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D E C I S I O N
of 10 June 2005

Case Number: T 1326/04 - 3.3.8

Application Number: 94912411.9

Publication Number: 0690912

IPC: C12N 15/86

Language of the proceedings: EN

Title of invention:
Recombinant avian adenovirus vector

Applicant:
COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANISATION

Opponent:
-

Headword:
Avian adenovirus vector/COMMONWEALTH CSIRO

Relevant legal provisions:
EPC Art. 123(2), 83, 84

Keyword:
"Main request - added subject-matter (no)"
"Clarity (yes)"
"Sufficiency of disclosure (yes)"

Decisions cited:
G 0001/03

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1326/04 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 10 June 2005

Appellant: COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANISATION
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 30 March 2004 refusing European application No. 94912411.9 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: P. Julià
M. B. Günzel

Summary of Facts and Submissions

I. The applicant (appellant) lodged an appeal against the decision of the examining division dated 30 March 2004 whereby the European patent application No. 94 912 411.9, which originated from an international application published as WO 94/24268 (to be referred to in the present decision as the application as filed), was refused pursuant to Article 97(1) EPC.

II. Claim 1 of the application as filed read as follows:

"1. A recombinant vector comprising a recombinant avian adenovirus incorporating, and capable of expression of at least one heterologous nucleotide sequence."

III. The decision under appeal was based on a main request and six auxiliary requests filed on 4 February 2004, the third, fifth and sixth auxiliary requests being amended during the oral proceedings before the examining division on 5 March 2004. The main request was refused by the examining division under Rule 86(3) EPC, whereas the first and second auxiliary requests were refused under Article 84 EPC and the third to sixth auxiliary requests were found to contravene Article 83 EPC.

IV. On 6 August 2004, the appellant filed the statement of grounds of appeal together with a main request and a first to fifth auxiliary requests, which corresponded to the main requests and to the first to fifth auxiliary requests on which the decision under appeal was based. The examining division did not rectify its

decision and referred the appeal to the board of appeal (Article 109 EPC).

V. The board sent a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal (RPBA) indicating its preliminary, non-binding opinion.

VI. Submissions in reply to the board's communication were filed on 10 May 2005 with a new main request, based on the claims as originally filed, and new first to third auxiliary requests in replacement of the requests on file.

VII. At the oral proceedings which took place on 10 June 2005, the appellant withdrew all previous requests and filed a new main request.

VIII. Claim 1 of the **main request** (claims 1 to 22) read as follows:

"1. A recombinant avian adenovirus vector incorporating, and capable of expression of, at least one heterologous nucleotide sequence, wherein the at least one heterologous nucleotide sequence is inserted into a non-essential region at the right terminal end of the genome of the avian adenovirus."

Claims 2 and 3 further defined the location of the right terminal end and the non-essential region referred to in claim 1 (at map units 92-100 and 97-99.9, respectively). Claims 4 to 13 related to further features of the said recombinant avian adenovirus vector. Claims 14 to 16 were directed to the use, in the preparation of a medicament, of the recombinant

avian adenovirus of claims 1 to 13. Claims 17 to 19 concerned a method of producing said recombinant avian adenovirus vector for use as a vaccine and claims 20 to 22 were directed to such a recombinant vaccine.

(The dependency of claim 3 on claim 6 is an obvious error and has to be read as a reference to claim 1).

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

D5: M. Sheppard and H. Trist, Virology, 1992, Vol. 188, pages 881 to 886,

D8: S. Chiocca et al., J. Virol., 1996, Vol. 70(5), pages 2939 to 2949,

D9: M. Hess et al., Virology, 1997, Vol. 238, pages 145 to 156,

D10: J. Pitcovski et al., Virology, 1998, Vol. 249, pages 307 to 315,

D11: M.A. Johnson et al., Vaccine, 2003, Vol. 21, pages 2730 to 2736.

X. The appellant's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

The application showed the production of recombinant avian adenoviruses and their use as vectors for delivering (at least) one heterologous nucleotide sequence to host organisms (birds) and eliciting a protective immune reaction against (viral) pathogens.

These avian adenovirus vectors presented several unexpected advantages, such as the possible insertion of large (heterologous) nucleotide sequences, a prolonged (immuno)protective (vaccination) effect, the use of common avian adenovirus serotypes, etc. Claim 1 required the insertion of the heterologous nucleotide sequence into a non-essential region at the "right terminal end" of the avian adenovirus genome.

The application as filed stated that by convention (avian) adenovirus genomes were normally oriented such that the terminal region from which no late mRNA were synthesised was located at the left end of the viral genome. Reference was explicitly made to non-essential regions located at the "right terminal end" of the (avian) adenoviral genome as being suitable for the purpose of replacement with or insertion of heterologous sequences. Thus, there was a basis in the application as filed for the claimed subject-matter (Article 123(2) EPC).

These references also showed that the terms "left terminal end" and "right terminal end" were conventional and well-established in the technical field. Therefore, the requirements of Article 84 EPC were also fulfilled.

The application as filed showed the characterisation of a non-essential region at the "right terminal end" of the fowl adenovirus (FAV) serotype 10 (CFA20) by cloning and sequencing a NdeI restriction fragment of 4249 bp (Figures 3 and 6). Restriction enzyme maps of other FAV serotypes containing similar suitable ("right terminal end") restriction fragments were also

disclosed in the application as filed (CFA15 and CFA19 in Figures 1 and 2, respectively). The identification of non-essential regions located at the "right terminal end" of the (avian) adenoviral genome represented no burden for the skilled person.

Moreover, the application also taught that, although more virulent avian adenovirus strains were better immunogens, non-pathogenic (immunogenic) avian adenovirus vectors had to be chosen. In fact, since evidence was provided showing that the insertion of (at least) one heterologous gene into the genome of a virulent avian adenovirus had a strong attenuating effect, the use of many avian adenovirus serotypes, including pathogenic serotypes (CFA19), was envisaged for the development of suitable recombinant avian adenovirus vectors.

Thus, the requirements of Article 83 EPC were also fulfilled.

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

Reasons for the Decision

Main request
Article 123(2) EPC

1. There is a formal basis in the application as filed for the feature "*a non-essential region at the right terminal end of the genome of the avian adenovirus*"

introduced in the claims for defining the insertion site of the (at least one) heterologous nucleotide sequence into the avian adenovirus genome.

2. Many references are found in the application as filed to the incorporation of heterologous nucleotide sequences into non-essential regions of the avian adenoviral genome (cf. *inter alia* page 7, lines 12 to 31, page 8, lines 15 to 17, page 11, lines 3 to 24, etc.). Reference is explicitly made to "*non-coding regions at the right terminal end of the viral genome*" as suitable "*non-essential regions ... for the purposes of replacement with or insertion of heterologous nucleotide sequences*" (cf. page 8, lines 18 to 20). The characterisation of a non-essential region at the right (terminal) end of the fowl adenovirus (FAV) serotype 10 (CFA20) is also exemplified (cf. page 16, line 20 to page 17, line 2 and Figure 6). Formal basis for the specific map units recited in claim 2 (map units 92 to 100) and claim 3 (map units 97 to 99.9) is found in the application as filed too (cf. page 16, line 30 to page 17, line 1 with Figure 6 and page 8, lines 21 to 22, respectively).

3. Thus, the requirements of Article 123(2) EPC are fulfilled.

Article 84 EPC: clarity of the feature "at the right terminal end"

4. The examining division, in considering the first and second auxiliary requests then on file, decided that the feature "in the right end" in relation to the avian adenovirus (AAV) genome was not clear and rejected

therefore the requests under Article 84 EPC. In the claims at issue here the said feature reads now "at the right terminal end".

5. Although the application does not disclose the exact length of the "right terminal end", this expression is commonly used in the fields of DNA and protein chemistry. Moreover, several explicit references are found in the present description which give a clear indication of what is meant and understood to be the "right terminal end" in the context of the present invention. In particular, when reference is made to the "*non-coding regions at the right terminal end of the viral genome*", it is further stated that "*preferably this region is located at the right end of the genome at* ***map units 97 to 99.9***" (cf. page 8, lines 18 to 22). The application also refers to the identification of the right end by cloning and sequencing of a FAV *NdeI/3* fragment (4249 bp) and to the characterisation of the entire gene organisation in the said right end of the FAV genome (contained in the *NdeI/3* fragment). Since one map unit is defined as being 0.45 kb (cf. page 14, line 34), the length of the FAV *NdeI/3* fragment corresponds to about 9.4 map units and thus, the *NdeI/3* fragment extends from about **90.6 to 100 map units** of the FAV genome. It is in this context too that Figure 6 is said to illustrate "*an expanded region from* ***92-100 map units*** *for the FAV CFA20 genome*" (cf. page 16, line 22 to page 17, line 2 and Figure 6). Subclaims 2 and 3 refer specifically to the "right terminal end" being located at **map units 92-100** and **97 to 99.9**, respectively.

6. In the light of this information, the board considers that, although the term "right terminal end" is not defined as a precise region, it can be nevertheless clearly identified within the AAV genome by way of the information provided by the application as filed. The presence of this term in claim 1 is considered to reflect only the fair balance between the interest of the applicant in obtaining adequate protection and the interest of the public in determining the scope of protection with reasonable effort as referred to in the established case law (cf. *inter alia* G 1/03 OJ EPO 2004, 413, point 3). Thus, the requirements of Article 84 EPC are considered to be fulfilled.

Article 83 EPC

7. The teachings of the application intend to be generally applied to avian adenoviruses (*Aviadenoviradae*) and reference is made in the application to several serotypes of the fowl adenovirus (FAV), such as the non-pathogenic isolates FAV CFA20 (serotype 10), CFA15 (serotype 10) and CFA19 (serotype 9) as candidates for vaccine vectors and vector development (cf. *inter alia* page 7, lines 3 to 10, page 9, lines 24 to 25). The application further discloses restriction enzyme maps of several FAV serotypes, such as FAV CFA15, CFA19 and CFA20 (cf. figures 1 to 3), which show the presence of restriction fragments comprising "right terminal ends" similar to the exemplified *NdeI/3* fragment of the FAV CFA20 (cf. figures 3 and 6). In the board's judgement, cloning, sequencing and the identification of the non-essential (non-coding) regions of these "right terminal ends" do not require any undue burden or inventive contribution from the skilled person. Nor are

they required for the production of restriction enzyme maps and suitable "right terminal ends" of other avian adenoviruses, such as the chicken embryo lethal orphan (CELO), FAV10, etc., as shown in the references cited in the application (cf. pages 4 and 5). Figure 1 of document D5 shows the HpaI and BglII restriction maps of FAV10 with restriction fragments of, respectively, 3.6 kb and 2.9/0.72 kb at the right end of the FAV10 genome.

8. At the priority date it was known that FAV genomes were larger (some 10 kb) than human adenovirus (HAV) genomes, e.g. the CELO virus genome being 30% longer than that of HAV (cf. *inter alia* page 3, lines 25 to 30, page 4, lines 10 to 11). Evidence is also on file showing the presence of nucleotide sequences at the right end of AAV genomes which are unique to avian adenoviruses, i.e. different from (or with no homology to) HAV (cf. for instance, Figure 1 on page 2941 of the post-published document D8, cited as expert opinion). Similar unique sequences are also present in the avian adenovirus genomes of groups other than the exemplified FAV group I, such as the hemorrhagic enteritis virus (HEV, group II) and the egg drop syndrome virus (EDSV, group III) (cf. figures 1 of post-published documents D9 and D10, cited as expert opinions). These post-published documents also show the presence of both coding and non-coding (non-essential) regions at the right end of the AAV genomes. Thus, on the evidence on file, no particular technical problems should be encountered by the skilled person when applying the general teachings of the present application to other avian adenoviruses.

9. Guidance is also provided by the application for the selection of avian adenovirus isolates - and serotypes thereof - suitable for the construction of vaccine vectors, namely low or non-pathogenic (or at least stably attenuated) but highly immunogenic or infectious isolates, and exemplified by the selection of CFA15, 19 and 20 isolates (cf. *inter alia* page 3, lines 11 to 16, page 6, lines 1 to 29, page 13, lines 10 to 15). Post-published evidence on file also shows a virulent FAV serotype (FAV8 CFA40) to be strongly attenuated when a heterologous gene is inserted into the "right terminal end" of its genome (cf. document D11, cited as expert opinion). In the light of this guidance, no undue burden or inventive skill is considered to be required in the selection of suitable avian adenovirus isolates for the purpose of the present application.

10. Thus, the requirements of Article 83 EPC are considered to be fulfilled.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the Examining Division for further prosecution on the basis of the main request filed during the oral proceedings.

The Registrar: The Chairman:

A. Wolinski L. Galligani