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D E C I S I O N
of 11 July 2006

Case Number: T 1300/05 - 3.3.08

Application Number: 96921473.3

Publication Number: 0847452

IPC: G01N 33/53

Language of the proceedings: EN

Title of invention:

Fluorescence resonance energy transfer screening assay for the identification of HIV-1 envelope glycoprotein-medicated cell

Applicant:

PROGENICS PHARMACEUTICALS, INC.

Opponent:

-

Headword:

RET screening assay/PROGENICS

Relevant legal provisions:

EPC Art. 83, 84

Keyword:

"Main request - clarity (yes)"
"Sufficiency of disclosure (yes)"

Decisions cited:

-

Catchword:

-



Case Number: T 1300/05 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 11 July 2006

Appellant:
(Applicant)

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Decision under appeal:

Decision of the Examining Division of the
European Patent Office posted 24 February 2005
refusing European application No. 96921473.3
pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: L. Galligani
Members: F. Davison-Brunel
C. Rennie-Smith

Summary of Facts and Submissions

I. European patent application No. 96 921 473.3 published as International application No. WO 96/41020 with the title "Fluorescence resonance energy transfer screening assay for the identification of HIV-1 envelope glycoprotein-mediated cell" was refused by the examining division.

Claims 10 and 11 of the main request then on file read as follows:

"10. An antibody determined to be capable of specifically inhibiting the fusion of a macrophage-tropic primary isolate of HIV-1 to a CD4⁺ cell susceptible to infection by a macrophage-tropic HIV-1, wherein such CD4⁺ cell is a primary human macrophage or a primary human T lymphocyte, using a method which comprises:

- (a) contacting (i) a primary human macrophage or a primary human T lymphocyte which is labeled with a first dye, with (ii) a Hela-env_{JR-FL} cell which is labeled with a second dye, in the presence of an excess of the antibody under conditions which would normally permit the fusion of the primary human macrophage or primary human T lymphocyte to the Hela-env_{JR-FL} cell in the absence of the antibody, the first and second dyes being selected so as to allow resonance energy transfer between the dyes;

- (b) exposing the product of step (a) to conditions which would result in resonance energy transfer if fusion has occurred;
- (c) determining whether there is a reduction of resonance energy transfer, when compared with the resonance energy transfer in the absence of the antibody;
- (d) contacting (i) a primary human T lymphocyte, which is labeled with a first dye, with (ii) a Hela-env_{LAI} cell which is labeled with a second dye, in the presence of an excess of the antibody under conditions which would normally permit the fusion of the primary human T lymphocyte to the Hela-env_{LAI} cell in the absence of the antibody, the first and second dyes being selected so as to allow resonance energy transfer between the dyes;
- (e) exposing the product of step (d) to conditions which would result in resonance energy transfer if fusion has occurred;
- (f) determining whether there is a reduction of resonance energy transfer, when compared with the resonance energy transfer in the absence of the antibody; and
- (g) comparing the determination made in step (c) with the determination made in step (f), wherein a decrease in transfer in step (c) but not in step (f) indicates that the antibody is capable of specifically

inhibiting fusion of the macrophage-tropic primary isolate of HIV-1 to CD4⁺ cells, but not capable of specifically inhibiting the fusion of a T cell-tropic isolate of HIV-1 to the CD4⁺ cells."

"11. An antibody capable of specifically inhibiting the fusion of Hela-env_{JR-FL} with primary human macrophages or primary human T lymphocytes, but not the fusion of Hela-env_{LAI} with primary human T lymphocytes."

Claim 12 related to the use of an antibody having the same properties as those of the antibody of claim 11 for the preparation of a pharmaceutical composition effective for treating HIV-1 infection.

In the auxiliary request, claim 10 was also directed to an antibody, the properties of which were defined by the same method steps as in claim 10 of the main request except for the fact that the relevant cell lines were otherwise identified in step (g). Claims 11 and 12 were identical to claims 11 and 12 of the main request.

II. The grant of a patent was refused for lack of clarity and lack of sufficient disclosure of the subject-matter of claims 10 to 12 of both requests for the same reasons:

- The claimed subject-matter was not clearly defined because it was defined by functional features whereas technical features such as sequence information, epitope information or accession number would have been

required. Defining the claimed subject-matter in technical terms was not an undue limitation because it would only be eliminating from the claim that which had not yet been invented. Furthermore, the skilled person could never be sure whether an already known antibody would fall within the scope of the claims or not (Article 84 EPC).

- It would be undue burden to isolate and characterize all potential antibodies to see if they fell within the scope of the claims (Article 83 EPC).

- III. The appellant (applicant) filed a notice of appeal against this decision, paid the appeal fee and submitted a statement of grounds of appeal together with a new main request and an auxiliary request.
- IV. The appealed decision was not rectified by the examining division and the case was remitted to the board of appeal (Article 109(2) EPC).
- V. The board sent a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal wherein a number of observations were made, in particular, under Article 123(2) EPC.
- VI. On 9 June 2006, the appellant sent a further submission together with a new main request and five auxiliary requests. Exhibits 1 to 12 were filed therewith.

The new main request comprised two claims which read as follows:

- "1. A monoclonal antibody generated against a cell-line susceptible to infection by macrophage-tropic HIV-1 isolates, and derived from the HuT 78 T lymphoblastoid cell line, wherein said antibody inhibits HIV-1 envelope glycoprotein mediated membrane fusion between Hela-env_{JR-FL} and said cell-line, but does not inhibit HIV-1 envelope glycoprotein mediated membrane fusion between Hela-env_{LAI} and Sup-T1 cells or between Hela-env_{LAI} and Hela-CD4⁺ cells.
2. Use of a monoclonal antibody according to claim 1 for the preparation of a medicament for the treatment of HIV-1 infection."
- VII. On 3 July 2006, the board informed the appellant's representative by telephone that the board was prepared to acknowledge clarity and sufficiency of disclosure in relation to the new main request and that it intended to send the case back to the first instance for further prosecution on the basis of this request.
- VIII. On 4 July 2006, the appellant's representative informed the board by telefax that in these circumstances, the appellant withdrew its request for oral proceedings under Article 116 EPC.
- IX. Oral proceedings which were to take place on 11 July 2006 were cancelled on 5 July 2006.
- X. The following documents are mentioned in this decision:
- Exhibit 2: Sun, L-Q. et al., Proc.Natl.Acad.Sci.USA,
Vol. 91, pages 9715 to 9719, October 1994;

- Exhibit 9: Lin, P-F. et al., Antimicrobiol. Agents and Chemotherapy, Vol. 40, No. 1, pages 133 to 138, January 1996;
- Exhibit 10: Extract from the 2006 NIH AIDS Research and Reference Reagent Program, on-line catalogue, reference n° 459 (Hela CD4 Clone 6C) and data sheet, and reference n° 1109 (Hela CD4 Clone 1022) and data sheet;
- Exhibit 11: Lusso, P. et al., Journal of Virology, Vol. 69, No. 6, pages 3712 to 3720, June 1995;
- Exhibit 12: Extract from ATCC 1983 catalogue, Accession ATCC TIB 161 (HuT 78), pages 437, 212, 6 and cover pages.
- Exhibit C: Koyanagi, Y. et al., Science, Vol. 236, pages 819 to 822, 15 May 1987;
- Exhibit H: Copy of e-mail correspondence between Dr. Maddon and Dr. Matocha Principal Investigator at the NIH AIDS Research and Reference Reagent Program confirming the availability of the Hela-CD4 cell line as from 1988.
- Exhibit J: Evidence from ATCC that plasmid pMA243 was deposited under the Budapest Treaty on 16 December 1993 with the accession number ATCC 75626.

XI. The appellant's arguments insofar as relevant to the present proceedings may be summarized as follows:

Article 123(2) EPC

The subject-matter of claim 1 of the new main request was supported by the application as filed at pages 60 and 61, in association with two explanatory passages of the description, at pages 52 and 58.

Claim 2 was a claim of the second medical indication type, referring back to the monoclonal antibody of claim 1. This subject-matter was supported by the original disclosure at the passages recited above for claim 1, and the therapeutic use of the agents of the invention was referred to for example at page 20, line 33; page 52, lines 3 to 9, and claim 6 as filed.

Articles 84 and 83 EPC

Claim 1 related to antibodies identified by the antigen to which they were raised, together with a precise indication of the properties of the antibodies in terms of their capacity to inhibit fusion mediated by the envelope glycoprotein of macrophage-tropic HIV-1 isolates, or by laboratory-adapted strains of HIV-1. The application as a whole related to the RET (Resonance Energy Transfer) assay system, allowing the determination of whether agents such as antibodies had the properties recited in the claims. The skilled person could therefore produce the antibodies without undue difficulty since their target cell was identified, and he/she could test their properties

using the RET assay system described in the application.

Monoclonal antibodies were traditionally defined by their target and in view of the manner in which antibodies were made, it was also generally accepted that if one was in possession of any particular antigen, one would also be in possession of its antibody. Moreover, the application provided working examples of such antibodies, and detailed information relating to their function and the way in which their function was tested.

The cell lines mentioned in claim 1 were available to the skilled person:

- SUP-T1 was cited in no less than 96 bibliographic references spanning the period from 1986 to the present day. Exhibit 2 provided evidence that at the filing date, it had already been deposited in ATCC under accession number CRL-1942.

- HeLa-CD4⁺ could then as now be obtained in particular from the NIH AIDS Research and Reference Reagent Program (see application as filed at page 42, lines 23 to 26 and Exhibit 10). The public availability of these cells from the indicated source at the filing date of the application was confirmed in Exhibit 9.

- HuT 78 was a well-known cell line. At the filing date, it had been available to the public from, in particular, ATCC under accession number TIB 161 (Exhibit 12).

The mention of these cell lines in claim 1 therefore provided a clear and reproducible technical teaching.

The claimed subject-matter thus met the requirements of Articles 83 and 84 EPC.

- XII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request or on the basis of one of auxiliary requests I to V filed with the letter dated 9 June 2006.

Reasons for the decision

Main request

Article 123(2) EPC

1. The subject-matter of claim 1 finds support in particular in Table 3 of the application as filed which shows the properties of four monoclonal antibodies which have been raised against PM1, a cell line which is derived from the HuT 78 lymphoblastoid cell line (page 52, lines 24 to 26 and Exhibit 11) and is sensitive to macrophage-tropic HIV-1. These monoclonal antibodies inhibit HIV-1 envelope glycoprotein-mediated membrane fusion between Hela-env_{JR-FL} and PM1 (Table 3, line 1) but do not inhibit HIV-1 envelope glycoprotein-mediated membrane fusion between Hela-env_{LAI} and SUP-TI or Hela-CD4⁺ cells (Table 3, lines 5 and 6).
2. The use of the monoclonal antibodies according to the invention for the preparation of a medicament for the treatment of HIV-1 infection (claim 2) is referred to for example in the paragraph bridging pages 20, line 33 and 21, line 12.
3. The requirements of Article 123(2) EPC are fulfilled.

Article 84 EPC; clarity and support

4. The monoclonal antibody of claim 1 is defined in terms of its origin and its properties. These features are described in a clear manner: the characteristics of the cells to which it is raised are unambiguous, its binding capacities are identified by reference to specific cell lines. In the board's judgment, the skilled person would have no difficulties in finding out whether or not an antibody answers to the terms of the claim (see also points 8 to 13, *infra*). Furthermore, the claimed subject-matter finds support in the application as filed, in particular, in the experimental protocol on page 60 which leads to the isolation and characterisation of four monoclonal antibodies having the relevant properties (Table 3).
5. The subject-matter of claim 2 which is worded as a second medical use claim also fulfils the requirements of Article 84 EPC.
6. The examining division came to a conclusion of lack of clarity of previous claims 10 and 11 on the ground that the claimed antibodies may have been better defined by technical features: sequence, epitopes and accession number. Yet, the sequence of an antibody is not likely to provide any useful information as to its characteristics, the determination of epitopes is a downstream development of the isolation of the monoclonal antibody *per se* and an accession number is not suited to characterize a family of antibodies. Thus, this approach to clarity cannot be followed.

7. The examining division also observed in relation to the subject-matter of the earlier claims 10 and 11 that the skilled person could never be sure whether or not an already known antibody would fall within the scope of the claim. Irrespective of the validity of this observation, it does not apply to the subject-matter of present claim 1 since, as already mentioned, the skilled person would have no problems in testing an antibody for the now claimed properties.

Article 83 EPC; sufficiency of disclosure

8. At the filing date, it was a matter of common general knowledge to raise antibodies against a given antigen - such as the cell line mentioned in the claim -, and there existed no less than three methods to quantify HIV-1 envelope protein-mediated membrane fusion between cell lines - see application as file at page 8 for a review of the prior art methods, and eg at page 10 for the RET method described in the application. Thus, the isolation and characterisation of the claimed antibody could have been reproduced - and still can - providing that all cell lines involved were either available to the skilled person or isolatable without undue burden. In its answer to the board's communication, the appellant provided numerous exhibits to show that it was indeed the case.
9. Exhibit 12 shows that the HuT 78 cell line has been deposited in the ATCC in 1983 under accession number TIB 161. Exhibit 11 teaches that a derivative cell line of HuT 78 which is sensitive to macrophage-tropic HIV isolates may be obtained by the limiting dilution technique followed by screening the clones on the basis

of their susceptibility to infection by a selectively macrophage-tropic isolate of HIV (page 3713, right-hand column, Results). The information is also given that by proceedings in this manner, one of several hundred clones tested was found susceptible to productive infection by the virus. Admittedly, testing several hundred clones amounts to much work but, in the board's judgment, it is not tantamount to undue burden, the more so that the testing method is known and that there is no doubt as to the outcome of the experiment. Thus, the cell line useful for generating the claimed antibodies is reproducible.

10. At the filing date, SUP-T1 cells had already been deposited in ATCC under number CRL-1942 (Exhibit 2).
11. The application as filed (page 42) discloses that at the filing date, Hela-CD4⁺ cells were available from, in particular, the NIH AIDS Research and Reference Reagent Program, a fact which is confirmed in Exhibit 9. The cell line is still available from the same source (Exhibit 10).
12. Exhibit C shows that HIV-env_{JR-FL} was isolated in 1987. Exhibit H provides evidence that it was available from the NIH AIDS Research and Reference Reagent Program as of 1988. In the board's judgment, cloning the env_{JR-FL} gene into Hela cells could be done as a matter of routine since Exhibit C (Figure 2B) taught the location of this gene on the restriction map of the viral DNA.
13. Hela-env_{LAI} cells can be produced without undue burden by transferring into Hela cells the env_{LAI} gene carried by plasmid pMA243 which is described in the present

- application (pages 19 and 43) and was deposited in the ATCC under accession number 75626 on 16 December 1993 (Exhibit J).
14. From these data, it is concluded that at the filing date, all cell lines necessary for the isolation and characterisation of the claimed monoclonal antibody were either available or reproducible without undue burden. As already mentioned in point 4 supra, the methods of isolation and characterisation themselves were also part of the state of the art. Sufficiency of disclosure is, thus, acknowledged.
 15. The board also considers that the use of the claimed monoclonal antibody for the preparation of a medicament (claim 2) requires no other measures than those routinely taken to formulate a medicament containing an antibody.
 16. The requirements of Articles 84 and 83 EPC are fulfilled.
 17. The examining division denied sufficiency of disclosure for the reason that it would be undue burden to obtain all antibodies falling within the scope of the claims. As explained above, it is the board's opinion that all necessary information for doing so is contained within the application. Thus, assuming for the sake of discussion that the skilled person would ever want to isolate all of the antibodies falling within the scope of the claims, the possibly undue amount of work involved would not stem from deficiencies in the way the invention was described but rather from the task which he/she chose to accomplish.

18. The appellant requested that a patent be granted on the basis of, in particular, the main request (see Section XII, supra). In view of the fact that the claim request now on file was not considered by the examining division which, thus, had no opportunity to assess whether it complies with the further requirements for patentability, the board considers it appropriate to remit the case for further prosecution under Art. 111(1) EPC.

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 for further prosecution on the basis of the main request filed on 9 June 2006.

The Registrar

The Chairman

A. Wolinski

L. Galligani