

**Internal distribution code:**

- (A)  Publication in OJ
- (B)  To Chairmen and Members
- (C)  To Chairmen
- (D)  No distribution

**D E C I S I O N**  
**of 15 December 2004**

**Case Number:** T 0219/01 - 3.3.04

**Application Number:** 91907077.1

**Publication Number:** 0527760

**IPC:** A61K 39/21

**Language of the proceedings:** EN

**Title of invention:**

Methods and compositions for vaccination against HIV

**Patentee:**

GENENTECH, INC.

**Opponent:**

Chiron Corporation

**Headword:**

HIV vaccine/GENENTECH

**Relevant legal provisions:**

EPC Art. 83, 100(b), 114(2)

**Keyword:**

"Main Request, First and Second Auxiliary - Sufficiency of disclosure (no)"

**Decisions cited:**

T 0409/91

**Catchword:**

-



Case Number: T 0219/01 - 3.3.04

**D E C I S I O N**  
of the Technical Board of Appeal 3.3.04  
of 15 December 2004

**Appellant I:** GENENTECH, INC.  
(Proprietor of the patent) 460 Point San Bruno Boulevard  
South San Francisco  
California 94080 (US)

**Representative:** Nicholls, Kathryn Margaret  
Mewburn Ellis LLP  
York House  
23 Kingsway  
London WC2B 6HP (GB)

**Appellant II:** Chiron Corporation  
(Opponent) 4560 Horton Street  
Emeryville, California 94608-2917 (US)

**Representative:** Hallybone, Huw George  
Carpmaels and Ransford  
43 Bloomsbury Square  
London WC1A 2RA (GB)

**Decision under appeal:** Interlocutory decision of the Opposition  
Division of the European Patent Office posted  
15 December 2000 concerning maintenance of  
European patent No. 0527760 in amended form.

**Composition of the Board:**

**Chair:** U. Kinkeldey  
**Members:** G. Alt  
S. Perryman

## Summary of Facts and Submissions

I. European patent no. 527 760 with the title "Methods and compositions for vaccination against HIV" was granted with 17 claims on European application No. 91 907 077. Claims 1, 2, 5, 12 and 13 as granted read:

"1. Unclipped HIV env for use in the prophylaxis or treatment of AIDS."

"2. The unclipped HIV env of claim 1 which comprises full length gp120 or a fragment thereof."

"5. An HIV vaccine comprising unclipped HIV env in a pharmaceutically acceptable carrier."

"12. A method for producing unclipped HIV env comprising the following steps:

(a) contacting a first preparation of HIV env with an antibody directed to an HIV env epitope spanning the clip site for a time sufficient to permit formation of a second, antibody-bound unclipped HIV env preparation;

(b) separating the second preparation from any HIV env which is not antibody bound; and

(c) recovering the unclipped HIV env from said second preparation."

"13. A method for the isolation of unclipped HIV env comprising affinity chromatography wherein antibody directed to an HIV env epitope spanning the clip site is bound to a carrier matrix and a solution containing

HIV env and unclipped HIV env is passed over the column and unclipped HIV env is selectively adsorbed to the matrix-bound antibody, the adsorbed antibody-unclipped HIV env matrix is washed to remove non-adsorbed material, and the unclipped HIV env is eluted."

II. The patent was opposed by two opponents on the grounds as set forth in Articles 100(a) EPC that the invention lacked novelty (Article 54 EPC) and inventive step (Article 56 EPC). Opponent II subsequently withdrew its opposition.

III. The opposition division raised Article 100(b) EPC as a ground of opposition on its own motion pursuant to Article 114(1) EPC.

IV. At oral proceedings the opposition division maintained the patent in amended form.

(a) The main request was refused, since it contained additional dependent claims 8 and 9 compared to the claims as granted, and so did not comply with the requirements of Rule 57a EPC since the addition of dependent claims could not be occasioned by a ground of opposition.

(b) The first auxiliary request was refused because its claim 5, corresponding to claim 5 as granted, was not novel under Article 54(3) EPC over document D14, WO-A-91/13906 and EP-A-0 519 001.

(c) The second auxiliary request was refused because a disclaimer introduced into claim 5 as granted in an

attempt to establish novelty over document D14, was not allowable under Article 123(2) EPC.

(d) The third auxiliary request was refused because claim 2 and other claims covered the possibility that a fragment of unclipped HIV was used that did not comprise the clip site, and on the evidence and arguments of the patentee himself as to the criticality of the presence of the clip site in the HIV env used as a vaccine such a fragment would not be useful in the prophylaxis or treatment of AIDS, so that the subject-matter of claim 2 as granted did not meet the requirement of sufficiency.

(e) The fourth auxiliary request with claims 1, 8 and 9 corresponding to claims 1, 12 and 13 as granted (see section I. above) and claims 2 and 5 reading:

"2. The unclipped HIV env of claim 1 which comprises full length gp120 or a fragment thereof comprising the clip site."

"5. An HIV vaccine comprising unclipped HIV env in a pharmaceutically accepted carrier, wherein the unclipped HIV env is other than a full-length, non-fusion glycosylated gp120 protein."

was considered to be in compliance with the EPC. The amendment to claim 2 to relate only to a fragment comprising the clip site removed the objection of insufficiency. Novelty could be acknowledged over the immunization regime of document D1 using recombinant HIV gp120 as this failed to prevent HIV infection in chimpanzees, whereas the patent succeeded and inventive

step could be acknowledged because the prior art did not suggest using unclipped HIV to improve efficacy.

- V. The patent proprietor (appellant I) and the opponent (appellant II) lodged an appeal against the interlocutory decision of the opposition division.
- VI. Each appellant filed replies to the statement of grounds of appeal of the other. Appellant I filed documents D40 to D52; appellant II filed documents D35 to D39.
- VII. The Board's summons to oral proceedings was accompanied by a communication summarising the parties requests and commenting on the admissibility of documents D35 to D39.
- VIII. In reply, appellant I submitted nine claim requests for consideration during oral proceedings.

The main claim request had claims 1 and 5 corresponding to claims 1 and 5 as granted (see section I. above).

- IX. Oral proceedings took place on 15 December 2004. During these appellant I filed a new first, second and third auxiliary claim request.
- X. Claims 1 and 3 of the first auxiliary request read:  
  
"1. Unclipped HIV env which is (i) full length gp120 or (ii) a fragment of gp120 comprising the clip site or (iii) a fusion of (i) or (ii) with another peptide, wherein the unclipped gp120 is at least 90% free of clipped gp120 fragments for use in eliciting a protective immune response against HIV."

"3. An HIV vaccine comprising unclipped HIV env which is (i) full length gp120 or (ii) a fragment of gp120 comprising the clip site or (iii) a fusion of (i) or (ii) with another peptide, wherein the unclipped gp120 is at least 90% free of clipped gp120 fragments in a pharmaceutically acceptable carrier."

XI. Claims 1 and 3 of the second auxiliary request read:

"1. Unclipped HIV env which is (i) full length gp120 or (ii) a fragment of gp120 comprising the clip site or (iii) a C or N terminal fusion of (i) or (ii) with an immunogenic hapten or heterologous polypeptide, wherein the unclipped gp120 is at least 90% free of clipped gp120 fragments for use in eliciting a protective immune response against HIV."

"3. An HIV vaccine comprising unclipped HIV env which is (i) full length gp120 or (ii) a fragment of gp120 comprising the clip site or (iii) a C or N terminal fusion of (i) or (ii) with an immunogenic hapten or heterologous polypeptide, wherein the unclipped gp120 is at least 90% free of clipped gp120 fragments in a pharmaceutically acceptable carrier."

XII. Claims 1 and 2 of the third auxiliary request corresponded to claims 12 and 13 as granted (see section I. above). The request also contained three further claims, dependent on claims 1 and 2.

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

- D1: Berman, P.W. et al., "Human immunodeficiency virus type 1 challenge of chimpanzees immunized with recombinant envelope glycoprotein gp120", PNAS, vol. 85, July 1988, pages 5200-5204
- D35: VaxGen Press Release "VaxGen announces initial results of its phase III AIDS vaccine trial"
- D36: Cohen, J., "AIDS vaccine trial produces disappointment and confusion", 28 February 2003, Science, vol. 299, pages 1290-1291
- D37: Cohen, J., "A setback and an advance on the AIDS vaccine front", 4 April 2003, Science, vol. 300, pages 28-29
- D38: Cohen, J., "Vaccine results lose significance under scrutiny", 7 March 2003, Science, vol. 299, page 1495
- D39: Watanabe, M.E., "Sceptical scientists skewer VaxGen statistics", April 2003, Nature Medicine, vol. 9, no. 4, page 376
- D40: Presentation at "AIDS Vaccine 2003" on 21 September 2003 showing analysis of the results of the AIDS VAX Phase III clinical trial
- D42: Mitka, M., "Critics Bash HIV vaccine trial analysis", 26 March 2003, JAMA, vol. 289, no. 12, page 1491
- XIV. The submissions made in writing and during the oral proceedings with regard to the main request and



auxiliary requests 1 and 2 by appellant II, insofar as they are relevant to the present decision, may be summarised as follows:

The argument during opposition proceedings that the positive chimpanzee data of the patent could not be extrapolated to humans were corroborated by the results of the AIDSVAX phase III clinical trial initially disclosed in February 2003. The overall result of this trial was judged negatively by the scientists working in the field of HIV research and even by the initiators of the study including one of the inventor's of the patent in suit. The reference to positive results for some racial subgroups of the participants were not convincing due to, for example, the small sample size. Consequently, the AIDSVAX trial is proof that the patent does not sufficiently disclose a substance useful for prophylaxis of AIDS or an HIV vaccine.

- XV. The submissions made in writing and during the oral proceedings with regard to the main and auxiliary requests 1 and 2 by appellant I, insofar as they are relevant to the present decision, may be summarised as follows:

The protection of two chimpanzees disclosed in the patent demonstrated that an unclipped HIV env composition provided a protective effect against HIV infection in vivo. The test for assessing sufficiency of a patent was a legal test, namely whether the invention was disclosed in the patent in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. The patent satisfied this test.

Investigations that rely on statistical analysis to assess their results, such as clinical trials, should not be used to judge sufficiency of disclosure for patent purposes.

Nevertheless, the clinical trial data indicated a statistically significant protection in certain subgroups as could be seen from the detailed statistical analysis of document D40. They thus provided evidence that the invention could be carried out.

Appellant II only relied on negative statements in reports commenting on the clinical trial although there were also statements that results of the trial were important and warranted further investigation.

XVI. Requests

Appellant I (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main claim request submitted on 15 November 2004, or of the first, second or third auxiliary claim request submitted at the oral proceedings on 15 December 2004.

Appellant II (opponent 1) requested that the decision under appeal be set aside and that the patent be revoked.

## Reasons for the Decision

### *Article 114(2) EPC - Admissibility of documents D35 to D52*

1. Documents D35 to D39 were submitted by appellant II in order to support the view that the invention was not sufficiently disclosed. Documents D40 to D52 were filed by appellant I to support the opposite view. None of the parties objected to the late filing of the documents. In view of this, and as the Board considered the evidence highly relevant not only to the issue of sufficiency, but to the issues of novelty and inventive step in view of the arguments relied on by the patentee in the proceedings before the opposition division that novelty and inventive step should be acknowledged because the patent provided for the first time evidence - the results obtained in two chimpanzees - that a prophylactic effect against AIDS would be obtained for a tested potential vaccine, the documents were admitted into the proceedings pursuant to Article 114(2) EPC.

### *Background*

2. Acquired immunodeficiency syndrome (AIDS) is caused by a retrovirus identified as the human immunodeficiency virus (HIV). A number of immunologic abnormalities have been described in AIDS, including abnormalities in B-cell function, abnormal antibody response and depressed natural killer and cytotoxic cell function.

The HIV particle is covered by an envelope derived from the outer membrane of the host cells. This membrane contains a population of virus-encoded envelope

proteins anchored in it (gp160). Each gp160 protein has two segments which are linked by a peptide bond. The N-terminal segment is termed gp120 and the C-terminal segment is termed gp41. In the patent in suit the term "HIV env" refers to the envelope glycoproteins gp160 and gp120 (page 4, lines 39 to 40).

HIV env proteins possess a proteolytic cleavage site located between residues 315 and 316 of gp120 (and also at the equivalent residues in gp160). Cleavage at this site leads to two products with, in the case of gp120, a relative molecular mass of 70K and 50K. That there are two products becomes apparent only after SDS-Page under reducing conditions, and this indicates that the two fragments are held together by a reducible disulphide bond.

An env-containing vaccine is designed to stimulate the production of anti-env antibodies and/or cellular responses that will either prevent infection by HIV or slow its replication (document D41) and thus delay any the outbreak of AIDS. The HIV envelope protein was already considered in the prior art to be a favoured candidate for a subunit vaccine due to its location on the surface of the virus, but some exploratory tests in chimpanzees did not confirm effectiveness (document D1).

3. According to the description of the patent in suit an env preparation is "unclipped" if the preparation is substantially free of env molecules cleaved at the clip site (page 4, lines 39 to 40; page 7, lines 41 to 42 of the published patent). The description states that by substantially free is meant "that the preparation should be greater than 50%, more preferably 60-70%,

still more preferably 80%, and most preferably at least 90% free of clipped HIV env fragments" (page 7, lines 42 to 44 of the published patent).

According to the patent in suit the unclippedness of env should make a critical difference to the effectiveness of a vaccine against AIDS compared to the prior art suggestion where "clipped" components would be present.

*Main Request - claims 1 and 5*

*Article 100(b) EPC - Sufficiency of disclosure*

4. It is established case law of the Boards of Appeal in judging sufficiency under Article 83 EPC or Article 100(b) EPC, that the subject-matter of a claim is only disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art can be carried, if this is true over the **whole breadth of the claim** (cf. T 409/91 of 18 March 1993, 3.5, second paragraph, last sentence). For the Board in relation to claim 1 which is drafted in the form of a first medical use claim with the only disclosed medical use specifically mentioned in the claim, a technical feature that requires to be sufficiently described in the patent is how to achieve prophylaxis or effective treatment of AIDS for the whole target group, here, humans, the only known organism developing AIDS after infection with HIV. Likewise for claim 5 to the vaccine, a technical feature that requires to be sufficiently described in the patent is how to achieve a vaccine for the whole target group, here again, humans.

5. AIDS VAX is a compound falling under the definition of unclipped HIV env of claims 1 and 5, and has been produced with the co-operation of the inventors at a date subsequent to the filing of the patent. The compound was the subject of a clinical trial the results of which were published in February 2003 (document D35). The Board can thus only assume that the results for AIDS VAX are representative of the best of what is achievable according to the teaching of the patent.

5.1 The AIDS VAX study took place in North America and the Netherlands. Its data and results are summarized in document D40 consisting of 29 Powerpoint slides.

A group comprising 5009 male and female participants from high risk groups was divided into a group of 1679 participants receiving three or more doses of a placebo and in 3330 participants receiving three or more doses of AIDS VAX ("unclipped env"). The presence of a HIV infection was evaluated by HIV serology after 0, 1, 6, 12, 18, 24, 30 and 36 months. AIDS VAX would be considered as effective if the vaccinated group was protected against an HIV infection at a statistically higher rate than the placebo group. The result was that of the 5009 trial participants receiving at least three vaccinations, 5,8% (98 persons) of those receiving placebo became infected with HIV compared to 5,7% (191 persons) receiving the vaccine. Commentators of the study (documents D35 to D39 and D42), and the parties, agreed that this showed no statistically significant difference between vaccine and placebo.

5.2 Hence, in summary, a large scale clinical trial involving more than five thousand persons whose lifestyle put them at risk of HIV infection, of whom two thirds were given AIDSVAX and the remaining third were a control given a placebo, showed that for the group as a whole there was no statistically significant effect attributable to AIDSVAX. Most of those partaking were white males, and for that subgroup, too, no beneficial effect attributable to AIDSVAX was shown. Prima facie the Board can only conclude that the information in the patent is not sufficient to enable a skilled person to achieve what is claimed in claims 1 and 5.

6. Appellant I has questioned whether results of a statistical analysis of a vaccine trial are appropriate means to challenge sufficiency of disclosure of a patent.

6.1 The statistically evaluated results of a vaccine trial allow predictions on the probability of the efficacy of a compound for prevention of an infection. In effect, the statistical evaluation of large groups is the only way to achieve conclusive results on efficacy in human beings, because of the unavailability for humans of any direct efficacy test such as is done in animals by vaccination with subsequent active infection with, for example, a virus. In this particular case, given that only humans infected with HIV develop AIDS, but chimpanzees infected with HIV do not develop AIDS, the Board considers that the results of the AIDSVAX vaccine trial are much more relevant evidence, than the results in chimpanzees so heavily relied on by the appellant I

before the opposition division as evidence of the effectiveness of what is claimed.

- 6.2 The Board is not stating that all vaccine trials or clinical trials are necessarily relevant, as some may relate to issues not relevant to the sufficiency of disclosure of a patent. However, it is common practice in proceedings before the EPO that a decision about the presence or absence of a certain medical effect of a compound is made on the basis of all sorts of evidence, be it in vitro or in vivo experiments provided that they render the intended effect credible.

This includes data filed after the filing date of the application, in particular where the issue is sufficiency of the patent disclosure in relation to medicines or vaccines, since highly relevant evidence concerning actual attempts to put the invention into practice may not be available until many years after the date of the patent, in contrast to in vitro or in vivo preliminary tests carried out to allow an initial assessment of the likelihood of success.

Amongst the available data in a certain case the highest evidential weight is adjudged to those experiments reflecting in the best way the envisaged use.

7. Even if the AIDSVAX clinical trial data were taken into consideration, appellant I argued that an analysis of the results of subsets of participants demonstrated that AIDSVAX was efficient in the prophylaxis of AIDS, in particular in human subgroups, namely women, Asians and Blacks, and this partial success was by itself



enough to support the presence of sufficiency of disclosure.

7.1 Leaving aside initially the question whether the subset results in fact demonstrated any success, which was in dispute between the parties, this argument for sufficiency fails for the Board because success for part of the area claimed in claims 1 and 5, does not compensate for lack of disclosure how to succeed for humans as a whole. The patent in suit contains no suggestion that the intended vaccine might succeed only for selected human groups, and certainly no identification of such groups. If what is claimed works only for some groups, this suggests that some other (unknown) factors are in play, and raises questions whether for these groups there is any significance in the difference between "unclipped" as claimed and the (partly) clipped env form present in the prior art suggestions.

7.2 For the subset analysis the entire sample of 5009 test persons was broken into the following "racial" groups (document D40): White (84% corresponding to 4185 persons), Hispanic (7% corresponding to 326 persons), Black (6% corresponding to 314 persons), Asian (2% corresponding to 73 persons), other (2% corresponding to 111 persons). In the White subgroup 5,4% of people receiving the placebo became infected versus 6,0% of the vaccine group. In the Hispanic group the infection rate was 5.3% in the placebo versus 5.2% in the vaccine group. The Black group showed an infection rate of 8.1% with placebo and 2.0% with the vaccine. The Asian subgroup had 10% infected people with placebo and 3.8% with vaccine and finally the

group of others had 15% infection with placebo and 8.5% with vaccine.

- 7.3 In contrast to the definite opinion about the whole-group results there is debate among the commentators in the literature as to whether the subset analysis is indeed suited to allow conclusions on the effectiveness of the vaccine in particular subgroups.

To cite but a few opinions:

Steven Self, biostatistician at the University of Washington, Seattle, specialized in AIDS Vaccines is cited in document D36 on page 11:

"Subset analyses are notoriously difficult to interpret, and they're doubly difficult when the overall result is nil, which is the case here."

Seth Berkley, head of the International AIDS Vaccine Initiative notes on page 11 of document D36 that VaxGen's subanalysis hinged on "just 13 infections" among black participants.

"Pull out 13 people from a large study - no matter whether they are left-handed homosexuals or whatever - and I certainly worry more about the results".

Dr. Peggy Johnston, assistant director for AIDS vaccines with the National Institute of Allergy and Infectious Diseases says in document D42:

"The [overall] result was negative - they asked a valid question and got a valid answer. But the subset results are intriguing and exploratory."

The author of document D42 adds to this comment that "subset analysis is very difficult, which is why subset analyses are considered exploratory and define what questions need to be asked in future trials".

Document D36 quotes on page 12 Stephen O'Brian, geneticist of the U.S. National Cancer Institute:

"It's not implausible that there would be differences in immune responses in different populations. But I wouldn't take this as a proof."

Again Steven Self in document D38:

"There's some marginal effect [of the vaccine], and it's worth going after, but it's not worth overblowing. It's a hypothesis-generating result."

Dr. Peter Pior, Executive Director of UNAIDS is cited in document D43, page 116, left-hand column:

"These results are promising. The trial provides clear evidence that the vaccine can work. However, there is an urgent need for more targeted research to find out why the vaccine only seems to work in certain population subgroups."

- 7.4 In summary, the Board concludes that the evidence at best shows that it might be worth investigating further whether the results for a larger sample of certain

subgroups would still come up with a protective effect, and then to carry out research to try and explain the cause for any real difference so established. But the evidence does not show that the teaching of the patent will ensure success.

8. Thus, the main request is rejected for non-compliance with the requirements of Article 100(b) EPC.

*First Auxiliary Request - claims 1 and 3*

*Article 123(2)(3) EPC, Article 84 EPC*

9. The difference in wording between claim 1 of the first auxiliary request and claim 1 of the main request is that the expression "in the prophylaxis or treatment of AIDS" is replaced by the expression "in eliciting a protective immune response against HIV" and that "HIV env" is defined as "(i) full length gp120 or (ii) a fragment of gp120 comprising the clip site or (iii) a fusion of (i) or (ii) with another peptide, wherein the unclipped gp120 is at least 90% free of clipped gp120 fragments."

The definition of HIV env in claim 3 to a vaccine is amended in the same way as in claim 1. No objections were raised by appellant II against the amendments pursuant to Article 123(2) or (3) EPC and the board, too, has none.

10. Appellant II argued that claim 1 was not clear. Since, however, these potential clarity problems do not affect the evaluation of the claim for the purpose of Article 83 EPC here, they are not further discussed.

*Article 83 EPC - Sufficiency of disclosure*

11. The reasons why the Board could not accept that there was sufficiency of disclosure for the subject-matter of claims 1 and 5 of the main request apply equally to claims 1 and 3 of the first auxiliary request, and so this request too must be refused.

*Second Auxiliary Request - Claims 1 and 3*

*Article 83 EPC - Sufficiency of disclosure*

12. Claim 1 of the second auxiliary request defines in point (iii) that the full length gp120 or a fragment thereof comprising the clip site may be C- or N-terminally fused with an immunogenic hapten or heterologous polypeptide. Vaccine claim 3 is similarly limited.
13. There being no disagreement that AIDS-VAX is a compound covered by the definition of "HIV env" claim 1 or 3 of this request, the reasoning set out above for refusal of the main request for lack of sufficiency applies equally to the claims of this request which must consequently be refused.

*Third Auxiliary Request*

14. All product claims have been deleted from this request. the remaining two independent claims are directed to methods for production and isolation of unclipped env together with three claims dependent on them.

These claims were maintained by the opposition division in the form as granted and are not in dispute in the

appeal. Therefore, there is no issue that the Board needs to consider in respect of this request.

## **Order**

### **For these reasons it is decided that:**

1. The decision under appeal is set aside.
2. The case is remitted to the first instance with the order to maintain the patent on the basis of claims 1 to 5 of the third auxiliary claim request submitted at the oral proceedings on 15 December 2004 and a description to be adapted thereto.

Registrar:

Chair:

P. Cremona

U. Kinkeldey