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D E C I S I O N
of 11 April 2003

Case Number: T 1084/00 - 3.3.8

Application Number: 94110658.5

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Language of the proceedings: EN

Title of invention:
HIV-3 retrovirus strains and their use

Applicant:
N.V. INNOGENETICS S.A.

Opponent:
-

Headword:
HIV-3 variants/INNOGENETICS

Relevant legal provisions:
EPC Art. 54, 56, 76, 83, 84, 123

Keyword:
"Main request - added subject-matter (no)"
"Disclosure - sufficiency (yes)"
"Clarity (yes)"

Decisions cited:
G 0010/93, T 0019/90, T 0190/99

Catchword:
-

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D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 11 April 2003

Appellant: N.V. INNOGENETICS S.A.
Industriepark Zwijnaarde 7
Box 4
B-9052 Ghent (BE)

Representative: Jaenichen, Hans-Rainer, Dr.
Vossius & Partner
Postfach 86 07 67
D-81634 München (DE)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 14 June 2000 refusing European patent application No. 94 110 658.5 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: P. Julia
C. Rennie-Smith

Summary of Facts and Submissions

I. An appeal was lodged by the applicant (appellant) against the decision of the examining division whereby the application No. 94 110 658.5 with the title "HIV-3 retrovirus strains and their use" was refused pursuant to Article 97(1) EPC on grounds of lack of clarity (Article 84 EPC) and of lack of sufficiency of disclosure (Article 83 EPC). The application was a divisional application of the earlier application No. 88 109 200.1 (publication No. 0 345 375) in accordance with Article 76 EPC.

II. The decision under appeal, based on a set of claims filed during the oral proceedings before the examining division, mainly referred to the subject-matter of claims 1 and 7, which read as follows:

"1. HIV-3 retrovirus strain having the essential morphological and immunological properties of the retrovirus deposited at the European Collection of Animal Cell Cultures (ECACC) under N° V88060301 and comprising in its nucleic acid sequence a contiguous R region and a U3 region sequence showing a homology of more than 70% with the nucleic acid sequence as represented in SEQ ID No.: 3, and provided that said HIV-3 retrovirus strain is not the strain deposited under ECACC N° V88060301."

"7. A nucleic acid molecule containing at least a portion of the cDNA corresponding to the entire RNA genome of the HIV-3 retrovirus strain of any one of claims 1 to 6 or the complementary strand thereof and which specifically hybridizes with the nucleotide sequence of the HIV-3 strain deposited under ECACC

N° V88060301 under stringent hybridization conditions; provided that said nucleic acid molecule does not comprise the sequences corresponding to the entire RNA genome of the HIV-3 strain ANT 70 deposited under ECACC N° V88060301."

III. In the Statement of Grounds of Appeal, the appellant filed a main request and auxiliary requests I to III, which were replaced by a new main request and auxiliary requests I to III with appellant's letter of 6 July 2001. The appellant stated in that letter that these new requests did not comprise any subject-matter relating to HIV-3 epitopes, antigens and monoclonal antibodies and that they substantially comprised the subject-matter dealt with by the decision under appeal, namely HIV-3 strain variants, nucleic acid molecules derived therefrom and embodiments dependent thereon.

IV. The Board issued a communication under Rule 11(2) of the Rules of Procedure of the Boards of Appeal wherein, with reference to the findings of decision G 10/93 (OJ EPO 1995, 172), the Board indicated its intention to assess the requirements of Articles 123(2) and 76(1) EPC for the requests on file.

V. In reply to the Board's communication, the appellant filed an auxiliary request IV and additional documents.

VI. Oral proceedings were held on 11 April 2003. During the oral proceedings the appellant withdrew all requests on file and filed a new main request.

VII. The new main request contained claims 1 to 15 for the Contracting States AT, BE, CH, LI, DE, FR, GB, IT, LU, NL and SE, wherein claim 1 read:

"1. Variants of the HIV-3 retrovirus deposited at the European Collection of Animal Cell Cultures (ECACC) under N° V88060301, said variants having the following essential morphological and immunological properties:

- The virus exhibits a tropism for T4 lymphocytes;
- The virus is cytotoxic for the lymphocytes that it infects;
- The virus has a diameter of approximately 120 nm;
- The virus possesses a magnesium dependent reverse transcriptase activity;
- It can be cultivated in T4 receptor-bearing immortalized cell lines;
- Lysates of the virus contain a p25 protein which is immunologically distinct from the p19 protein of HTLV-I and the p24 proteins of HIV-1 and HIV-2 as determined by Western blot analysis and partial CNBr-cleavage, respectively;
- Lysates of the virus contain a gp120 protein which is immunologically distinct from the gp110 protein of HTLV-1, the gp120 of HIV-1 and the gp120 of HIV-2 as determined by Western blot analysis;
- The lysate of the virus contains in addition a gp41 glycoprotein with a molecular weight of 40,000-45,000;
- The genomic RNA of the variant HIV-3 hybridizes neither with the sequences of HIV-1 nor with the sequences of HIV-2 under stringent hybridization conditions;
- Lysates of the virus contain a p16 protein which differs from the p17 of HIV-1 and HIV-2 as determined by partial CNBr-cleavage;
- Lysates of the virus contain a p31 endonuclease which differs from the p31 endonuclease from HIV-1 and HIV-2 as determined by partial CNBr-cleavage;

and said variants having CNBr- and BNPS-skatole cleavage patterns of the p25 protein, the p16 protein, the p31 protein and the reverse transcriptase as illustrated in Fig. 13."

Claim 2 was directed to a variant of claim 1 comprising in its nucleic acid sequence a contiguous R region and a U3 region sequence hybridizing under stringent hybridization conditions with the nucleic acid sequences as represented in Tables II and III.

Claim 3 read:

"3. A nucleic acid molecule containing at least a portion of the cDNA corresponding to the entire RNA genome of a variant HIV-3 retrovirus strain of claim 1 or 2 or the complementary strand thereof and which specifically hybridizes with the nucleotide sequence of the HIV-3 strain deposited under ECACC N° V88060301 under stringent hybridization conditions."

Claim 4 was directed to the nucleic acid molecule of claim 3 comprising the sequences corresponding to the entire RNA genome of the HIV-3 retrovirus strain of claim 1 or 2.

Claim 5 read:

"5. A nucleic acid molecule portion of the cDNA corresponding to the entire RNA genome of the HIV-3 retrovirus strain deposited under ECACC N° V88060301 or the complementary strand thereof and which specifically hybridizes with the nucleotide sequence of said HIV-3 strain under stringent hybridization conditions."

Claims 6 to 15 were directed to further embodiments dependent on claims 1 to 5, such as a probe and an (expression) vector comprising the nucleic acid molecules of any one of claims 3 to 5 (claims 6 to 8), a host cell transformed with such a vector (claim 9), a process for the production of an HIV-3 retrovirus strain of claim 1 or 2 (claim 10), a composition comprising a total extract or lysate of the HIV-3 retrovirus strain of claim 1 or 2 or produced according to said process of production (and further comprising a lysate of HIV-1, HIV-2, or a mixture of both) (claims 11 and 12), a kit comprising the above defined probe or composition (claim 13), a method for detection of an HIV-3 retrovirus strain or of its RNA in a biological liquid or tissue using said probe (claim 14) and the use of said nucleic acid molecules, probes or kits for the in vitro detection of HIV-3 or in vitro diagnosis of HIV-3 infection (claim 15).

Claims 1 and 2 of the main request for the Contracting States ES and GR were as claims 1 and 2 for the other Contracting States (cf *supra*), whereas claims 3 to 15 were correspondingly formulated as process claims.

VIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request and amended description filed during oral proceedings.

Reasons for the Decision

Main request

Article 76(1) EPC

1. The subject-matter of claim 1 is a combination of claims 1 and 2 of the parent application with the

additional immunological and chemical cleavage features found on page 19, line 11 to page 20, line 26 of the published parent application. Claim 2 has a basis in claims 1 to 3 of the parent application with, *inter alia*, page 8, line 53 to page 9, line 38 and page 12, line 54 to page 13, line 9 of the published parent application referring to the specific hybridization of HIV-3 retrovirus strains to the cDNA clone iso 70-11 (ANT 70). This iso 70-11 clone is further characterized on page 20, line 51 to page 23, line 25 of the published parent application.

2. The nucleic acid molecules of claims 3 to 5 have a basis in claims 26 to 27 of the parent application and, *inter alia*, on page 12 line 54 to page 13, line 4 of the published parent application which refers to such nucleic acid molecules as well as to their use as hybridization probes for the specific detection and diagnosis of HIV-3 infection.

3. Claims 6 to 9 have a basis in claims 31 to 33 and claim 37 of the parent application with, *inter alia*, page 12, line 58 to page 13, line 19. Claims 10 to 12 have a basis in claims 34, 35 and claim 7 of the parent application in combination with, *inter alia*, page 9 lines 45 to 53, page 10 lines 16 to 22 and in particular page 13, lines 30 to 36. Claims 13 to 15 can be derived from claims 18, 20 and 33 of the parent application with, *inter alia*, page 12, line 56 to page 13, line 4 and page 13 lines 20 to 29 of the published parent application.

4. The Board further notes that both the description of the application as originally filed and the description of the parent application are identical. Thus, and in

view of the foregoing, the Board is satisfied that the application as filed and in particular the subject-matter of claims 1 to 15 fulfil the requirements of Article 76(1) EPC.

Article 123(2) EPC

5. The application as originally filed refers to HIV-3 retrovirus variants having the essential morphological and immunological properties of the HIV-3 retrovirus strain deposited in the European Collection of Animal Cell Cultures (ECACC) under N° V88060301 (cf page 2, lines 50 to 52 of the application as published). These essential morphological and immunological properties are further defined in claim 2 of the application as filed as well as on pages 20 to 21 and Figure 13 in the corresponding published application. Thus, claim 1 has a basis in the application as originally filed.

6. Since all the claims have a valid basis in the description of the parent application (cf points 1 to 4 *supra*), claims 1 to 15 are also considered to fulfill the requirements of Article 123(2) EPC.

Articles 83 and 84 EPC

7. It is well-known that human immunodeficiency viruses have a high genetic variability and that genetic variants thereof arise spontaneously and with high frequency (cf page 2, lines 23 to 24 of the published application). The presence of HIV-3 variants is shown in the application by the isolation and partial characterization of the ANT 70 NA strain. The deposited HIV-3 retrovirus (ANT 70 strain, ECACC N° V88060301) provides a reliable reference which allows the skilled

person readily to recognise variants of the same which, as stated in the claim, are characterized by having a series of specific morphological and immunological properties.

8. These essential morphological and immunological properties of the variants of the deposited HIV-3 retrovirus are explicitly recited in claim 1. Thus, the objection raised in the decision under appeal arising from the absence of such a definition is overcome by present claim 1. The referred properties are clearly identified as being essential and capable of differentiating the HIV-3 variants from the known HIV-1 and/or HIV-2 retroviruses and thus they characterize the claimed HIV-3 variants in a clear manner.

9. The objections raised in the decision under appeal are mainly concerned with subject-matter directed to (short) nucleic acid molecules, ie the subject-matter of present claims 3 and 5. The Board notes in this respect that:

9.1 The wording "at least a portion of the cDNA" and "portion of the cDNA" in claims 3 and 5 respectively, cannot be read alone but has to be understood in the context of the whole claim and is particularly limited by the required (specific) hybridization to the deposited HIV-3 strain. The length of these portions is not arbitrarily short but restricted by this functional requirement.

9.2 General "stringent conditions" for hybridization are well-known to the skilled person and they are clearly and unambiguously defined in the description (cf *inter alia* page 7, lines 28 to 32; page 16, lines 55 to 58;

page 18, lines 1 to 14 of the published application).

9.3 In agreement with the established case law of the Boards of Appeal (cf *inter alia* T 190/99 of 6 March 2001, not published in OJ EPO) and taking into account the whole disclosure of the application (Article 69 EPC), the only technically sensible interpretation of the wording "specifically hybridizing" is an hybridization to the deposited HIV-3 strain but not to HIV-1 and HIV-2. The genetic variability of HIV-1/HIV-2 retroviruses as well as their regions of greater overall genetic stability and of highest degree of variability are already well-known in the prior art and there is no technical problem to determine whether or not a nucleic acid molecule hybridizes to HIV-1 and/or HIV-2 (cf page 2, lines 23 to 42 of the published application). Moreover, claims 3 and 5 only require the nucleic acid molecule portion to hybridize to the deposited HIV-3 strain and not to each and every possible HIV-3 variant, ie the claims are not directed to a general or universal HIV-3 probe.

9.4 The application provides experimental evidence showing nucleic acid molecule portions of the deposited HIV-3 strain fulfilling the requirements of claim 5, ie a specific hybridization to the deposited HIV-3 strain but not to HIV-1 and HIV-2 strains: in particular, the entire HIV-3 iso 70-11 clone and a Sal I-Bgl II fragment comprising the env gene (cf page 8, line 54 to page 9, line 5 of the published application). The application further shows that several HIV-1 and HIV-2 probes do not hybridize to the deposited HIV-3 strain: in particular, a HIV-1 gag-pol probe (cf page 9, lines 6 to 11 of the published application), a HIV-1 SacI-BgIII fragment comprising a portion of the 5'LTR, including the R region, the entire gag gene and most of the pol gene and a HIV-2 env probe (cf page 21, lines 26 to 35 of the published application). The nucleic acid molecule portions of claim 5 can easily be achieved from the deposited HIV-3 strain and the skilled person can always check whether a particular nucleic acid molecule is also present in the nucleotide sequence of the deposited HIV-3 strain.

9.5 There is no doubt that such nucleic acid portions can easily be obtained from the claimed HIV-3 variants too. Moreover and, as stated in the decision under appeal, in the light of the prior art concerned with general HIV genetic variability and with the knowledge of HIV-1 and HIV-2 variants (cf 9.3 *supra*), there should be no technical difficulty in determining whether a **long** nucleic acid molecule fulfilling the hybridization requirements of claim 3 corresponds to a fragment of the nucleotide sequence of a HIV-3 variant from the deposited HIV-3 strain (identification by homology of putative genes). The actual isolation or the complete characterization of the HIV-3 variant would be irrelevant and unnecessary for such a determination. It remains, however, to be assessed whether such a determination would be possible for **short** nucleic acid molecules fulfilling the hybridization requirements of claim 3.

9.6 The decision under appeal refers to these short nucleic acid molecules derived from non-viral (HIV-3) sequences as "unrelated probes". The existence of these unrelated probes is merely hypothetical and no technical evidence let alone verifiable facts have been provided to support their actual presence in the prior art (cf *inter alia* T 19/90 OJ EPO 1990, 476). Since the deposited HIV-3 strain is said to be related to known HIV-2 and (even more) to HIV-1 strains (cf page 6, lines 46 to 53 of the published application), the existence of "unrelated probes" for these known HIV strains (or alternatively the presence in their sequences of regions with low homology to the corresponding regions of other HIV strains but with high homology to unrelated (non-viral) sequences) would have supported the doubts of the examining division. However, this evidence is clearly missing in the contested decision. In the absence of such evidence, the skilled person would normally assume that each and every (short) nucleic acid molecule hybridizing to the deposited HIV-3 strain but not to HIV-1 and HIV-2 is derived from the nucleotide sequence of the deposited HIV-3 strain or from a variant thereof, irrespective of whether or not such a HIV-3 variant has already been identified and/or isolated.

9.7 In the Board's view, the essential technical feature of claims 3 and 5 is the required "specific hybridization" which can be clearly and unambiguously assessed using the deposited HIV-3 strain. Claims 3 and 5 must be read as a combination of functional and structural features and it is this specific combination, and not some of these features arbitrarily removed from the others, which must be clear (Article 84 EPC) and reproducible without undue burden (Article 83 EPC).

9.8 In view of the foregoing, the Board considers that the subject matter of claims 3 and 5 fulfils the requirements of Articles 83 and 84 EPC.

10. None of the other claims (or the corresponding subject-matter) has been objected to in the decision under

appeal and, as the remaining subject-matter is directly or indirectly dependent on claims 1 to 5, the Board sees no reason to raise any further objection under Articles 83 and/or 84 EPC.

11. Thus, claims 1 to 15 are considered to fulfill the requirements of Articles 83 and 84 EPC.

Articles 54 and 56 EPC

12. The parent application (EP 0 345 375) was granted with claims directed to the deposited HIV-3 retrovirus strain as well as to purified antigens thereof and nucleic acid molecules encoding them. No opposition was filed within the prescribed time limit. During the prosecution of that case, no relevant prior art was cited which could affect the novelty and/or inventive step of the deposited HIV-3 strain and/or of the variants thereof. No such prior art is available in the present case (cf 9.6 *supra*).

13. In view of the foregoing and in the absence of any relevant prior art, the claimed subject-matter is considered to fulfil the requirements of Articles 54 and 56 EPC.

Amendments to the description

14. The description was amended to bring it into line with the invention as claimed. The amendments do not contain subject-matter which extends beyond the original application.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to grant a patent on the basis of the main request and amended description as filed during the oral proceedings, and the figures as originally filed.

The Registrar: The Chairman:

P. Cremona L. Galligani