to 24

40. The appellants/opponents argue that Example 8 of priority documents (P1) to (P3) is not enabling for obtaining what is claimed because the starting material

from which the p25 and p16 gag proteins are isolated is the **viral extract** comprising no p16 gag protein but merely the p6 gag degradation product thereof. Attention is drawn to documents (A53) and (A54), according to which an **HIV-Infected cellular extract** (Example 8 of the patent in suit) contains a p15 gag (precursor) protein, whereas a viral extract merely comprises the p6 gag degradation product thereof.

41. The board observes that a possible discrepancy between Example 8 of the priority documents and the patent in suit as regards the starting material (viral versus HIV-infected cellular extract) from which the p25 and p16 gag proteins are isolated would be immaterial to the p25 gag protein's fate. This is because this protein does not undergo further processing in the infected cell and is also detected as such (ie in undegraded form) in the viral extract (virions). A "p24" band can indeed be noted in Figure 2, lane HIV-1_{MN} of document (A54), showing the SDS-PAGE carried out on a viral extract (see also the legend to Figure 1: "HIV-1_{MN} virions were disrupted"). Therefore, the only issue left is whether the priority documents are enabling for obtaining the p16 gag (fusion)protein of claims 22 and 24, once the discrepancy pointed out by the appellants/opponents is taken into account.

42. In contrast to Example 8 of the priority documents and of the patent in suit, relating to the **native** p16 gag protein cut from polyacrylamide gel, claims 22 and 24 are directed to **recombinant** p16 gag (fusion)proteins. Therefore, the decisive question is whether this recombinant p16 gag is "the same invention" in the priority documents and in the patent in suit. This question has already been answered positively under

point 33 supra. Moreover, since the patent in suit has been found to be enabling for obtaining the recombinant p16 (fusion)proteins of claims 22 and 24 (see point 27 supra), this conclusion has to be extended to priority document (P1), disclosing the "same invention".

Claims 1, 5, 7, 9, 13, 16, 18 and 25-28

43. It is objected by the appellants/opponents that claims relating to "HIV-I" are not "the same invention" as the one disclosed in the priority documents dealing with "ARV-2" (see eg bottom of page 3 of priority document (P1)).

As already stated above (see point 5 supra), renaming as "HIV-I" in the claims at issue the virus termed "ARV-2" in the priority documents in no way alters the technical information content, bearing in mind that the claims at issue directly or indirectly define the virus by means of the DNA sequence of Figure 2, corresponding to Figure 4 of the priority documents. That is a technical feature which unambiguously identifies the virus, regardless of any arbitrary name.

Claim 29

44. The appellants/opponents maintain that the claim cannot enjoy the priority date of documents (P1) to (P3) because the figure "180 bp" in the limiting feature "wherein said polynucleotide is not greater than 180 bp" finds no basis in priority documents (P1), (P2) or (P3).

45. The board considers that no change in either the nature of the invention or in the identity of inventions takes

place by introduction into claim 29 of the upper length boundary "180 bp" in order to overcome an objection of lack of novelty over documents (D1), (D7) and (D35) which are deemed prior art pursuant to Article 54(3) EPC. This is because the claimed gag or env polynucleotides "not greater than 180 bp" have their counterpart (and are the same invention as) in eg page 4, lines 15-16 of priority document (P1) disclosing such polynucleotides. As for the absence of the precise figure "180 bp" in the priority documents, it should be noted that, according to the established case law on "disclaimers" (see point 11 supra), where an overlap occurs between the prior art and the claimed subject-matter, specific prior art may be excluded by disclaimer to establish novelty even in the absence of support for the excluded matter in the application as filed. Where, as here, this prior art is formed by third party patent applications which are prior art only by the deeming provision of Article 54(3) EPC, so that the later applicant could not know of their contents and so could not formulate his originally filed claims to avoid their contents, it seems justifiable on a balanced interpretation of the European Patent Convention to allow the later applicant to limit his claims to what is novel over the Article 54(3) EPC prior art by means of a disclaimer. In this situation a too literal insistence on a precise basis in the original disclosure for the purposes of Article 123(2) EPC would have the effect of extending the deemed publication provisions of Article 54(3) EPC to matter which was not disclosed in the earlier applications. The board is aware that since coming to its decision on the claims in this case, there have been published decisions of other boards of appeal (in particular T 323/97 of 17 September 2001) expressing a

different view on the allowability of disclaimers, but for the case of Article 54(3) EPC prior art this board still considers the view taken above the more appropriate interpretation of the European Patent Convention.

Claims 1-6, 9-21, 24-27 and 29

46. It is the appellants/opponents' opinion that the above claims, owing to the lack of reproducibility of Example 9 of priority documents (P1) and (P2), relating to the expression of the env protein, are not entitled to the priority dates of documents (P1) and (P2), insofar as they relate to env proteins. It is pointed out that this deficiency is due to the presence of other start codons (inter alia, of tat and rev) upstream of the env coding region in the 3,300 bp EcoRI-KpnI insert of plasmid pSV-7c/7D, which precludes expression of any env protein. To buttress this view, the appellants/opponents provided a test report (see document (A72)) showing that no env protein expression occurs by repeating Example 9 of priority documents (P1) and (P2), whereas successful expression takes place in a similar experiment involving a shorter env insert of 3,200 bp devoid of the tat and rev start codons upstream of the env coding region (see document (A72)).

47. The board firstly observes that the experiment carried out by the appellants/opponents significantly differs from the protocol of Example 9 of the priority documents. The comparison list (A63) indeed highlights twelve differences, namely, to only mention four, (i) the choice of "HIV1-ARV2"-infected HUT78-cells instead of the deposited clone ATCC No. 40143 available to

anybody upon request; (ii) the use of the PCR technique for amplifying DNA fragments instead of restriction enzymes for cutting the EcoRI-KpnI insert (Example 9); (iii) the use of the expression vector pZeoSV instead of the expression vector pSV-7c/7D (Example 9) and (iv) the use of a single monoclonal antibody "anti-gp41 Mak" to detect the expression product instead of an antiserum comprising a population of different antibodies to the envelope protein (Example 9). These differences from Example 9 as set out may have introduced variations in the DNA insert ((i) and (ii)), affected the level of expression ((iii)) or reduced the level of detectable signal ((iv)). In view of this, the experiment provided by the appellants/opponents cannot be treated by the board as a bona fide attempt to reproduce Example 9 of priority documents (P1) and (P2). Therefore there is no satisfactory evidence before the board from which any conclusion that this specific example is not reproducible can be drawn.

48. Furthermore, it must be noted that the excision of the exemplified "flawed" EcoRI-KpnI insert is not the only possibility open to the skilled person wishing to excise an env insert. Fig 4 of document (P1) indeed proposes a further eleven restriction sites located between the "5752 ecor1" and the first env start codon ATG at nt 6236 as env insert's 5'-end. The appellants/opponents do not dispute that these "5'-trimmed" env inserts would lead to env protein expression. In conclusion, the appellants/opponents did not succeed in convincing the board that Example 9 would result in an uncertainty of reproducibility which would amount to undue burden and that the remaining technical information afforded by priority document (P1) cannot heal this particular situation.

Claim 1

49. The claim is not entitled, in the appellants/opponents's view to the filing date of documents (P1) to (P3), owing to the discrepancy between the expressions "21 bp in reading frame" (claim 1), covering three possible reading frames and "having an open reading frame" (claim 15 of documents (P1) to (P3)) relating to one reading frame only. Yet, the board is not able to follow this objection because both claim 1 and claim 15 of document (P1) require that a HIV-I polypeptide be expressed. This only occurs if the codons are in reading frame with the "control sequences which regulate transcription and translation" (Claim 1) or "the transcriptional and translational initiation and termination signals" (claim 15 of document (P1)). Hence, only one and the same "reading frame" satisfying these requirements is relevant to any particular construct in claim 1 and in claim 15 of the priority document (P1), and no discrepancy giving rise to an objection can be seen.

Claim 9

50. It has been argued by the appellants/opponents that the feature in this claim "free from other cells which do not express the antigenic HIV-I amino acid sequence" is not derivable from priority documents (P1) and (P2). The board disagrees. This feature can be derived from eg the passage bridging pages 12 and 13 ("selection of transformed or transfected hosts") of priority document (P1).

Claim 17

51. Contrary to the appellants/opponent's contention, the embodiment of claim 17, relating to an immunoassay involving at least one env **and** one gag polypeptides to bind the antibodies, finds basis eg on page 14, lines 17-20 of priority document (P1). The claim is thus entitled to the filing date of document (P1) for the purpose of the right to priority.

Claim 29

52. Contrary to the appellants/opponent's allegation, the wording "gag or env region" in this claim finds a basis in eg priority documents (P1) (see claims 5 to 8). The claim is thus entitled to the filing date of document (P1) for claiming priority.

Claim 18

53. The appellants/opponents argue that the claimed reagent or immunogen is not entitled to the filing date of document (P1) for priority because the claim is not limited to recombinant proteins or fragments as in the priority document (P1) but also covers natural or synthetic viral proteins and fragments thereof to be used as immunogens or reagents, an argument which was used also in the context of Article 123(2) EPC (see point 8 supra). For the same reasons there given, the board considers this objection has not been made out.

Conclusion (Right to priority)

54. Thus, none of the numerous objections to the entitlement to priority raised by the appellants/opponents have been made out, and the board comes to the conclusion that the same invention within

the meaning of Article 87 EPC is claimed and disclosed in priority document (P1) for the claims in dispute.

Novelty

Claims 1-17 and 19-29

55. Conflicting European patent application (D1) claims priority from inter alia document (D1.1) filed on 23 October 1994, ie before priority document (P1). Therefore, document (D1) is relevant to the novelty of the claims at issue insofar as its subject-matter is supported and enabled by document (D1.1). Figure 3 of document (D1.1) represents a 3,112 bp long DNA sequence. It is stated on page 5, lines 1-2 of the description that "Fig. 3 shows nucleotide sequences for HTLV-III DNA which encompasses the env region".

56. The appellants/opponents maintain that the preparation of fragments of the sequence of Figure 3 is implicitly disclosed in priority document (D1.1). The skilled person could thus have synthesized specific probes in the light of Figure 3 and screened a gene library by means of colony hybridization in order to isolate the HIV-I gene, as done in Example 4 of document (D1.1). The so-obtained HIV-I DNA could be "shot-gunned" in an expression vector according to Example 2 or page 7, lines 12-28 of document (D1.1) in order to obtain by expression polypeptides reactive with sera of AIDS-infected patients.

57. However, the board observes that document (D1.1) discloses neither the source of material containing the HIV-I DNA nor a method for its isolation. Moreover, no deposit of clones containing the HIV-I DNA has been made and no suitable library was publicly available.

Therefore, it must be concluded that this route of "shot-gunning" random 200-500 bp fragments was not practicable.

58. No deposit of the clone has been made, but the board would agree that another route to subject-matter having potentially novelty-destroying merit might have been to depart from the DNA sequence of Figure 3 of document (D1.1) and identify and synthesize and/or express the env sequence of HIV-I. However, the appellants/opponents do not dispute that only 883 bp of the 3,112 bp of the DNA sequence of Figure 3 belong to the env region, meaning that the skilled person would not inevitably select a DNA stretch in the env region. Moreover, it has been pointed out by Prof. Young (see document (A30), paragraphs 25 to 32) that an "A" insertion at position 2437 causes a translational frame shift in the partial env gene resulting in only 63 triplets to be correct. Further deficiencies are emphasized in document (A30), such as eg partial lack of legibility (G mistaken for C and vice-versa). In view of this, it is the board's opinion that the skilled person is not taught how to identify the HIV-I env ORF in the DNA sequence of Figure 3. It must be concluded that document (D1.1) does not represent a direct and unambiguous disclosure of the claimed subject-matter. Document (D1) is thus not novelty destroying pursuant to Article 54(3) EPC.

59. Conflicting European application (D7) claims priority from inter alia document (D7.1) filed on 19 September 1984, ie before priority document (P1). Therefore, document (D7) is also citable against the novelty of the claims at issue insofar as its subject-matter is supported and enabled by document (D7.1).

60. The appellants/opponents argue that clone ë-J19 has been deposited in connection with priority document (D7.1) on 11 September 1984. Figure 2 of document (D7.1) shows the restriction map of the LAV virus. The paragraph bridging page 4 and 5 of this document identifies the env, gag and pol regions. On page 13 thereof, it is suggested to "shot-gun" the proviral DNA in expression vectors to get fusion proteins. Therefore, document (D7.1) makes available to the skilled person the HIV-I genome and fragments thereof as well as the means for arriving at the claimed subject-matter.

61. The board agrees that document (D7) can rely on document (D7.1) for the purpose of the right to priority of clone termed ëJ19 in both documents (on the arguments stated in decision T 824/94 of 18 November 1999, point 34 of the reasons). However, the mere deposit of the ëJ19 clone in connection with priority document (D7.1) is not a disclosure of the env and gag coding regions, as this would need additional technical information for the skilled person to be able to select a DNA molecule falling within the env or gag region of the HIV-I genome and arrive at the claimed subject-matter. Document (D7.1) itself also fails to disclose any DNA sequence, let alone the env and gag coding sequences. It is true that the paragraph bridging page 4 and 5 of this document gives an approximate identification of the env (6,100 to 9,150) and gag (800 to 3,500) regions. However, this information has turned out to be incorrect (see document (A31)).

62. As for the possibility of arriving at the claimed subject-matter by "shot-gunning" the proviral DNA in expression vectors to get fusion proteins (page 13 of

document (D7.1)), it is the board's view that "shot-gunning" of imprecisely defined random fragments does not make any information available to the public as to how to actually get env, gag fusion proteins, and thus cannot be novelty-destroying.

63. The appellants/opponents also relied on conflicting European patent application (D35) for questioning the novelty. Document (D35) claims priority from document (D35.1) filed on 22 August 1984, ie before priority document (P1).

64. The board notes that the disclosure of document (D35.1) is similar to that of document (D7.1) since clones BH10, BH8 and BH5 have been deposited in connection with priority document (D35.1) (see page 6) and Figure 2 thereof shows the restriction map of three clones termed ë-BH 10, ë-BH8 and ë-BH 5. Like document (D7.1), this document fails to disclose any DNA sequence, let alone the env and gag DNA coding sequences. But the disclosure of document (D35.1) is even less complete compared with that of document (D7.1), as no mention is made of protein expression in the former. It is true that the term "expression" is to be found in claim 5 in relation to expressing the cDNA sequence of HTLV-III reverse-translated from the mRNA extracted from the H9 cell line. However, putting the process of claim 5 into practice does not provide any information as to which expressed molecules (if any) fall within the env or gag region.

65. In view of the foregoing, the conclusion arrived at by the board under points 61 and 62 supra in relation to document (D7) also applies to document (D35).

66. In summary, priority documents (D1.1), (D7.1) and (D35.1) fail to directly and unambiguously disclose DNA sequences encoding gag or env amino acid sequences, unlike priority document (P1), which the board has accepted to disclose the same invention as that now claimed (see point 35 supra).

Claim 18

67. In the appellants/opponents' view this claim was not limited to recombinant proteins and lacked thus novelty vis-à-vis documents (D9) and (D13) disclosing immunoassays involving HIV-I natural proteins.

68. This argument is the same as in relation to Article 123(2) EPC (see point 8 supra) and Article 87 (see point 53 supra) and here again the board concludes that the wording in the claim "consists of an antigen" (rather than "comprises") relates to a single antigen, ie a defined molecular species, different from naturally-occurring polymorphic protein mixtures to be found in wild-type viral sources (see documents (D120), (D121) and (D122), cited as expert's opinion).

Conclusion (Article 54 EPC)

69. In view of the above findings, the board concludes that no case has been made out that the claims of the main request do not satisfy the requirements of Article 54 EPC.

Inventive step
Closest prior art

70. In view of the board's decision on priority (see

point 55 supra), the relevant state of the art for consideration of inventive step is that as of 31 October 1984, ie the filing date of priority document (P1). There was, at that date, no clear identification of the agent(s) responsible for AIDS. It was proposed that AIDS could be caused by a fungal infection (see document (A11)) or by a mutant hepatitis B virus or even a prion-like agent (see document (A12)). However, three groups at the forefront of the field succeeded in isolating three independent retroviruses, whose presence alone or in combination was believed to be responsible for AIDS. The group headed by Montagnier (see document (D49)) termed LAV (lymphadenopathy associated virus) the presumed agent causative for AIDS and believed it to be similar to equine infectious anaemia virus (EIAV) (see documents (D42), (D64) and (D80)). The Levy group (see document (D34)) named it ARV (AIDS-associated retrovirus) but it is stated in document (D34) that "the relation of ARV to the recently described HTLV-III is still unknown" (page 842, r-h column). The group led by Gallo (see document (D42)) believed this agent (HTLV-III) to be related to the known human T-cell leukaemia viruses HTLV-I and HTLV-II, also sometimes isolated from AIDS patients' sera (see documents (D82) and (D22)). In addition to publications (D42), (D49) and (D34) by the three researcher groups, an article (document (D88)) in the San Francisco Chronicle of 10 September 1984 announced the successful cloning by Chiron of ARV. A passage therein recites "Levy's ARV is believed to be virtually identical in form and molecular structure to the virus HTLV-III discovered by Dr Robert Gallo at the National Cancer Institute, and another called LAV first identified by Dr Luc Montagnier at France's Pasteur Institute".

71. As regards this statement in document (D88), any skilled person would have taken in the sense it was said: a belief that could not be verified, as no DNA sequence information from HTLV-III and LAV was available to anybody for comparison purposes. Comparison of the viral DNAs is indeed the ultimate proof of identity (or not) among viruses (see eg document (D4), page 304, l-h column, cited as expert opinion: "These issues could fully be resolved by comparing the DNA sequences of the genomes of retroviruses associated with AIDS (LAV, HTLV-III, and ARV)". That ARV, HTLV-III and LAV "were similar enough to be considered variants of the same virus", ie the AIDS virus (now called HIV-I) became evident to the scientific community only in March 1985 (see document (D123), page 451, r-h column), ie after the filing date of priority document (P1), but before the filing date (30 October 1985) of the application underlying the patent in suit. Before March 1985, the three research teams did not (and could not) know that they were working on a variant of the same virus and each group filed patent applications (inter alia (D1) and (D7)) on their investigations' results. Thus, a notionally skilled person, instead of being provided by this situation with a reliable starting point for solving any "downstream" problem rather faced a confusing picture.

Problem to be solved

72. Departing from this state of the art, the problem to be solved by the patent in suit can be defined as the cloning and characterization of the agent responsible for AIDS ("HIV-I") and the localization of the env and gag coding regions thereof in order to provide a ready

supply of proteins and DNA of the virus suitable for diagnosis and therapy of AIDS. This problem is solved by the provision of the DNA sequence of Figure 2 of the patent in suit encoding HIV-I gag or env proteins and fragments thereof. In view of eg, Examples 9 and 13 of the patent, relating to the expression of the HIV-I gag and env protein, respectively, the board is satisfied that the above problem has been solved.

Inventive step

73. Because of the confused nature of the state of the art emphasised above, in the board's judgement, the appellants/opponents' choice, as closest prior art, of one particular document such as document (D88) (and document (D34) easily retrievable by cross-reference), includes already the knowledge of the solution of the problem set out above, ie the use of hindsight. This is because the nature of the agent(s) responsible for AIDS was not certain at all (it could be one or more of a fungus, a mutant hepatitis B virus, a prion-like agent, a T-cell leukaemia virus (HTLV) or an equine infectious anaemia-like virus (EIAV)). Therefore, the skilled person might reasonably have departed from any other of above cited documents (A11), (A12), (D49) and (D42) as well. Whatever the starting point, though, the expectation of having entered the "right" way leading to the claimed subject-matter, was low. Hence, in the board's view, the presence of an inventive step for the claimed subject-matter has already to be acknowledged on this ground alone.

Stably infected cell line

74. But even assuming that the skilled person would have

given the preference to the "retroviral hypothesis" as a cause for AIDS and turned to document (D88) (and document (D34) easily retrievable by cross-reference), as the appellants/opponents argue, the board observes that HIV-I is a cytopathic virus which kills virus-infected cells (see eg document (D42), page 497, r-h column). In order to clone the HIV-I genome and arrive at the claimed subject-matter, a decisive first step is thus the identification and production of a special cell line capable of sustaining growth (propagation) upon infection by the virus, with no cytopathic effects, so as to recover substantial quantities of the virus.

75. The question arises of whether or not document (D34) provides sufficient information for the skilled person to produce such a stably infected cell line. As regards this special cell line, reference is made in document (D34) to a HIV-I high producer "HUT-78 line (8)". The appellants/opponents maintain that this cell line was available from the ATCC under the number ATCC TIB 161 (see document (A8)). In order to prepare a stably infected HUT-78 cell line, in the board's view, the skilled person has to follow a detailed infection protocol. That a protocol for infecting cell lines with HIV-I has to be detailed is demonstrated by the twenty lines of the legend to Table I on page 840 of document (D34), disclosing how the infection and post-infection of the peripheral mononuclear cell (PMC) primary culture have to be carried out. As many details are also provided in the legend to Table 2 of document (D42), disclosing the infection with HTLV-III (HIV-I) of a series of HT subclones. Turning to the instructions given by document (D34) for infecting the HUT-78 cells, there is only a short passage on

page 842, l-h column: "we infected human T-cell lines in the presence of antiserum to interferon and Polybrene", without any details as to how to perform the infection and the post-infection (no virus titre, no reagent levels, no timing, no temperatures). Besides this lack of information concerning how to infect the HUT-78 cells with the virus, the skilled person would have been faced with the further problem that many HIV-I isolates failed to productively (stably) infect the cell line HUT-78 (see document (A46) taken as expert opinion, page 3415, r-h column, first full paragraph). In view of these findings, the board considers that the skilled person would not have arrived at a HIV-I-infected high producer cell line, even by starting from a HUT-78 cell line obtained from the ATCC.

76. Document (D42) also refers to a high producer cell line termed HT (see paragraph bridging central and r-h column). As regards the possibility that the skilled person could have arrived at this HIV-I-stably infected cell line, the board notes that the above passage ends with a reference to citation "(30)", (ie document (D43)), which is a paper by the same authors in the same issue of "Science" of 4 May 1984. However, the reader of document (D43) (page 502, top of r-h column) looking for more information about the origin or the preparation protocol of the high producer cell line is referred back to citation "(3)", which is document (D42) itself. In view of this, it must be concluded that the above circular reference (D42/D43) represents a barrier preventing the skilled person from arriving at the HIV-I-producing cell line HT disclosed in document (D42), let alone at the H9 sub-clone of HT (see Table 1 thereof).

77. As for the high producer cell line FR8 described in document (D49), it is an Epstein-Barr virus (EBV)-transformed B lymphoblastoid cell line. It is stated on page 64 (central column) that an earlier passage of LAV (from July 1983) could not grow in the FR8 lymphoblastoid cell line. But during successive passages in vitro, LAV acquired "a new property" (change in tropism) enabling its growth in the FR8 lymphoblastoid cell line. Therefore, in the board's judgement, arriving at the infected FR8 cell by the Montagnier's team (document (D49)) was a highly random event which would not be reproducible by the skilled person.

78. In conclusion none of documents (D88), (D34), (D42) and (D49) provided the skilled person with adequate information to arrive at this special stably infected cell line. There remains the question of whether the authors of documents (D34), (D42) and (D49) made their infected cell lines available to the public.

79. As regards the HUT-78 infected cell of the Levy team (document (D34)), it has been exclusively given to the present patent proprietor. In addition, the cell line has been deposited on 9 August 1984 in connection with US patent No. 4,716,102 (document (D162)) and became available only at the grant and publication of the patent (29 December 1987).

80. As regards the Gallo's HT cell and its subclone H9 referred to in document (D42), the appellants/opponents argue that it was not in all cases so that Gallo refused to release the cell to other scientists. Attention is drawn to document (A41), according to which the HIV-I high producer cell line referred to in

document (D42) had freely been distributed to several outside laboratories for research before the priority date of the patent in suit. Reference is also made to document (A13), page 2 of 11: "Collaboration at will for Dr Weiss. O.K. R. Gallo" instead of "work performed will be on a collaborative basis" (see document (A71)), to the Declaration of Prof. Robin Weiss (document (A70)) and to the Material Transfer Agreement between Dr R. Gallo and Prof. G. Hunsmann (document (A71)).

81. These statements have to be balanced with one of Dr M. G. Sarngadharan who says under point 3 of his declaration (A41) that recipients of the cell had to sign a very restrictive material transfer agreement before they could receive the material. As regards Prof. Weiss, it is true that Prof. Weiss was free to collaborate with Gallo at will. But the permission to hand over the cells to colleagues had nevertheless to be asked (see bottom of page 2 of document (A70): "I received permission from Dr. Gallo"). Document (A71) confirms that recipients of the cell had to sign a very restrictive material transfer agreement before they could receive the material. Therefore, no evidence is before the board that Gallo has freely distributed to the public the HT cell and its subclone H9 referred to in document (D42). No evidence is before the board either that the cell recipients freely delivered the cell to third parties. The board has thus to conclude that, as the biological material was restricted to a group of person linked by a research programm (see decision T 576/91 of 18 May 1993, point 2.3), it cannot be treated as something made available to the public in the sense of Article 54(2) EPC.

82. As for the cell FR8 of the Montagnier's group (document

(D49), no evidence is before the board that Montagnier has freely distributed the FR8 cell to anybody.

83. The appellants/opponents argue that a stably-infected cell line was not necessary for cloning the virus, provided enough virus could be obtained. The skilled person would have established a PMC culture from infected patients and purified the virus from which the RNA could have been isolated, reverse translated in the presence of ^{32}P and the 9800 nt (cf. document (D88)) labelled cDNA used as a probe for screening a DNA library containing proviral DNA.

84. However, this appellants/opponents' proposition is contradicted by documents (D42) (see page 500, final paragraph: "the lack of a cell system...permissive for the virus represented a major obstacle") and (D49) (see paragraph bridging pages 65 and 66: "Our finding is of practical importance because LAV can now be produced continuously by some permanent cell lines growing in suspension without noticeable cytopathic effects"). These passages suggest that the provision of a special cell line capable of sustaining the virus growth without cytopathic effects is a critical step in the process of cloning the HIV-I gene and that an alternative such as transient cell cultures, did not work.

85. Document (D60) has been cited by the appellants/opponents for showing that the cloning of the HIV-I gene might have occurred without a stably-infected cell line. This document deals with the cloning of the adult T-cell leukemia virus (ATLV) in the absence of a stably-infected cell line. However, the board notes that ATLV is a transforming virus, not

a cytopathic one as HIV-I, which kills the cell (see document (D42), page 497, r-h column, lines 3-6). Therefore, a comparison of the cloning of HIV-I with that of ATLV is not relevant in the given context.

86. Therefore, even assuming that the skilled person turned to documents (D88)/(D34), (D42) and (D49) for further research on the AIDS-causing agent, in the attempt to clone the sought virus and arriving at the claimed subject-matter, he/she would not have overcome without inventive skill the blockage represented by obtaining a stably-infected cell line.

Conclusion (inventive step)

87. The subject-matter of claim 1 cannot be derived in an obvious manner from the prior art. This conclusion has to be extended to claims 2 to 8 since they relate to specific embodiments of the recombinant DNA construct of claim 1. The above conclusion also applies to the cell of claims 9-12, the method of claims 13-15, the immunoassay of claims 17, the diagnostic reagent of claim 18, the recombinant polypeptide of claims 19-24, the article of manufacture of claims 25-26, the DNA sequence of claim 27, the recombinant DNA construct of claim 28 and the isolated polynucleotide of claim 29. For any of this claimed subject-matter to be carried out, one must have available the knowledge of the DNA sequence of Figure 2 recited in claim 1. Thus, since inventive step can be acknowledged for the DNA construct of claim 1, it can be acknowledged for all these other claims as well.

88. No need arises to consider the "secondary indicators of inventive step" pointed out by the appellant/patentee

(see point XI.G.b supra).

Adaptation of the description
Main request

89. In the communication dated 27 July 2001 (see paragraph VIII supra), the board referred to two categories of amendments:

A. Passages that have to be deleted because they do not contribute anything to the clarity or understanding of the claims as maintained by the board and cast legal uncertainty on the scope thereof (see decision T 996/92 of 23 March 1993, point 1 of the Reasons and further decisions cited therein).

B. Passages that may be kept because they contribute to the clarity or understanding of claims as maintained by the board and are not in contradiction therewith, without casting any uncertainty on their scope. They may also illustrate further developments in which the claimed subject-matter can find use.

90. In addition to the amendments already effected by the appellant/patentee, the appellants/opponents further request deletion from the description of the following passages:

(i) Example 14 on page 20 referring to SOD-p31.

(ii) The reference to "p31" on page 5, last line.

(iii) The expression "as vaccines" (page 4, line 52);

the sentence on page 4, lines 54-55 ending with "to be used for vaccination"; the passage on page 5, lines 1 to 9 relating to vaccines.

(iv) The reference to labelled DNA probes on page 6, lines 41-43.

91. As for requested deletion (i) above, it seems to fall under Category B above of passages that may be kept. Example 14 is indeed useful for illustrating how (concentrations, buffers, absorbency wavelength, positive/negative cut-off, etc) an embodiment of claim 17 at issue can be put into practice, since it discloses an immunoassay involving the p25 gag and env proteins, ie "an immunoassay wherein **at least** one env amino acid sequence and one gag amino acid sequence are used to bind the antibodies" (claim 17; emphasis added by the board). Owing to the wording "at least", the three component immunoassay of Example 14 falls under the scope of claim 17. Since p31 referred to at the bottom of page 5 is one antigen of the three (p31, p25 gag and env) involved in the immunoassay according to claim 17, this conclusion has to be extended mutatis mutandis to amendment (ii). As regards amendments (iii) and (iv), these also belong to Category B above since they are useful for illustrating further developments in which the claimed subject-matter may find use, eg for making labelled probes or vaccines (see eg page 4, line 50 of the patent in suit: "The polypeptides may find use ...in a variety of ways"). These passages are not in contradiction with the claims as maintained by the board and do not obscure the scope thereof. Requested amendments (i) to (iv) above are thus not necessary for an adequate adaptation of the description to the claims maintained by the board.

92. Yet, the appellant/patentee has introduced a reference "see EP-A-0181150" on page 20, line 36 after "0.1 % SDS, pH 7.2". Published application EP-A-0181150 underlying the patent in suit comprises Example 16 (pages 44-46) relating to the construction and expression of the SOD-p31 fusion protein.

93. The introduction of a reference "see EP-A-0181150" on page 20 of the description is equivalent to incorporating therein Example 16 (pages 44-46) of EP-A-0181150. As this example does not contribute to the clarity or understanding of the claims as maintained by the board, but rather merely casts legal uncertainty upon the scope thereof in the light of the fact that the claims as maintained no longer refer to p31 as such, it belongs to Category A above of non allowable amendments.

94. In view of this, the main request in relation to the adaptation of the description has to be refused.

Auxiliary request

95. Compared with the one of the main request, the amended description of this request no longer comprises the contested reference "see EP-A-0181150" on page 20, line 36, after "0.1 % SDS, pH 7.2". Therefore, it can be accepted by the board.

Order

For these reasons it is decided:

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 the claims submitted as main request at the oral proceedings on 26 January 2001, pages 6-15, and 21 and 22 of the description as granted and pages 3 to 5, 16 to 20 and 23 of the description submitted as auxiliary request at the oral proceedings on 15 January 2002, and Figures 1 to 7 of the Figures as granted.

The Registrar: The Chairwoman:

P. Cremona U. M. Kinkeldey