BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

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

Datasheet for the decision of 21 January 2010

Case Number: T 2001/07 - 3.3.04

Application Number: 91113062.3

Publication Number: 0462627

IPC: C07K 14/16

Language of the proceedings: EN

Title of invention:
Antigens and peptides of LAV

Patentees:
INSTITUT PASTEUR, et al

Opponent:
Bayer HealthCare LLC

Headword:
Antigens of LAV/INSTITUT PASTEUR

Relevant legal provisions:
EPC Art. 54, 56, 76(1), 83, 123(2)

Keyword:
"Novelty (yes)"
"Inventive step (yes)"
"Right to priority (yes)"
"Sufficiency of disclosure (yes)"
"Added subject-matter (no)"

Decisions cited:
T 0301/87, T 0422/92, T 0188/97, T 0351/98, T 0179/01

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 2001/07 **-** 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 21 January 2010

Appellant: (Opponent)
Bayer HealthCare LLC
511 Benedict Avenue
NY 10591-5097 Tarrytown (US)

Representative:
Taormino, Joseph Paul
Hoffmann Eitle
Patent- und Rechtsanwälte
Arabellastrasse 4
81925 München (DE)

Respondents: (Patent Proprietors)
INSTITUT PASTEUR
28, rue du Docteur Roux
75724 Paris Cédex 15 (FR)

CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE
15, quai Anatole France
75007 Paris (FR)

Representative:
Desaix, Anne
Ernest Gutmann - Yves Plasseraud S.A.S.
3, rue Auber
75009 Paris (FR)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 17 August 2007 concerning maintenance of European patent No. 0462627 in amended form.**

Composition of the Board:

Chairman: M. Wieser
Members: R. Gramaglia
D. S. Rogers

Summary of Facts and Submissions

I. European patent No. 0462627 is based upon European patent application No. 91113062.3 filed on 18.10.85 and claiming priority from FR 8416013 filed on 18.10.84 (document P1), GB 8429099 filed on 16.11.84 (document P2) and GB 8501473 filed on 21.01.85 (document P3). The application underlying the patent in suit is a divisional application of European patent application No. 90105190.4 published as EP-A-0387915, which in turn is a divisional application of European patent application No. 85905513.9, published as W0-A-86/02383 (hereafter: "the original parent application").

II. Notice of opposition was filed by the opponent (appellant) requesting the revocation of the European patent on the grounds of Articles 100(a), (b) and (c) EPC.

III. The opposition division decided that granted claim 1 of the patent proprietors' (respondents') main request did not meet the requirements of Article 123(2) EPC, but that claims 1 to 18 of the first auxiliary request filed at the oral proceedings met all requirements of the EPC.

Claims 1 to 4 and 18 of the first auxiliary request read as follows:

"1. Purified pol antigen having the backbone of the polypeptide encoded by the nucleotidic sequence extending from nucleotide position 1631 to nucleotide 4639 of the LAV virus genome represented on figure 4, or an antigen having the same polypeptide backbone and

whose aminoacid sequence is contained in the sequence in figure 4 extending from nucleotide position 1631 to 4639."

"2. Purified DNA capable of encoding the pol antigen according to claim 1, said purified DNA being distinct from the fragment comprised between the KpnI site (3500) and the BglII site (6500) as shown in the restriction map in figure 3 and distinct from the complete LAV genome of λJ19 clone deposited under CMCMI-338."

"3. Purified DNA having a nucleotidic sequence extending from nucleotide 1631 to nucleotide 4639 from the nucleotidic sequence of the LAV genome represented on figure 4."

"4. DNA fragment comprised in a DNA sequence according to claim 3, characterized in that it codes for a polypeptide containing an epitope specifically recognized by monoclonal antibodies directed against the corresponding antigen according to claim 1, and said DNA fragment is not the fragment comprised between the KpnI site (3500) and the BglII site (6500) as shown in the restriction map in figure 3."

"18. Method of detection of a nucleic acid hybridizing with a nucleotide sequence according to anyone of claims 2 to 5, wherein the DNA according to any of claims 2 to 5 is used as a hybridization probe."

Claims 5 to 17 related to DNA sequences, DNA hybridization probes, recombinant vectors, microorganisms, antibodies, processes, uses and methods

based on the pol antigen and/or the DNAs according to claims 1 to 4.

IV. The appellant (opponent) filed an appeal against the decision of the opposition division.

V. Oral proceedings were held on 21 January 2010.

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

B1 Rey M.A. et al., Biochem. Biophys. Res. Comm., Vol. 121(1), pages 126-133 (1984);

B2 Popovic M. et al., Science, Vol. 224, pages 497-500 (1984);

B3 Hahn B.H. et al., Nature, Vol. 312, pages 166-169 (1984);

B4 EP-A-173529;

B4/Prio USSN 643306;

B5 EP-A-178978;

B5/Prio GB 8423659;

B6 EP-A-181 150;

B6/Prio USSN 667501;

B7 Shaw G.M. et al., Science, Vol. 226, pages 1165-1170 (December 1984);

B8 Luciw P.A. et al., Nature, Vol. 312, pages 760-763 (December 1984);

B9 EP-A-187041;

B10 Wain-Hobson S. et al., Cell, Vol. 9, pages 9-17 (January 1985);

B11 Schübach J. et al., Science, Vol. 224, pages 503-505 (1984);

B12 Sarngadharan M.G. et al., Science, Vol. 224, pages 506-508 (1984);

B16 NC001802 excerpt from the NCBI databank;

B17 Pettit S.C. et al., J. Virol., Vol. 78, No. 6, pages 8477-8485 (2004);

B19 Barré-Sinoussi F. et al., Science, Vol. 220, pages 868-871 (1983);

B20 Biochemistry by A. Lehninger, Worth Publ., NY, pages 106-108 (1981).

VII. The submissions by the appellant, insofar as they are relevant to the present decision, can be summarized as follows:

Articles 76(1) and 123(2) EPC

- On page 25 of the original parent application, the pol gene was defined as a reverse transcriptase

(hereafter: RT) gene encoding a protein of up to 1003 amino acids. However, this definition was completely absent from the application underlying the patent in suit, which related to a different subject-matter, namely the "pol antigen". This change in definition of the pol gene in the application underlying the patent in suit over the original parent application infringed Articles 76(1) and 123(2) EPC.

- The "pol antigen" as defined in present claim 1 did not correspond to the reverse transcriptase as it occurred in nature. Hence, the claimed "pol antigen" had no counterpart in the original parent application.

Sufficiency of disclosure

- The DNA fragments of claim 4 were defined with respect to their ability to encode a polypeptide containing an epitope specifically recognized by monoclonal antibodies directed against the antigen of claim 1. However, it could not be deduced from the patent how to proceed to obtain the polypeptide referred to in claim 4, encoded by the pol DNA sequence (or to obtain a fragment of the "pol antigen"), which polypeptide/fragment had the same immunological properties of the "pol antigen". Another board confronted with a similar situation denied sufficient disclosure (see decision T 188/97 of 8 February 2001).

- According to paragraphs [0016], [0030] and [0031] of the patent, the antigens of the invention had to be

purified by means of lectins such as concanavaline A. However, these techniques could not be applied to the "pol antigen" since it has turned out to be unglycosylated.

– The N-terminus of the "pol antigen" in Fig. 4 was wrong, in the sense that the 8 N-terminal amino acids did not belong to the pol gene. Thus it was not possible to make pol antigens including these 8 N-terminal amino acids.

Priority rights of claims 4 and 18

– Claim 4 could not enjoy the priority date of priority document P2 (see paragraph I supra) because the claim was directed to a DNA fragment defined in relation of its capacity to code for a polypeptide specifically recognized by monoclonal antibodies recognizing the antigen according to claim 1, whereas the passage on page 15, lines 30-33 of priority document P2 merely related peptides suitable for the production of specific antibodies.

– Claim 18 could not enjoy the priority date of priority document P2, in view of several differences between present claim 18 and priority document P2.

Novelty

– Peak "RT" in Fig. 2 document B1 was the "pol antigen" of LAV (hereafter: HIV) and hence the subject-matter of present claim 1 lacked novelty over this document, the more so as the wording of

present claim 1 required that the pol protein be neither purified, nor in "sufficient quantities".

- The skilled person had no difficulties in infecting with HIV normal T-lymphocytes from either newborn or adults and in growing the virus to high titres.

- The two "Ono et al." references on page 127 (Reference "9") and on page 132 (Reference "16") of document B1 would have provided further details as to how RT had to be purified.

- The legend to Fig. 3 in document B19 disclosed how to lyse the virus and how to separate the viral proteins by electrophoresis.

- The patent in suit did not disclose the purification of a "pol antigen" (RT), let alone the purification of a "pol antigen" to a higher degree of purity than in document B1.

- Document B5 described restriction fragments hybridizing with the pol $KpnI^{3500}$-$BglII^{6500}$ fragment, which were inherently capable of encoding the pol antigen.

- The $PstI^{800}$- $KpnI^{3500}$ fragment described in document B5 had to be disclaimed because it also included the pol gene.

Inventive Step

- Departing from document B1 as closest prior art, the problem to be solved by the subject-matter of present claim 1 was purifying a RT from the HIV virus. However, the skilled person would have used the common general knowledge in order to further isolate the HIV RT described in document B1 and would have obtained in an obvious way a pol antigen according to present claim 1.

- The contested patent itself failed to show that particular steps were necessary in order to obtain the purified "pol antigen".

- The subject-matter of claims 2, 4 or 5 lacked inventive step in view of the disclosure in B3, in combination with the common general knowledge.

VIII. The submissions by the respondents, insofar as they are relevant to the present decision, can be summarized as follows:

Articles 76(1) and 123(2) EPC

- There has been no change in definition of "pol" in the divisional application underlying the patent in suit in comparison with the original parent application.

- The term "antigen" in claim 1 had a basis in the first paragraph on page 1 of the original parent application.

Sufficiency of disclosure

- The claimed subject-matter was sufficiently disclosed since the patent in suit provided access to the sequence of the ORF of the pol gene and to deposited clones containing this sequence.

- The claimed pol antigen was not the naturally occurring protein.

Priority rights of claims 4 and 18

- The passage on page 15 of priority document P2, relating to peptides suitable for the production of specific antibodies, in combination with the passage which relates to the DNA fragments which necessarily encode peptides (see page 17, lines 12-16), were sufficient support for claim 4 relating to the same invention as disclosed in document P2.

- The passages on page 1, lines 28-35, page 2, lines 17-22 and page 14, lines 11-18 and 33-36 of priority document P2 were a sufficient support for claim 18 to relate to the same invention as disclosed in document P2.

Novelty

- The claimed subject-matter was novel over documents B1, B2 and B19. The method for the purification of the virus in B1 to B2 was not enabled and the reverse transcriptase had not been purified.

– At the publication date of document B1, the skilled person would not have been able to prepare lymphocytes appropriate for the culture of the HIV virus necessary for its purification and the purification of the viral proteins.

– The cells referred to in B19 were not made available through the mere publication of this document. Attempts to obtain the virus in culture led to poor results.

– Documents B3 and B4 could not affect the novelty of present claims 2, 4, 5, 10 and 18.

Inventive step

– Document B1 neither enabled the virus to be obtained in sufficient quantities, nor the purification of the product present in the peak showing the RT activity.

– The disclosure of documents B1, B2, B3 and B19 failed to teach how to obtain high titres of the virus, so as to gain access to its nucleotide sequence and to the ORF enabling the definition of the expressed product.

– The deficiencies pointed out above could not be overcome by reference to documents B11 and B12, describing immunoprecipitation techniques or to document B20 relating to obtaining protein fragments by hydrolysis.

IX. The appellant requested that the decision under appeal be set aside and the patent be revoked.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

Articles 123(2) and 76(1) EPC

1. The appellant maintains that a change in definition of "pol" in the divisional application in comparison with the original parent application infringed Articles 123(2) and 76(1) EPC. On page 25, lines 1 to 4 of the original parent application, the pol gene was defined as a reverse transcriptase gene encoding a protein of up to 1003 amino acids. However, this definition was completely absent from the divisional application, which related to a different subject-matter, namely the "pol antigen".

However, in the board's opinion, the "pol antigen" referred to in the divisional application is defined as being the polypeptide encoded by the ORF pol described in Table 1 (see page 26), wherein the first and last codons of the pol gene in the sequence of Fig. 4 are clearly identified. This definition in Table 1 is in keeping with the definition given in present claim 1.

As for the term "antigen" in the wording "pol antigen" in present claim 1, it finds a basis on page 1, first paragraph, pages 45, lines 22-26 and page 46, lines 11-22, taken in combination with page 39, lines 16-23, of the original parent application. These passages show

that the main intended use of the proteins or polypeptides disclosed in the original parent application was the detection of antibodies in body fluids or the induction of an immune response, by relying on their antigenic properties.

2. Relying on documents B16 and B17, the appellant also maintains that the "pol antigen" as defined in present claim 1 does not correspond to the pol antigen as it occurs in nature referred to on page 4, lines 22-23 of the original parent application ("antigenic determinants expressed by the LAV genome occurring in nature"). Hence the appellant concludes that the now claimed "pol antigen" had no counterpart in the original parent application.

Yet, the proteins or polypeptides disclosed in the original parent application were not limited to antigenic LAV proteins occurring in nature (see page 39, lines 16-23).

3. Therefore, the divisional application does not extend beyond the content of the original parent application.

Sufficiency of disclosure

4. The DNA fragments of claim 4 are defined with respect to their ability to encode a polypeptide containing an epitope specifically recognized by monoclonal antibodies directed against the antigen of claim 1. The appellant disputes that the skilled person was able to arrive at these polypeptides in the light of the information provided by the patent in suit. Relying on decision T 188/97, the appellant also expresses the

view that it could not be deduced from the patent how to proceed to obtain fragments of the "pol antigen" having the same immunological properties as the "pol antigen".

In the board's view, though, obtaining monoclonal antibodies against a protein and assaying polypeptides against such antibodies was within the usual practice of skilled person at that time, as illustrated in paragraphs [0035] to [0038] of the patent in suit. Paragraph [0042] deals with obtaining polypeptide fragments and monoclonal antibodies recognising both these fragments and the original larger polypeptide. It is true that these passages relate to viral antigen "gp 110", however, the board does not see any reason why the techniques disclosed in paragraphs [0035] to [0038] and [0042] of the patent could not be applied by the skilled person to the claimed "pol antigen".

Moreover, the fact that another board denied sufficiency of disclosure in case T 188/97 cannot alter the present board's view. This decision is not relevant to the present case, since the search for peptide antigens dealt with in T 188/97 involved testing the peptides against (not available) "qualifying panels" of antibodies (see point 70 of T 188/97), not to speak of the further burden of isolating HCV strains having at least 40% sequence homology with the deposited strain (see point 72 of T 188/97).

5. In a further line of argument, the appellant maintained that the description in paragraphs [0016], [0030] and [0031] relating to the purification of the antigens of the invention, prescribed the use of lectins such as

concanavaline A, or concanavaline A fixed to a Sepharose®-column, and dissociation of the complex with O-methyl-α-D-mannopyranoside. The appellant points out that these techniques could not be applied to the "pol antigen" since naturally-occurring pol was unglycosylated and, consequently, it did not form complexes with concanavaline A.

In the board's judgement, the claimed "pol antigen" (as defined in claim 1) is not alleged to be the naturally occurring protein. No such statement is contained in the contested patent, and especially in the claims.

6. A further appellant's objection under Article 83 EPC is based on the fact that the patent in suit contains statements that are in contradiction with the actual properties of pol, such as the N-terminus of the pol antigen in Fig. 4, eight amino acids of which have turned out not to belong to the pol gene.

7. However, present claim 1 does not relate to the reverse transcriptase occurring in nature, nor to its further processed molecular forms arising in the infected cell, but to polypeptides (whether designated as pol or RT) falling within the amino acid sequence as defined in Table 1, in figure 4 and claim 1. The patent in suit provides access to the sequence of the ORF of the pol gene and to deposited clones containing this sequence. Consequently, it was possible to prepare any polypeptide encoded by the particular sequence of figure 4 of the patent.

8. In conclusion, the claimed subject-matter satisfies the requirements of Article 83 EPC.

Priority rights of claims 4 and 18

9. The respondents are of the opinion that the present claims are validly supported by the second priority document P2 (see paragraph 4 of the decision under appeal and the bottom of page 22 of the appellant's submission dated 10 December 2007).

10. However, the appellant argues that claim 4 can not enjoy the priority date of priority document P2, because the claim is directed to a **DNA** fragment defined in relation to its capacity to code for a polypeptide specifically recognized by monoclonal antibodies recognizing specifically the antigen according to claim 1, whereas the passage on page 15, lines 30-33 of priority document P2 merely relates to **peptides** suitable for the production of specific antibodies.

It is the board's view that the passage on page 15, lines 30-33 of document P2 (relating to peptides suitable for the production of specific antibodies), taken in combination with the passage on page 17, lines 12-16, relating to DNA variants provides a proper basis for claim 4 to enjoy the priority date of document P2. These DNA variants encode peptides which in turn are suitable for the production of specific antibodies.

11. The appellant is also of the opinion that claim 18 can not enjoy the priority date of priority document P2, in view of several differences between claim 18 and priority document P2.

The board is of the opinion that the general concept of detecting LAV viruses (see page 1, line 28-35), in combination with the reference to "additional DNA fragments, hybridisable with the genomic RNA of LAV" (see page 2, lines 17 to 22) and with the passage relating to the definition of probes (see page 14, lines 11-18 and 33-36, in particular the term "probe" without limitations on page 14, line 12) can be regarded as being a sufficient support for claim 18 to relate to the same subject-matter as disclosed in document P2.

12. In conclusion, the present claims can validly enjoy the priority date of the second priority document P2.

Novelty

Claim 1

Document B1

13. Document B1 relates to the characterization of the reverse transcriptase (hereafter: RT) activity associated with the lymphadenopathy associated virus (LAV; now HIV) (see the abstract on page 126). The authors of this document envisaged to establish whether the RT activity noted in extracts of LAV-infected cells were associated with the virus particles.

14. Accordingly, departing from the cell free supernatant from T lymphocytes infected with LAV "as previously described (1)" (see document B1, page 127, under "Cells"; reference "1" is document B19), the authors of document B1 subjected this supernatant to PEG precipitation and purification by banding on a 5 to 35% linear Nycodenz gradient and collected a fraction

comprising the virus particles (labelled with ^{3}H-uridine) (see the legend to Figure 1 and the paragraph bridging pages 129 and 130). As shown in Fig. 1, plotting the banding fractions versus RT activity (■.—.■) and amount of radioactively-labelled virus (●...●) gave two coincident peaks at a density of about 1.10 g/ml.

15. Paragraph 3 of document B1 has the title "Purification of RT from LAV infected lymphocytes by phosphocellulose chromatography" and describes the isolation of a fraction exhibiting RT activity (see peak "RT" in Fig. 2) eluting from the phosphocellulose column at 0.2 M KCl.

16. It is the appellant's view that peak "RT" in Fig. 2 was the "pol antigen" of LAV (HIV) and that hence the subject-matter of present claim 1 lacked novelty over document B1.

In the board's view, the relevant issue to be decided is whether or not the teaching in document B1 discloses in an enabling manner the isolation and the identification of a molecule structurally identical to the "purified pol antigen having the backbone of the polypeptide encoded by the nucleotidic sequence extending from nucleotide position 1631 to nucleotide 4639 of the LAV virus genome represented on figure 4, or an antigen having the same polypeptide backbone and whose aminoacid sequence is contained in the sequence in figure 4 extending from nucleotide position 1631 to 4639" (see claim 1).

17. A first step for isolating and characterizing the RT of the prior art was that the skilled person had first to

obtain a sufficient quantity of the virus to render possible the purification of the RT to an extent that it unambiguously fell under the term of claim 1. According to document B1 (see page 127, under "Cells"), T lymphocytes "were cultured and infected with LAV as previously described (1)". Reference "(1)" is document B19.

18. Relying on the sentence on page 869, l-h column, 2nd full paragraph of document B19 ("... a relatively high titre of reverse transcriptase activity was detected in both of the cord lymphocytes cultures..."), the appellant argues that the skilled person had no difficulties in infecting normal T-lymphocytes from either newborns or adults with HIV and in growing the virus to high titres.

19. However, in the board's opinion, document B19 also shows that not just any lymphocytes were suitable for obtaining cultures of the virus (see page 870, l-h column, first paragraph: "Only a minor portion of the cells (about 1 percent) reacted with the patient serum. This may indicate that only this fraction was infected and produced the virus"; see ibidem, second paragraph: "These lymphocytes [from patient 2] did not produce viral reverse transcriptase"). Moreover, it can be derived from document B19 that virus production decreased in parallel with the decline of lymphocyte proliferation (see the sentence bridging pages 868 and 869).

20. Therefore, in order to obtain high titres of the virus, the researchers had to turn to the identification and production of special cell lines capable of sustaining

growth (propagation) upon infection by the virus, with no cytopathic effects (i.e., no decrease in virus production/lymphocyte proliferation), so as to recover substantial quantities of the virus (see e.g. document B2, page 497, bottom of r-h column). That it was critical to have these special cell lines for obtaining high titres of the virus, and hence sufficient quantities of immunologic reagents and nucleic acid probes is supported by document B2, page 498, r-h column, lines 3-9 and by document B12, page 507, l-h column, lines 7-9, referring to document B2. The passage on page 167, l-h column, lines 20-26, of document B3 ("The **crucial step** allowing us to isolate and characterize HTLV-III, and to produce sufficient purified viral reagents for serological assays, was the successful transmission of HTLV-III to an immortalized human T-cell line (HT) and to clones derived from this cell line which were significantly resistant to the cytopathic effect of the virus"; emphasis by the board) further confirms this view, referring back to B2. Therefore, the passages above from documents B2, B3 and B12 do not support the appellant's arguments that it was possible to obtain high titres of the virus by simply infecting T-lymphocytes.

21. In conclusion, the disclosure of document B1, even when read in the light of document B19, already fails at this first step of recovering substantial quantities of the virus via special cell lines, and hence sufficient purified viral components.

22. In the appellant's opinion peak "RT" in Fig. 2 was nothing else than the "pol antigen" of LAV (HIV) according to present claim 1, the more so as the

wording of present claim 1 required neither that the pol protein be purified (but could be in admixture with the other viral components), nor that the protein be in "sufficient" quantities".

However, in the board's judgement, the disclosure by document B1 of a fraction possessing RT activity did not automatically mean that the molecule harbouring said enzymatic activity became part of the state of the art. This is because, according to the jurisprudence of the boards of appeal, the mere putative presence of a molecule within a mixture does not make this molecule available to the public, if the skilled person is not able to isolate, identify and compare this molecule with the claimed subject-matter (see decision T 301/87, OJ 1990, 335, point 5.8). When applying this principle to the present case, the board observes that (i) the "RT" peak in Fig. 2 overlapped other peaks including "α-DNA POL", "β-DNA POL" and possibly other impurities and that (ii) document B1 was silent as to how to isolate the RT enzyme from the other enzymatic activities and impurities present in peak "RT" in Fig. 2.

23. The board notes a further hindrance (iii) represented by the fact that any enzyme, owing to its catalytic nature, can exhibit a measurable activity, although it is present only in trace amounts in a fraction (a known amplification effect used in ELISA). By implication, although the skilled person was able to establish whether a cell was infected by a virus belonging to the retrovirus family (the RT activity was measurable), he/she could not take for granted that the RT enzyme (as a molecule and not as an activity) was in

"sufficient" quantities" in peak "RT" in Fig. 2 for its identification by sequencing.

24. Therefore, facts (i) to (iii) above do not assist the appellant's line of argument that the disclosure in document B1 made available to the public the enzyme having RT activity, either.

25. The appellant maintains that the two "Ono et al." references on page 127 (Reference "9") and on page 132 (Reference "16") of document B1 would have provided further details as to how RT had to be purified.

However, Reference "9" merely deals with the RT activity, not with the isolated enzyme, whereas Reference "16" is said to be "in press", i.e., not available to the public. Inclusion of a candidate virus into (or exclusion from) the retrovirus family did not require the isolation and the sequencing of the enzyme, but merely measuring RT activity, i.e., measuring how much radio-labelled deoxynucleotide monophosphate was incorporated into the product DNA (see legend to Fig. 2 in document B1).

26. The appellant also maintains that the legend to Fig. 3 in document B19 (referred to as "(1)" on page 127 of document B1, under "Cells") disclosed how to lyse the virus and how to separate the viral proteins by electrophoresis.

However, reference "(1)" (document B19) in the above quote from document B1 can be read in connection with document B1 only in regard to the source of the HIV infected cells used to obtain the HIV RT and not in

regard to other features mentioned in document B19, such as for example the electrophoresis of the viral proteins mentioned in the legend to Fig. 3. This experimental data should not be considered as incorporated into document B1 (see decision T 422/92 of 21 February 1995, point 2.3.1). Furthermore, even assuming that the skilled person was able to obtain (i) sufficient virus quantities (which has been denied: see point 21 supra) and (ii) amino acid sequence information from any of the proteins on the polyacrylamide-SDS gel slab of Fig. 3 in document B19, the absence of reference sequences would prevent him/her from identifying the protein exhibiting such amino acid sequence.

27. Finally, the appellant emphasizes that the patent in suit does not disclose the purification of a "pol antigen" (RT), let alone the purification of a "pol antigen" to a higher degree of purity than in document B1.

As already stated under point 7 supra, in the context of sufficiency of disclosure, the patent in suit provides access to the sequence of the ORF of the pol gene and to deposited clones containing this sequence. These are the means (missing in document B1) for preparing, in any grade of purity, polypeptides encoded by the particular sequence of figure 4 of the patent. Moreover, the knowledge provided in the patent of the amino acid sequence (in order to identify the protein), would render possible the isolation of the protein of the invention by applying the method described in paragraph [0021] of the patent.

28. In view of the foregoing, the board is not convinced that the technical information provided by document B1, even when read in the light of document B19, disclosed in an enabling manner the isolation and/or the characterization of the RT of the prior art to an extent that it unambiguously fell under the term of claim 1.

29. In conclusion, since novelty can only be affected by a document of the prior art if there is no doubt that the claimed subject-matter is directly and unambiguously disclosed in this document and that it can be reproduced, and none of these conditions are met by document B1, the latter does not anticipate the claimed subject-matter.

Document B2

30. The legend to Fig. 2B of document B2 relates to the sucrose density gradient banding of the virus, showing a peak of RT activity at a density of 1.16 g/ml.

As already pointed out under point 20 supra, the authors of document B2 succeeded in isolating special cells lines ("HT" and sub-clones "H4" and "H9") capable of sustaining growth upon infection by the virus, with no cytopathic effects (see document B2, page 497, bottom of r-h column), so as to recover substantial quantities of the virus in the order of 10^{11} viral particles/l of culture (see page 499, end of l-h column). Having access to these special cell lines was thus critical for obtaining high titres of the virus, and hence sufficient quantities of immunologic reagents (see document B2, page 498, r-h column, lines 3-9 and

document B12, page 507, l-h column, lines 7-9, referring back to document B2.

In point 76 of decision T 351/98 of 15 January 2002, the present board in a different composition already decided that the skilled person was not in a position to arrive at the high producer HT cell line and its sub-clones H4 and H9 referred to in document B2 ("document (D42)" in T 351/98). These clones were also not available from a deposit or otherwise.

31. In view of the foregoing, it must be concluded that the technical information provided by document B2 did not enable the skilled person to isolate and/or characterize the RT of the prior art to an extent that it unambiguously fell under the terms of claim 1.

Claims 2, 4, 5, 10 and 18
Document B3

32. Document B3 relates to the molecular cloning of the HTLV-III (later termed LAV and HIV-1) genome, i.e., the isolation of clones λBH10, λBH5 and λBH8. The appellant maintains that clones λBH5 and λBH10, whose restriction maps are shown in Fig. 2, are capable of encoding the pol antigen according to claim 1. Hence they are novelty-destroying for the subject-matter of claims 2, 4, 5, 10 and 22.

33. However, the authors of document B3 were in possession of a special cell line (HT) and clones derived from this cell line (see page 167, l-h column, lines 20-26), which were crucial for allowing them to clone and isolate clones λBH10, λBH5 and λBH8 and characterize

HTLV-III. Cell line H9 was then used for the detection of the viral proteins (see page 167, l-h column, last paragraph). The skilled person was not in a position to arrive at the high producer HT cell line and its sub-clones H4 and H9 without a deposit of these cells (see point 30 supra). Hence, in view of its non-enabling character, document B3 is not novelty-destroying for the subject-matter of claims 2, 4, 5, 10 and 22.

Document B4

34. This document describes clones BH10 and BH5 from LAV/HIV-1 (identical to clones λBH10 and λBH5 disclosed in document B3) and states that these clones have been deposited (see page 6, lines 1-8). Document B4 also disclosed individual fragments EcoRI-EcoRI, BglII-BglII and KpnI-KpnI (see Fig. 2). In the appellant's view, clones BH10 and BH5 and fragments EcoRI-EcoRI, BglII-BglII and KnI-KpnI were novelty-destroying for the subject-matter of claims 2, 4, 5, 10 and 22 because it was an inherent feature of these DNAs to encode the pol antigen according to claim 1.

35. However, according to decision T 179/01 of 6 April 2005 (see points 13 and 14), if a decision of lack of novelty is to be reached on the basis of inherency, then it is necessary that inherency be proved. This means that the evidence produced in this respect in the relevant document of the state of the art must provide a clear, unambiguous and enabling lead to the inherent properties.

36. However, document B4 disclosed (see legend to Fig. 4 on page 3 and in Fig. 4) the organization of the gag/pol

region of HTLV-III (later termed LAV and HIV-1) as presenting sequence homology with the other known members of the HTLV family (HTLV-I, HTLV-Ib, HTLV-II), which eventually proved to be erroneous. It was in fact reported that the gag/pol genes did not overlap (i.e., there is a fragment between gag and pol), contrary to Fig. 4 of the patent in suit. In conclusion, there is no evidence before the board that the teaching of document B4 would have enabled the skilled person to properly identify the correct location of the pol gene and to obtain the protein according to claim 1. In summary, clones BH10 and BH5 and restriction fragments EcoRI-EcoRI, BglII-BglII and KpnI-KpnI disclosed in document B4 cannot affect the novelty of the present claims.

Document B5

37. The opposition division held that the $KpnI^{3500}$-$BglII^{6500}$ fragment and the entire λJ19 HIV genome as deposited under CMCMI-338 anticipated claim 2. Consequently, the claims as maintained by the opposition division comprise disclaimers to the entire λJ19 HIV genome and to the $KpnI^{3500}$-$BglII^{6500}$ fragment.

In spite of that, the appellant maintains an objection of lack of novelty on the basis of the combination of the sentence on page 5 of document B5 ("KpnI (3500) - BglII (6500) fragment is thought to correspond at least in part to the pol gene") with the general teaching in document B5 relating to proposed uses of the described cloned fragments, especially their use as hybridization probes (see e.g. page 15, lines 17-21 of document B5). The appellant thus maintains that document B5 also

describes restriction fragments hybridizing with the pol KpnI^{3500}-BglII^{6500} fragment, which are inherently capable of encoding the pol antigen.

38. However, the board observes that the disclosure in document B5, of a restriction fragment which would hybridize, at least in part, with the pol gene, does not equate the disclosure of the pol gene. Indeed, based on the statement in document B5 (page 4) the KpnI (3500) - BglII (6500) fragment may also comprise a sequence of a gene other than the pol gene and may not comprise the complete sequence of the pol gene. Furthermore, no disclosure of the location of an ORF for the pol gene is made available in document B5, which would further include the disclosure of a correct reading frame (among the three possible reading frames) to express an amino acid sequence. In conclusion, these DNAs hybridizing, at least in part, with the pol gene, would suffer from the same deficiency pointed out in document B4, i.e. the failure to provide a clear, unambiguous and enabling lead to the inherent property of these DNAs to encode the pol antigen according to claim 1 (see points 35 and 36 supra).

Therefore the objection of lack of novelty of claims 2, 4, 5, 10 and 18 over document B5 is not justified.

39. The appellant also argued that the PstI^{800}- KpnI^{3500} (see page 5 of document B5) should be disclaimed because it includes the pol gene, however the appellant provided no evidence for this view.

Document B6

40. The patent in suit can be assigned the priority date of the second priority document P2 filed on 16 November 1984 in relation to the claimed subject-matter (see point 12 supra). Document B6 and its first priority document ("B6/Prio") do not disclose the same subject-matter insofar as the organisation of the pol gene is concerned (compare page 9, lines 19-25 of document B6/Prio with page Fig. 2-1 of document B6). Thus the benefit of the priority date of 31 October 1984 cannot be assigned to document B6 in relation to the (correct) reading frame indicated in this document, which should be treated as a post-published document.

In view of this conclusion, document B6 cannot affect the novelty of the claims.

Documents B7 to B10

41. Since, the present claims are validly supported by the second priority document P2, post-published documents B7 to B10 should be disregarded in respect of the novelty issue.

Inventive Step

42. The documents relevant for inventive step are documents B1 to B3 and B19.

Document B1

43. Departing from this document, in the appellant's view, the problem to be solved by the subject-matter of

present claim 1 was purifying a RT from the HIV virus. The appellant is of the opinion that the skilled person would have used common general knowledge (e.g. known chromatography techniques) in order to further isolate the HIV RT described in document B1 and obtain in an obvious way a pol antigen according to present claim 1.

44. The analysis of document B1 made in relation to the novelty issue (see points 13 to 21 supra) shows that the choice of a suitable cell line was a crucial step for obtaining high titres of the virus, and hence sufficient quantities of viral material which allowed the isolation of the protein, and that document B1, even when read in the light of document B19, already failed at this first step, let alone at the step of how to isolate the RT enzyme from the other enzymatic activities and impurities present in peak "RT" in Fig. 2.

45. The appellant relies on documents B11 and B12, describing immunoprecipitation techniques, or on document B20 relating to obtaining protein fragments by hydrolysis, to buttress its view that it was obvious to purify the pol antigen and to obtain fragments thereof.

However, in the board's judgement, in order that the skilled person applies the immunoprecipitation techniques described in documents B11 and B12, or the peptic cleavage referred in document B20, he/she had first to overcome the deficiencies pointed out above, which was not possible (see point 21 supra).

46. Therefore, the isolation and purification of the protein corresponding to the pol gene according to

present claim 1 is not considered to be obvious in the light of document B1, even when read in the light of document B19 and/or when supplemented by the common general knowledge. The appellant argues that the contested patent itself failed to show that particular steps were necessary to obtain the purified "pol antigen", rather, "any method known in itself" (see paragraph [0021] of the patent in suit) could be applied.

However, the patent refers to deposited clones for obtaining sufficient quantities of viral material, which is then further processed according to the techniques described in paragraphs [0018] to [0020] of the patent. Compared to the prior art disclosure, the patent thus provides means and technical information not made available by document B1, even when combined with the teaching of document B19 and/or the common general knowledge.

Document B2

47. The analysis of document B2 made in relation to the novelty issue (see points 30 and 31 supra) shows that this document suffers from the same deficiencies as document B1, as the skilled person was not in a position to arrive at the high producer HT cell line and its sub-clones H4 and H9 referred to in document B2.

Therefore, the isolation and purification of the protein corresponding to the pol gene according to present claim 1 is not considered to be obvious in the light of document B2, even when read in the light of

documents B1 and/or B19 and/or the common general knowledge.

Document B3

48. Claims 2, 4 and 5 are directed to DNA molecules encoding the pol antigen as defined in claim 1 or directed to a variant thereof, hybridizing under stringent conditions with the particular DNA molecule represented in Figure 4 between positions 1631 and 4639 of the nucleotides. The appellant maintains that the subject-matter of these claims lacks an inventive step in view of the disclosure in B3, in combination with the common general knowledge.

The analysis of document B3 made in relation to the novelty issue (see points 32 and 33 supra) shows that this document failed to give access to the clones of HTLV-III described therein (which were the same as in document B2), necessary to provide a sufficient quantity of HTLV-III to later obtain its nucleic acid sequence.

Moreover, the board observes that Figure 4 of document B3 provides the misleading information that the gag/pol region is separated by a non identified sequence, contrary to Figure 4 of the patent in suit, according to which the gag and pol genes overlap.

In view of the foregoing, the provision of DNA molecules according to present claims 2, 4 and 5 is not considered to be obvious in the light of document B3, even when supplemented by the common general knowledge.

Conclusion

49. The subject-matter of claims 1, 2, 4 and 5 cannot be derived in an obvious manner from the prior art. The above conclusion also applies to the DNA sequences, the DNA hybridization probes, the recombinant vectors, the microorganisms, the antibodies, the processes, the uses and methods of claims 3 and 6 to 18. For any of this claimed subject-matter to be carried out, one must have available the protein of claim 1 or the DNA sequence of Figure 4 recited in these claims. Thus, since inventive step is acknowledged for the protein of claim 1 or the DNA of claim 2, it can be acknowledged for all these other claims as well.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

P. Cremona M. Wieser