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D E C I S I O N
of 26 March 2003

Case Number: T 0757/00 - 3.3.4

Application Number: 95117311.1

Publication Number: 0711564

IPC: A61K 39/145

Language of the proceedings: EN

Title of invention:

Cross-reactive influenza A immunization

Applicant:

UNIVERSITY OF MASSACHUSETTS MEDICAL CENTER

Opponent:

-

Headword:

Influenza A immunization/UNIVERSITY OF MASSACHUSETTS MEDICAL CENTER

Relevant legal provisions:

EPC Art. 84, 76(1)

Keyword:

"Main request - clarity (no)"

"First and second auxiliary requests: added matter over the parent application (yes)"

Decisions cited:

-

Catchword:

-



Case Number: T 0757/00 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 26 March 2003

Appellant: UNIVERSITY OF MASSACHUSETTS MEDICAL CENTER
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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 31 January 2000
refusing European patent application
No. 95 117 311.1 pursuant to Article 97(1) EPC.

Composition of the Board:

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

Summary of Facts and Submissions

I. European patent application No. 95 117 311.1 (publication No. 0 711 564), filed as a divisional application on European patent application No. 91 915 798.2, published by the WIPO under number WO 92/02250 was refused by a decision of the examining division. The decision was based on claims 1 to 3 of the first main request filed on 18 November 1999 during the oral proceedings, claims 1 and 2 of the second main request filed on 2 February 1999 and claims 1 and 2 of the auxiliary request also filed during the oral proceedings. Claims 1 to 3 of the first main request read as follows:

"1. A cytotoxic T lymphocyte, wherein the cytotoxic T lymphocyte is stimulated by influenza A virus NS1 protein and provides a subtype cross-reactive immunity against Influenza A Virus.

2. The cytotoxic T-lymphocyte, according to claim 1, producible by stimulation by A/PR/8 virus.

3. A vaccine composition for use in immunotherapy, the vaccine providing sub-type cross-reactive immunity against Influenza A virus by stimulating a cytotoxic T-lymphocyte according to claim 1 or claim 2."

Claims 1 and 2 of the second main request read as follows:

"1. Use of a recombinant vector containing a gene which encodes the influenza A virus NS1 protein (or homologues/fragments thereof in which amino acids have been deleted, inserted or substituted without

essentially detracting from the immunological properties thereof) for the manufacture of a medicament for use in immunotherapy, which immunotherapy comprises the steps of:

- a) providing an effective amount of the NS1 protein (or homologue/fragment thereof) to an individual, whereby
- b) an NS1 specific T-cell response is stimulated, which
- c) provides subtype cross-protective immunity against Influenza A virus in said individual.

2. The use of claim 1 wherein the T-cell response is a cytotoxic and/or helper T-cell response."

Claims 1 and 2 of the auxiliary request read as follows:

"1. Use of a cell which contains a truncated portion of the gene encoding the NS1 protein which contains a T-cell epitope for the manufacture of a medicament for use in immunotherapy, which immunotherapy comprises the steps of:

- a) providing an effective amount of the NS1 protein (or homologue/fragment thereof) to an individual, whereby
- b) an NS1 specific T-cell response is stimulated, which
- c) provides subtype cross-protective immunity against

Influenza A virus in said individual.

2. The use of claim 1 wherein the T-cell response is a cytotoxic and/or helper T-cell response."
- II. The examining division decided not to admit into the proceedings the claims of the first main request because, inter alia, claim 1 of this request did not relate to searched subject-matter, while claim 3 thereof was open to an objection under Article 84 EPC. The claims of the second main request and of the auxiliary request were considered to infringe Article 76(1) EPC.
- III. An appeal was lodged against this decision. The Statement of Grounds of Appeal comprised a main request and a first and a second auxiliary requests, all corresponding substantially to the three claim requests pending before the examining division, except for the addition of the wording "or homologues/fragments thereof in which amino acids have been deleted, inserted or substituted without essentially detracting from the immunological properties thereof and the cytotoxic lymphocyte" after "NS1 protein" in claim 1 of the main request compared to claim 1 of the first main request pending before the examining division.
- IV. The appellant was duly summoned to oral proceedings on 26 March 2003. The oral proceedings took place, which the appellant did not attend, as had been foreshadowed in his representative's faxed letter of 25 March 2003.
- V. The submissions in writing by the appellant can be summarized as follows:

Main request

- The search examiner carried out the search on the basis of the alleged effect of the composition namely, a T-cell response against an NS1 epitope in the individual resulting in a sub-type cross-reactive protective response against influenza A virus. Therefore, the search must have covered the subject-matter of claims 1 and 2.
- The prior art failed to disclose a T-lymphocyte which provided a T-cell response against an epitope found on the NS1 protein.
- Claim 3 was directed to a vaccine composition for stimulating the T-cell of claims 1 or 2, according to which the T-cells had to be stimulated by the NS1 protein or fragments thereof.
- The application taught that a cytotoxic T-lymphocyte endowed with sub-type cross-reactive properties could be raised against influenza A virus. The skilled person could thus reproduce the invention by following the directions given in the application and using his normal skill and knowledge. Therefore the claims of the main request were clear as required by Article 84 EPC and satisfied the requirements of Article 83 EPC.

First auxiliary request

- The present application and its parent application taught that one aspect of the invention was immunotherapy by expression in general of the NS1 protein in an individual. It was true that the

present application exemplified this teaching by a method of using a recombinant virus to introduce the NS1 gene into the host, however, this was merely a specific exemplification of the general teaching of the application.

- Therefore, there was no added subject-matter over the parent application in generalising the nature of the expression vehicle to "recombinant vector" in claim 1. This was because it could be derived from the passages on page 10, line 29 to page 11, line 9 and on page 6 lines 17 to 20 of the present application as filed that the nature of the expression vehicle was immaterial.
- The passage bridging pages 8 and 9 (*ibidem*) showed that the expression vehicle could be a cell.

Second auxiliary request

- Claim 1 was based on the last incomplete paragraph on page 8 of the present application ("Alternatively, a truncated portion of the gene encoding the NS1 protein which contains a T cell epitope can be expressed in a cell"). There was thus no added subject-matter over the parent application.

VI. The appellant (applicant) requested in writing that the decision under appeal be set aside and that a patent be granted on the basis of the claims of the main request, or of the first or second auxiliary request, all filed on 6 June 2000.

Reasons for the Decision

1. The appeal is admissible.

Main request

Clarity (Article 84 EPC)

2. The ingredient(s) of the "vaccine composition" of claim 3 of this request is/are not defined, the "vaccine composition" being rather defined by the technical effect to be achieved and the biochemical mechanism underlying this effect. It is the appellant's view that the vaccine preparation of claim 3 must of necessity contain the NS1 protein or fragments thereof by virtue of its relationship to claim 1 or 2. However, the board firstly notes that claim 2, although formally dependent on claim 1, in fact relates to an alternative agent to stimulate a cytotoxic T lymphocyte and thus it is not in line with claim 1: it relates to stimulation by the A/PR/8 virus rather than by means of the NS1-epitopes as in claim 1. Secondly, a "vaccine composition" comprising cells of the CTL clone A-11 (see pages 18 and 19 of the WO 92/02250 application, under the heading "Reduction of the pulmonary virus titres etc") is also said to provide "sub-type cross-reactive immunity against Influenza A virus by stimulating a cytotoxic T-lymphocyte" ("These results reflect the in vitro cross-reactivity of CTL clone A-11 shown in Table 1") since it reduces the virus titres by the same mechanism. In conclusion, claim 3 of this request lacks clarity as to what is covered by this claim and the appellant's main request is not allowable.

First auxiliary request

Article 76(1) EPC

3. In claim 1 of this request, it is specified that the active agent to be used in the manufacture of an immunotherapeutical medicament is a "recombinant vector containing a gene which encodes the influenza A virus NS1 protein". The claim thus relates to immunotherapy by in situ expression in the host of the NS1 protein by means of recombinant vector in general such as a virus, a plasmid, a cosmid or any other DNA/RNA vector.

4. The appellant considers that the broader term "recombinant vector" embracing any NS1-expressing vector is supported by the general teaching of the application which is immunotherapy by expression of the NS1 protein in an individual without limitation to a particular vector.

5. However, the board observes that the only passage dealing with immunotherapy by expression in the host of a NS1-encoding DNA is that on page 10, line 29 to page 11, line 9 and claims 2 and 5 of the application as filed (corresponding to page 10, line 29 to page 11, line 9 and claims 2 and 7 of the published parent application WO 92/02250). The wording "recombinant vector" is to be found nowhere in these passages but reference is made therein to **recombinant viruses** only, such as the vaccinia virus. It must be concluded that the skilled person could not derive from the parent application that "recombinant vectors" in general could be used in order to achieve immunotherapy. The board's view is strengthened by the fact that, during the examination phase, the then applicant did not dispute that recombinant vectors other than viral vectors were not available at the filing date of the present parent

application (see paragraph 2.3 of the decision under appeal referring back to the third paragraph of the communication dated 30 July 1998).

6. The appellant emphasizes the passage bridging pages 8 and 9 of the present application, which in his opinion, shows that the expression vehicle could be a cell, ie something different from a virus. However, in the board's view, the passage relied upon by the appellant relates to the expression of a truncated portion of the gene encoding the NS1 protein in a cell and its isolation and purification in vitro (ie not in the host). The conclusion cannot be drawn that the cell is used as an expression vehicle to be injected into the host.

7. Under these circumstances, the board concludes that the term "recombinant vector" in claim 1 of this request represents an inadmissible generalisation of the term "recombinant virus" disclosed in the parent application. Therefore, claim 1 does not satisfy the requirements of Article 76(1) EPC and the appellant's first auxiliary request is not allowable either.

Second auxiliary request

Article 76(1) EPC

8. In claim 1 of this request, it is specified that the active agent to be used in the manufacture of an immunotherapeutical medicament is "a cell which contains a truncated portion of the gene encoding the NS1 protein which contains a T-cell epitope". The appellant considers that the above wording is supported by the passage bridging pages 8 and 9 of the parent application ("Alternatively, a truncated portion of the

gene encoding the NS1 protein which contains a T cell epitope can be expressed in a cell").

However, as stated in the preceding paragraph, the passage which the applicant considers as a counterpart of claim 1 does **not** mean that "a cell containing a truncated portion of the gene encoding the NS1 protein" is used **as such** in the medicament. The cells merely serves for expressing in vitro (not in the host) the NS1 fragment, which after isolation (see *ibidem*, page 9, lines 1 to 2) is used as the final medicament. Expression of the NS1 fragment in transformed cells is merely an alternative (cf "Alternatively") to oligopeptide chemical synthesis (see *ibidem*, page 8, lines 27 to 28).

9. In view of the foregoing, it must be concluded that claim 1 does not satisfy the requirements of Article 76(1) EPC since it comprises added subject-matter over the parent application. The appellant's second auxiliary request is thus not allowable either.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairwoman:

P. Cremona

U. M. Kinkeldey