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D E C I S I O N
of 21 October 2005

Case Number: T 0524/01 - 3.3.08

Application Number: 90913914.9

Publication Number: 490972

IPC: C12N 15/11

Language of the proceedings: EN

Title of invention:

Recombinant negative strand RNA virus expression systems and vaccines

Patentee:

MEDIMMUNE VACCINES, INC.

Opponent:

American Cyanamid Company

Headword:

Recombinant influenza virus/MEDIMMUNE

Relevant legal provisions:

EPC Art. 83, 84, 111(1), 114(2), 123
EPC R. 57a

Keyword:

"Main and first auxiliary request - sufficiency of disclosure (no)"

"Second auxiliary request - not allowed"

"No further requests allowed into the proceedings"

Decisions cited:

T 0409/91, T 0435/91, T 0322/93, T 0794/94, T 0113/96,
T 0950/99, T 0716/01

Catchword:

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Case Number: T 0524/01 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 21 October 2005

Appellant: MEDIMMUNE VACCINES, INC.
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Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted
9 March 2001 concerning maintenance of European
patent No. 490972 in amended form.

Composition of the Board:

Chairman: L. Galligani
Members: M. R. Vega Laso
K. Garnett

Summary of Facts and Submissions

I. European patent No. 0 490 972 based on application No. 90 913 914.9 (published as WO 91/03552) and having the title "Recombinant negative-strand RNA virus expression systems and vaccines" was granted with 50 claims for all designated Contracting States.

II. Claims 1, 26 and 45 as granted read:

"1. A recombinant RNA molecule comprising a binding site specific for an RNA-directed RNA polymerase of a negative-strand RNA virus, operatively linked to a heterologous RNA sequence comprising the reverse complement of an mRNA coding sequence."

"26. A chimeric virus comprising a negative-strand RNA virus containing a heterologous RNA sequence comprising the reverse complement of an mRNA coding sequence, operatively linked to a polymerase binding site of the negative-strand RNA virus."

"45. A chimeric, negative-strand RNA virus containing a heterologous RNA sequence comprising the reverse complement of an mRNA coding sequence operatively attached to a negative-strand RNA virus polymerase binding site."

Independent claim 11 and dependent claim 28 concerned recombinant ribonucleoprotein complexes (RNPs) comprising a recombinant RNA molecule as claimed in the patent, mixed with purified RNA-directed RNA polymerase. Claim 27 (partly dependent on claim 1) and claim 29 (partly dependent on claim 26) concerned specific

embodiments of, respectively, a recombinant RNA molecule containing a viral polymerase binding site, and a chimeric virus. Independent claims 30, 33 and 42 were directed to recombinant DNA molecules encoding recombinant RNA molecules claimed in the patent, and independent claims 34 and 37 to a method for gene expression using host cells transfected with a recombinant RNP as claimed. Independent claims 38 and 43 related to a method for producing a chimeric negative-strand RNA virus, and dependent claim 44 to a particular embodiment of the method of claim 43. Dependent claims 46 to 49 concerned specific embodiments of the chimeric negative-strand RNA virus of claim 45.

Subject-matter related to influenza virus was claimed in claims 2 to 10 and, in part, claim 27 (recombinant RNA molecules); claims 12 to 15 and, in part, claim 28 (recombinant RNPs); claims 16 to 25, 29 (partly) and 50 (chimeric viruses); claims 31 and 32 (recombinant DNA molecules); claims 35 and 36 (methods for gene expression) and claims 39 to 41 (methods for producing a chimeric influenza virus).

- III. An opposition was filed relying on the grounds of Article 100(a) EPC, in particular lack of inventive step (Article 56 EPC), and of Article 100(b) and (c) EPC. During the opposition procedure, the opponent withdrew its opposition in so far as it was directed against claims specifically relating to influenza.
- IV. In an interlocutory decision posted on 9 March 2001, the opposition division found that the opposition ground of Article 100(b) EPC prejudiced the maintenance

of the patent as granted (main request), on the grounds that the subject-matter of independent claims 1, 11, 26, 42 and 45, as well as claims depending thereon or referring thereto, insofar as they related to negative-strand RNA viruses other than influenza virus, was not disclosed in the patent in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

In particular, the subject-matter of claim 26 (cf. Section II *supra*) was considered as not being sufficiently disclosed over the whole range claimed, because specific technical instructions for preparing **non-segmented** negative-strand RNA viruses were not provided in the patent. In the view of the opposition division, the evidence presented by the proprietor, notably post-published documents D19, D22 and D27, did not demonstrate that a chimeric non-segmented negative-strand RNA virus could be prepared by the methodology disclosed in the patent. In these documents, host cells were transfected with a "naked" RNA construct containing the heterologous gene, whereas an essential step of the method disclosed in the patent was the use of a recombinant RNP, i.e. a viral polymerase complex comprising the recombinant RNA template mixed with viral RNA-directed RNA polymerase proteins (P proteins) and nucleoprotein (NP). The opposition division observed that, since the patent in suit stated that no expression of the heterologous gene was obtained when host cells infected with a helper virus were transfected with "naked" recombinant influenza RNA (cf. page 18, lines 33 to 35 of the patent), the skilled person would understand that in the method disclosed in the patent the viral proteins provided by

the RNP were indispensable for amplification of the recombinant RNA template and rescue of the chimeric virus. The same conclusions were reached for the subject-matter of claim 45 (cf. Section II *supra*).

Furthermore, the opposition division found that the amendments introduced into claim 1 of the first auxiliary request filed during the oral proceedings offended against Article 123(2) EPC. Claims 1 to 40 of the second auxiliary request filed also during the oral proceedings, which were limited to subject-matter relating to influenza, were however considered to satisfy the requirements of the EPC. Thus, pursuant to Article 102(3) EPC the patent was maintained on the basis of the second auxiliary request and a description amended accordingly.

- V. An appeal against the interlocutory decision of the opposition division was lodged by the patent proprietor (appellant). In its statement setting out the grounds for appeal, the appellant requested that the decision under appeal be set aside and the patent be maintained on the basis of either the main request (claims as granted) or the first auxiliary request filed at the oral proceedings before the opposition division. Reference was made to, *inter alia*, seven new documents (D46 to D53) which were filed with the statement.

The respondent submitted its observations on the grounds for appeal, together with fourteen additional documents (D54 to D67).

Both the appellant and the respondent requested as a subsidiary request that oral proceedings be held under Article 116 EPC.

- VI. The parties were summoned to oral proceedings. In a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal attached to the summons, the board drew the attention of the parties to some of the issues to be discussed at the oral proceedings, and in particular to the issue of sufficiency of disclosure with respect to claims 1, 11, 26, 38, 43 and 45.
- VII. In response to the board's communication, the appellant submitted three new auxiliary requests and fourteen additional documents (D68 to D81), three of which were declarations of experts in the field of negative-strand RNA viruses.
- VIII. The respondent filed observations including three new documents. In a subsequent submission, it requested that the three declarations filed by the appellant in response to the board's communication not be allowed into the proceedings on the grounds of being late-filed. In the event that the board decided to allow the declarations, the respondent filed an additional document.
- IX. Two days ahead of the date fixed for the oral proceedings, the appellant and the respondent each filed a submission including additional documents and evidence. The appellant indicated that the first auxiliary request considered by the opposition division in its decision was maintained as fourth auxiliary

request. A further submission of the respondent was received on the eve of the oral proceedings, this submission including a new document that replaced another document previously filed.

- X. Oral proceedings were held on 21 October 2005. At the outset of the proceedings, the board, after hearing the parties, decided which of the documents filed on appeal were to be allowed into the proceedings, and asked the parties to refer in their arguments only to the documents allowed. The issue of sufficiency of disclosure with respect to claims 26 and 45 of the main request was then discussed. After deliberation, the board expressed a provisional opinion adverse to the position of the appellant, indicating that the same conclusions would apply to three of the four auxiliary requests then on file. The auxiliary requests in question were withdrawn by the appellant. With regard to the remaining auxiliary request, the board pointed to several formal deficiencies in the claims, and adjourned the proceedings in order to give the representatives of the appellant the opportunity to file an amended request taking into account the objections raised by the board.

The oral proceedings were resumed and, instead of the envisaged amended request, a new auxiliary request derived from the main request was filed. The board expressed its doubts as to whether the amendments introduced into some of the claims of the new auxiliary request complied with Article 123(2) EPC. Upon request of the appellant, the oral proceedings were adjourned again.

XI. An amended auxiliary request (claims 1 to 40), which in the following will be referred to as the **first auxiliary request**, was then filed. This request differs from the main request in that claims 11, 34, 38, 43, 44 and 46 to 50 are deleted, the remaining claims renumbered and the back-references amended accordingly. Additionally, both claims 25 and 40 (derived from claims 26 and 45 as granted) are amended to include the phrase "*wherein the negative-strand RNA virus is either influenza or respiratory syncytial virus*" at its end, and the back-reference to claim 26 in claim 28 (derived from claim 29 as granted) is deleted.

The issue of sufficiency of disclosure with respect to the subject-matter of claims 25 and 40 was discussed. After hearing the parties, the board indicated that the conclusions reached for the corresponding claims of the main request would equally apply to the auxiliary request and, upon request, the appellant was again given the opportunity to submit an amended request.

XII. Amended claims 1 to 43 - referred to in the following as the **second auxiliary request** - were filed. Claims 1, 25 and 39 read:

"1. A recombinant RNA molecule comprising a **3' non-coding flanking sequence containing** a binding site specific for an RNA-directed RNA polymerase of the negative-strand RNA virus, operatively linked to a heterologous RNA sequence comprising the reverse complement of an mRNA coding sequence **and a 5' non-coding flanking sequence of said negative-strand RNA viral genome.**"

"25. A chimeric **influenza** virus containing a heterologous RNA sequence comprising the reverse complement of an mRNA coding sequence, operatively linked to a **3' non-coding flanking sequence containing the** polymerase binding site of the negative-strand RNA virus, **and a 5' non-coding flanking sequence of said negative-strand RNA viral genome.**"

"39. A chimeric **influenza** virus containing a heterologous RNA sequence comprising the reverse complement of an mRNA coding sequence operatively attached to a **3' non-coding flanking sequence containing a** binding site for an **RNA-directed** RNA polymerase of a negative-strand RNA virus, **and a 5' non-coding flanking sequence of said negative-strand RNA viral genome.**"

(Amendments made in respect of the corresponding claims as granted are shown in bold-type characters.)

XIII. The following documents will be referred to in the present decision:

D4: W. Luytjes et al., Cell, Vol. 59, December 1989, pages 1107 to 1113;

D5: M.J. Schnell et al., EMBO J., Vol. 13, No. 18, 1994, pages 4195 to 4203;

D6: N.D. Lawson et al., Proc. Natl. Acad. Sci. USA, Vol. 92, May 1995, pages 4477 to 4481;

D12: P. Calain and L. Roux, J. Virol., Vol. 67, No. 8, August 1993, pages 4822 to 4830;

- D19: K.H. Park et al., Proc. Natl. Acad. Sci. USA,
Vol. 88, July 1991, pages 5537 to 5541;
- D20: P.L. Collins et al., Proc. Natl. Acad. Sci. USA,
Vol. 88, November 1991, pages 9663 to 9667;
- D22: A. Kato et al., Genes to Cells, Vol. 1, June 1996,
pages 569 to 579 (1 to 15 in the copy filed);
- D27: A.P. Durbin et al., Virology, Vol. 235, 1997,
pages 323 to 332;
- D31: P.L. Collins et al., Proc. Natl. Acad. Sci. USA,
Vol. 92, December 1995, pages 11563 to 11567;
- D42: M.S. Sidhu et al., Virology, Vol. 208, 1995,
pages 800 to 807;
- D45: S. Hausmann et al., RNA, Vol. 2, 1996, pages 1033
to 1045;
- D46: D. Kolakofsky et al., J. Virol., Vol. 72, No. 2,
February 1998, pages 891 to 899;
- D48: K. Dimock and P.L. Collins, J. Virol., Vol. 67,
No. 5, May 1993, pages 2772 to 2778;
- D49: P.L. Collins et al., Virology, Vol. 195, 1993,
pages 252 to 256;
- D66: A.K. Pattnaik and G.W. Wertz, J. Virol., Vol. 64,
No. 6, 1990, pages 2948 to 2956;

- D68: Declaration of Dr Richard M. Elliott of 3 October 2005;
- D70: Declaration of Dr Atsushi Kato of 21 January 2003;
- D71: A.M. Dzianott and J.J. Bujarski, Nucleic Acid Research, Vol. 16, No. 22, 1988, page 10940;
- D72: A.M. Dzianott and J.J. Bujarski, Proc. Natl. Acad. Sci. USA, Vol. 86, July 1989, pages 4823 to 4827;
- D77: B.P. De and A.K. Banerjee, Virology, Vol. 196, 1993, pages 344 to 348;
- D79: S.K. Samal and P.L. Collins, J. Virol., Vol. 70, No. 8, August 1996, pages 5075 to 5082;
- D80: A.K. Pattnaik et al., Virology, Vol. 206, 1995, pages 760 to 764.

XIV. The arguments put forward by the appellant, either in writing and at oral proceedings, can be summarized as follows:

Allowance of late-filed documents

Documents D68, D70, D71, D72, D77, D79 and D80 were filed in response to the communication by the board and should, therefore, be admitted into the proceedings.

Main request - Sufficiency of disclosure - Claims 26 and 45

The patent provided fundamental principles for the construction of negative-strand RNA viral templates to express heterologous gene products and/or rescue the gene in viral particles. It described for the first time the location of cis-acting sequences required for RNA transcription, replication and packaging of negative-strand RNA viruses. While the invention was described in terms of influenza, the principles could be analogously applied to construct other negative-strand viral RNA templates and chimeric viruses, as all negative-strand RNA viral genomes shared the same basic organization and mode of replication. The application of reverse genetics had confirmed that the cis-acting signals required for transcription, replication and packaging of all negative-strand RNA viruses, including both segmented and non-segmented viruses, were found in the 5' and 3' untranslated regions of the genome.

The opposition division misconstrued the methods of the patent as requiring the identification of the minimal polymerase binding site of each negative-strand RNA virus. However, the claims did not require that the minimal polymerase recognition site be used, nor that it even be identified. Rather, the patent clearly and unambiguously taught that the **entire** 3' and 5' termini of the viral genome of segmented and non-segmented RNA viruses provided all the signals required for transcription, replication and packaging of the viral genome. The sequence of the complete 3' and 5' non-coding termini was readily accessible for the skilled artisan using reverse transcription and PCR cloning

techniques that were available at the priority date. A detailed knowledge of the genome, be it segmented or non-segmented, was not required.

As provided in the patent, correct 3' termini of viral RNA transcribed *in vitro* from a suitable DNA construct was generally achieved by engineering a restriction enzyme site at the appropriate position corresponding to the correct viral termini. The plasmid DNA encoding the viral RNA was then cleaved at that position so that the RNA transcribed *in vitro* had a perfect or nearly perfect 3' end.

There was documented evidence on file, e.g. documents D20, D42, D19, D48, D49 and D22, demonstrating the successful application of the methods of the invention to rescue negative-strand RNA viruses other than influenza. The claims did not require that the rescued chimeric virus be infectious nor that it be generated from full-length viral template. Nevertheless, the teachings of the patent were not limited to minigenome systems. There was no evidence to support the opposition division's conclusion that the applicability of the claimed invention to minireplicons did not extend to the rescue of genomes derived from non-segmented RNA viruses of greater length. Nor had any additional factors been mentioned which were needed for the rescue of full-length negative-strand RNA viruses that could not be obtained by or extrapolated from the rescue of minigenomes or minireplicons.

The opposition division had ignored the evidence provided by document D22. This document described the successful rescue of Sendai virus from an RNA template

consisting of the complete 5' and 3' noncoding termini of Sendai virus flanking the coding region of the Sendai viral genome. When the full-length genomic RNA was transfected into host cells engineered to provide viral polymerase proteins, this resulted in the rescue of viral particles. Thus, document D22 demonstrated that the length of the RNA template was not a bar to the recovery of the viral RNA.

In its decision, the opposition division limited the teachings of the patent to the disclosure in the scientific publication of the inventors (document D4). However, whereas document D4 described only one approach corresponding to the example in section 7 of the patent, i.e. mixing the viral RNA with polymerase proteins to form RNPs which were used to transfect host cells, the patent provided other methods, for instance, transfecting viral RNA into host cells engineered to provide the viral polymerase proteins. The working examples provided in the patent demonstrated that both approaches were successful. The skilled person would understand from the patent that the RNP approach was applicable to influenza, whereas non-segmented RNA viruses could be obtained using "naked" RNA templates to transfect host cells. Even if the exact components of the polymerase complex required for intracellular encapsidation had not yet been identified, the patent disclosed in the passage on page 18, line 47 to page 19, line 13 that rescue of the chimeric viruses could be accomplished by infecting host cells with temperature sensitive mutants, or viruses with altered growth characteristics or plaque morphology.

Knowledge of the "rule of six" was not obligatory in order to properly handle the expression of non-segmented negative-strand RNA templates, as the rule of six was only arguably applicable to the efficient replication of the genomes of the measles and Sendai viruses, but not to RSV, VSV or rabies virus. Furthermore, the opposition division ignored the evidence on record demonstrating that the RNA genomes of measles and Sendai virus have inherent mechanisms in place to correct any aberrant genomes that are not multiples of six (D45, D46). The opposition division incorrectly relied on document D12, ignoring the authors' own recognition of the insensitivity of the assay system.

Document D42 was also cited in the impugned decision. However, the results reported in D42 merely confirmed the teaching of the patent that "wild type" non-coding termini should be used to achieve optimal replication efficiency (page 14, lines 7 to 8 of the patent), that the addition of extra polylinker sequences to the 3' non-coding terminus results in inefficient replication of the transcript (page 14, lines 8 to 10 of the patent), and that the deletion of a single nucleotide in the 5' nontranslated region resulted in the inability to achieve rescue (page 19, lines 1 to 4 of the patent). Thus, the patent taught that the entire and complete 5' and 3' termini, without the addition or deletion of sequences, should be used to flank a heterologous sequence. Furthermore, the entire transcript should be the same length as the viral genomic template. Thus, one skilled in the art following the teachings of the patent would not incur any problems with respect to the rule of six or with

respect to mutations made to the 5' and 3' noncoding termini. Furthermore, if one engineered a viral transcript to additionally encode heterologous sequences, and that transcript was not a multiple of six, then the transcript, if it did not correct itself to be a multiple of six, would be copied less efficiently, but nevertheless copied.

The patent taught that the viral polymerase proteins must be provided at a sufficient concentration to allow for replication and packaging of the viral genome. It also described a number of approaches to provide sufficient concentrations of viral polymerase proteins within a host cell to encapsidate, transcribe and replicate the engineered RNA templates, including:

(1) infecting the host cell with wild-type or helper virus; (2) engineering the host cell to transiently or stably express the viral polymerase proteins; or (3) infecting the host cell with viral vectors which encode the viral polymerase proteins (page 16, lines 21 to 39 and line 55 to page 17, line 10 of the patent).

First auxiliary request - Sufficiency of disclosure - Claims 25 and 40

In document D49, rescue of a chimeric respiratory syncytial virus (RSV) consisting of the heterologous CAT gene and approximately 50% of the wild-type viral genome was shown. According to the authors of D49, the ability to rescue such a chimeric virus suggested that an absolute restriction against the recovery of large RNA viruses did not exist. The "rule of six" would not constitute an obstacle, because, as indicated in document D31 and confirmed by document D46, the rescue

of infectious RSV did not appear to be constrained by a strict requirement of genome length.

Second auxiliary request - Articles 123(2) and 84 EPC

According to the patent, the 3' and 5' non-coding flanking sequences contain the appropriate terminal sequences to enable the viral RNA-synthesizing apparatus to recognize the RNA template. Support for amended claim 1 was found in claim 8 and the statements on page 22, lines 23 to 31 and page 26, lines 19 to 24 of the application as filed.

- XV. The arguments submitted by the respondent were essentially as follows:

Main request - Sufficiency of disclosure - Claims 26 and 45

The principles described in the patent for influenza virus could not be analogously applied to generate non-segmented negative-strand RNA viruses. The transcription processes of influenza and non-segmented viruses were very different. For instance, whereas a promoter was present at the 3' end of each segment of the influenza genome, non-segmented negative-strand RNA viruses had a single promoter at the 3' end and a stop/start mechanism of transcription necessitated by the presence of intergenic regions, these regions having no counterpart in influenza virus.

The *in vitro* RNP approach described in the patent for influenza virus never worked to rescue a full-length non-segmented RNA virus. In the examples of the patent

no naked viral RNA, but only RNPs were used to transfect host cells. The approach of propagating the recombinant virus by co-cultivation with wild-type virus did not allow for the rescue of an autonomously replicating, full-length non-segmented negative-strand RNA virus. Document D19 was not of probative value with regard to full-length rescue because, as explained in D6, the efficiency of rescue declined dramatically as the length of the non-segmented viral minireplicon or minigenome increased (page 4481, left column, first paragraph). Only after the antigenomic approach was described in 1995, could infectious non-segmented negative-strand RNA viruses be recovered. All publications subsequent to D5 used the antigenomic approach for the recovery of infectious non-segmented RNA viruses.

The patent did not teach how to establish suitable cell lines, nor the appropriate stoichiometric ratios for the polymerase proteins of influenza virus, or for the N, P and L proteins (or their counterparts) of non-segmented viruses. The need for "engineered" host cells was mentioned in the patent, but no details were provided as to how the host cells were to be engineered. The patent was also silent on the need for a ribozyme or other heterologous element to generate an authentic 3' terminus.

The rule of six applied to all viruses of the Morbillivirus, Rubulavirus and Respirovirus genera tested to date, and its violation greatly reduced the efficiency of the already inefficient process of rescue, often resulting in no detectable rescue. If an heterologous gene with a length which violated the rule

of six was inserted, then rescue, which had a low efficiency to begin with, would have an even more reduced efficiency, which may result in no detectable recovery at all.

First auxiliary request - Sufficiency of disclosure - Claims 25 and 40

In document D31, RSV was not recovered according to the teachings of the patent, but applying the antigenomic approach.

Second auxiliary request - Article 123(2) EPC

The passages of the application as filed cited by the appellant in connection with the introduced feature "3' and 5' non-coding terminal sequence" merely related to genomic segments of RNA templates of influenza virus, and not to other negative-strand RNA viruses.

- XVI. The appellant requested that the decision under appeal be set aside and that the patent be maintained as originally granted or on the basis of the first or second auxiliary requests filed during the oral proceedings.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

Allowance into the proceedings of documents filed on appeal

1. In their submissions, both parties have relied on additional documents filed for the first time on appeal. The appellant filed seven new documents with the statement of grounds for appeal, fourteen further documents - three of which were declarations - on the last day of the time limit laid down by the board for filing submissions in preparation for the oral proceedings, and three additional documents only two days ahead of the oral proceedings. The respondent, in turn, submitted fourteen new documents with its response to the grounds for appeal, and six additional documents on or well after the final date for submissions fixed by the board. Thus, in addition to the 49 documents filed in opposition proceedings, the board was confronted with 44 further documents filed at various stages of the appeal proceedings.

2. Article 114(2) EPC empowers the boards of appeal to disregard facts or evidence which are not submitted in due time by the parties concerned. According to the jurisprudence of the boards of appeal, an appeal should, in principle, be essentially based on facts and evidence which were available to the department of the first instance. However, additional evidence, especially when filed at the outset of the appeal, is not necessarily to be considered as being "late-filed" (cf. decision T 950/99 of 11 November 2002, point 4 of the reasons). In contrast, unless exceptional circumstances arise, documents submitted by the parties

at a later stage of the proceedings are considered generally as being late-filed.

3. In the present case, the board judges that a distinction should be made between, on the one hand, the documents filed by the parties during the early stages of the appeal proceedings, i.e. either with the statement setting out the grounds for appeal (documents D47 to D53) or with the response thereto (documents D54 to D67), and, on the other hand, documents submitted later in the proceedings (document D68 onwards).

4. In the board's view, the filing of new documents by the appellant with its statement of grounds for appeal was aimed essentially at refuting the reasons given by the opposition division in its decision, and did not introduce into the proceedings new lines of argumentation, but merely reinforced the existing line which had not succeeded before the opposition division (cf. T 113/96 of 19 December 1997). As for the documents submitted by the respondent with its response, they only served to support its counterarguments to the grounds for appeal, no new line of attack being introduced. For these reasons, in the present case the board considers it fair to the parties to admit into the proceedings the documentary evidence submitted at the outset of the appeal (documents D47 to D67).

5. With regard to the documents filed at later stages of the proceedings, the criteria established in the jurisprudence of the Boards of Appeal for late-filed documents (cf. "Case Law of the Boards of Appeal of the European Patent Office", 4th edition 2001, chapter VI.F.3.1) must be applied. No exceptional

circumstances that justify the late-filing of these documents have been advanced by the parties. Having examined the late-filed documents as to their *prima facie* relevance for the outcome of the appeal proceedings, the board considers that, when compared to the documents already on file, the late-filed documents do not add any further elements such as might convince the board to adopt a different position as regards the issues being judged, and ultimately change the outcome of the decision.

6. The appellant has contended that the late-filed documents, in particular documents D68, D70, D71, D72, D77, D79 and D80 address issues raised by the board in its communication under Rule 11(1) of the Rules of Procedure. The board is, however, not aware of any new issues raised for the first time in this communication with regard to claims directed to chimeric negative-strand RNA viruses, the sole issue mentioned in the board's communication that had not been discussed in detail in the impugned decision being the extent of the burden put on a skilled person when trying to prepare recombinant RNA molecules derived from the genome of non-segmented negative-strand RNA viruses.

7. However, none of the documents cited by the appellant specifically addresses this issue. Rather, amongst the documents cited above (cf. point 6) some concern issues, such as the extent of the "rule of six" requirement (documents D68 and D79) or the use of minigenomes (documents D77 and D80), which had been discussed in the decision of the opposition division and for which documentary evidence was already on file (see, for instance, documents D45, D46, D19 and D27 referred to

in the impugned decision). Documents D71 and D72 address an issue not even mentioned in the communication, namely the generation of precise 3' ends. The declarations D68 and D70, the allowance of which into the appeal proceedings was opposed by the respondent, either represent the author's views on the disclosure content of the patent in suit (D68), or provide general comments on methods and results disclosed in document D22 (D70). In the board's view, these declarations do not contain, *prima facie*, any relevant information that goes beyond the evidence already on file.

8. Although the boards of appeal, and in particular this board, have occasionally admitted into the proceedings documents filed on appeal, even if of lesser evidential weight in relation to other documents already in the case (cf. decision T 950/99, *supra*), in the present case the sheer number of new documents, the late procedural stage at which they were filed, and the scarcity of reasons - if any - put forward by the parties to justify the late filing, amount to a behaviour that verges on procedural abuse. For these reasons, the board, availing itself of the discretionary power conferred by Article 114(2) EPC, decides to disregard the late-filed evidence, i.e. all documents filed by either the appellant or the respondent after the appointment of oral proceedings, i.e. document D68 onwards.

Main request (claims as granted)

Claims 26 and 45 - Sufficiency of disclosure

9. Claims 26 and 45 as granted are directed to a chimeric negative-strand RNA virus containing a heterologous RNA sequence operatively linked/attached to a polymerase binding site of the/a negative-strand RNA virus.
10. In the decision under appeal, the opposition division found that claims 26 and 45 were not allowable under Article 83 EPC because the patent in suit did not disclose the methodology for manipulation of all negative-strand RNA virus in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (cf. point 2.3.3 of the decision).
11. It is undisputed that the teachings of the patent enable the skilled person to prepare chimeric viruses derived from influenza virus, the description and examples of the patent providing ample technical information in this respect. As the opponent withdrew its opposition in so far as it concerned claims specifically relating to influenza virus, the patent was maintained by the opposition division on the basis of a set of claims restricted to this subject-matter (cf. point 4 of the decision under appeal).
12. In view of the decision of the opposition division and the submissions of the parties (cf. Sections XIV and XV, *supra*), the issue subject to dispute on appeal with regard to claims 26 and 45 is whether or not the patent in suit provides the skilled person with adequate and sufficient technical information that enables him/her

to carry out the invention over the **whole scope** of these claims (cf. Case Law of the Boards of Appeal of the EPO, 4th edition 2001, chapter II.A, and in particular decisions T 409/91, OJ EPO 1994, 653; T 435/91, OJ EPO 1995, 188; and T 716/01 of 10 November 2004).

13. As no specific definition is given in the patent in suit for the terms "*chimeric virus comprising a negative-strand RNA virus*" in claim 26 and "*chimeric, negative-strand RNA virus*" in claim 45, with a view to identifying the subject-matter encompassed by the claims under consideration, these terms have to be construed broadly. Thus, even though claims 26 and 45 do not specify that the claimed chimeric viruses must be infectious, the claimed subject-matter is not limited to chimeric viruses containing viral minigenomes, i.e. subgenomic viral RNA molecules that can replicate only in a host cell infected with the corresponding wild-type virus. Rather, the claims encompass also chimeric infectious (i.e. non-defective) viruses which, having been genetically modified to insert a heterologous gene into their genome, still contain genetic information for all viral functions necessary for replication and packaging in a host cell in the absence of a helper virus.
14. Thus, the specific question at issue is whether the skilled person could obtain chimeric **infectious** negative-strand RNA viruses other than influenza virus, in particular chimeric viruses derived from **non-segmented** negative-strand RNA viruses, applying the teachings of the patent supplemented with the common

- general knowledge of the person skilled in the art at the priority date.
15. Whether or not the patent in suit discloses how to obtain such viruses in a manner sufficiently clear and complete within the meaning of Articles 100(b) and 83 EPC must be decided by appraising the information contained in the examples as well as other parts of the description in the light of the common general knowledge of the skilled person at the priority date (cf. T 322/93 of 2 April 1997). All examples in the patent relate exclusively to the preparation of chimeric influenza virus. It is however stated in the general description of the invention that the principles disclosed in the patent are analogously applicable to the construction of further negative-strand RNA chimeric viruses including, amongst others, paramyxoviruses such as parainfluenza virus, measles virus and respiratory syncytial virus (cf. page 12, lines 50 to 55).
16. In the decision under appeal, the opposition division argued that the method disclosed in the patent for the recovery of chimeric influenza virus (i.e. transfection of host cells with a recombinant viral RNP) could not be applied to the rescue of non-segmented negative-strand RNA viruses, in particular paramyxoviruses, these viruses having much larger genomes than the genomic segments of influenza virus. This finding has not been contested by the appellant.
17. Pointing to the statements on, *inter alia*, page 7, lines 46-54 of the patent in suit, the appellant has nevertheless contended that the teachings of the patent

are not limited to the *in vitro* encapsidation of recombinant viral RNA to generate recombinant viral RNPs which are then used to transfect host cells, a method that allows the recovery of chimeric influenza virus. Rather, the patent would also disclose the recovery of other chimeric negative-strand RNA viruses by transfecting host cells with "naked" recombinant viral RNA and providing for encapsidation *in vivo*. In the appellant's view, the skilled person reading the patent would understand that viral RNPs should be used for the rescue of influenza virus, whereas "naked" RNA is suitable for the rescue of negative-strand RNA viruses other than influenza virus, for instance of paramyxoviruses.

18. The board cannot agree with this view. It is true that the use of "naked" (i.e. non-encapsidated) recombinant viral RNA to transfect host cells is mentioned in various passages of the patent in suit. In the section "Summary of the invention" (cf. page 7, lines 46 to 52 of the patent), it is stated that:

*"As demonstrated by the examples described herein, recombinant negative-sense influenza RNA templates may be mixed with purified viral polymerase and nucleoprotein (i.e., the purified viral polymerase complex) to form infectious RNPs. These can be used to express heterologous gene products in host cells or to rescue the heterologous gene in virus particles by cotransfection of host cells with recombinant RNPs and virus. Alternatively, **the recombinant RNA templates** or recombinant RNPs may be used to transfect transformed cell lines that*

express the RNA dependent RNA-polymerase and allow for complementation." (emphasis added by the board)

The second sentence of this passage is also found almost verbatim in the section "Description of the invention" on page 12, lines 4 to 5 of the patent.

19. However, all technical details given in the passages of the patent preceding or following the passage quoted above concern the recovery of chimeric **influenza** virus by transfection of host cells with recombinant **RNPs** (cf. page 7, lines 52 to 57; and page 12, lines 6 to 28), no technical information whatsoever being provided for the recovery of chimeric non-segmented negative-strand RNA viruses (e.g. paramyxoviruses) by transfection of host cells with "naked" viral RNA.
20. The appellant has pointed also to following statements in section 5.2 of the patent:

*"In an alternate embodiment of the invention, **the recombinant templates** or the rRNPs may be used to transfect cell lines that express the viral polymerase proteins in order to achieve expression of the heterologous gene product."* (cf. page 16, lines 34 to 39; emphasis added by the board)

As the title of the section ("Expression of heterologous gene products using recombinant RNA template") indicates, the quoted passage concerns exclusively the expression of an heterologous gene product from a recombinant (naked or encapsidated) RNA template, and cannot possibly be considered as a sufficient disclosure of a method leading necessarily

and directly towards the rescue of chimeric infectious viruses.

21. Transfection of host cells with naked recombinant viral RNA is also mentioned in section 5.3 of the patent ("Preparation of chimeric negative-strand RNA virus"). The specific passage cited by the opposition division in the decision under appeal (cf. point 2.3.3.1) reads:

"..., neither transfected naked recombinant RNA alone in the presence of infecting helper virus, nor recombinant RNP complex in the absence of infecting helper virus is successful in inducing CAT activity. This suggests that influenza viral proteins provided by the incoming RNP, as well as by the infecting helper virus, are necessary for the amplification of the recombinant RNA template." (cf. page 18, lines 33 to 37)

22. It is apparent from this passage that transfection of host cells with naked recombinant RNA in the presence of infecting helper virus did not lead to expression of the genetic information contained in the recombinant RNA template and replication of the template. Even if it is true that the quoted passage concerns only influenza virus, the board cannot accept the appellant's argument that the skilled person, seeking to obtain chimeric negative-strand RNA viruses other than influenza virus, would infer from said passage that transfection of host cells with "naked" viral RNA constitutes the method of choice for the successful recovery of such viruses. Since the patent contains no explicit indication as to which of the two suggested approaches (RNP or "naked" RNA) is suitable for the

- recovery of chimeric non-segmented negative-strand RNA viruses, the skilled person is confronted - already at this early stage - with an uncertainty with regard to the material to be used for transfection of host cells, a considerable amount of experimentation being then required to establish that, contrary to the assertion in the patent that the principles disclosed for influenza virus are analogously applicable to the recovery of other negative-strand RNA viruses, transfection of host cells with an RNP containing recombinant viral RNA derived from the genome of a non-segmented virus does not allow its rescue.
23. The respondent argued that the patent did not provide sufficient guidance for the skilled person to attain recovery of infectious non-segmented negative-strand RNA viruses from "naked" viral RNA, technical measures which are essential for the recovery of such viruses, *inter alia*, the provision in the cell of the set of viral proteins required for *in vivo* encapsidation upon transfection of the naked recombinant RNA, and the ratio of expression of these proteins, not being disclosed in the patent.
24. It is apparent from the documentary evidence submitted by the appellant in the opposition proceedings that, as far as non-segmented negative-strand RNA viruses are concerned, the naked form of the viral RNA **alone** cannot be a template for replication and transcription (cf. document D22, page 2, first full paragraph). To become an active template, the RNA must be tightly packed with nucleocapsid proteins and the viral RNA polymerase protein(s), and assembled into the nucleocapsid (ribonucleoprotein complex). Thus, in

order for *in vivo* encapsidation, replication and expression of the viral RNA to be accomplished, a minimum subset of viral proteins must be provided in the cell to be transfected with the naked viral RNA. For influenza virus, the patent in suit discloses that the three polymerase proteins (PB2, PB1 and PA) and the nucleoprotein (NP) are required (cf. page 7, lines 54 to 56). For non-segmented negative-strand RNA viruses, however, no information on the required proteins is provided in the patent. Whether or not and to what extent knowledge about the specific proteins required for *in vivo* encapsidation, replication and expression of non-segmented negative-strand viral RNA formed part of the common general knowledge of the skilled person at the priority date of the patent is not apparent from the evidence on file.

25. At oral proceedings, the appellant pointed to the passages on page 12, lines 6 to 29, and page 16, lines 31 to 33 of the patent, allegedly indicating that sufficient levels of polymerase proteins must be provided for *in vivo* encapsidation. The first passage cited describes an experiment in which recombinant RNA derived from **influenza** virus is mixed ***in vitro*** with isolated influenza A virus polymerase proteins, and the reconstituted RNP is then used to transfect host cells infected with influenza virus. In the latter passage, transformed cell lines that express all three **influenza** virus polymerase proteins (PB2, PB1, PA) and possibly other viral functions or additional functions such as NP, are suggested as appropriate host cells. These passages relating exclusively to influenza virus, they cannot be considered as an adequate and sufficient disclosure of the minimum subset of viral proteins

- necessary for *in vivo* encapsidation of a viral RNA derived from a **non-segmented** negative-strand RNA virus.
26. It is also apparent from the evidence on file that, at least for certain non-segmented negative-strand RNA viruses, the viral polymerase protein(s) and the nucleocapsid proteins must be supplied *in vivo* at an optimal ratio to support the full replication and transcription of the viral RNA (cf. document D22, page 2, second full paragraph, first sentence), and that virus recovery is strongly affected by a change in the relative amounts of these proteins. Yet, the patent in suit does not provide any information whatsoever on the viral protein ratio required for the recovery of a non-segmented negative-strand RNA virus.
27. In this respect, the appellant has pointed to the statements in section 5.2.2. of the patent, and documents D22 and D66. However, it is noted that section 5.2.2 ("High concentrations of polymerase are required for Cap-primed RNA synthesis") relates solely to *in vitro* encapsidation and that, as the reference to section 6 confirms, its teachings are restricted to **influenza** virus RNA. The content of documents D22 and D66, published in 1996 and 1990, respectively, cannot remedy the deficiencies in the disclosure of the patent in suit. Not being available to the skilled reader at the priority date, these documents do not, in principle, form part of the common general knowledge in the field of negative-strand RNA viruses, and cannot contribute to the sufficiency of the disclosure.
28. The appellant has cited documents D19, D20, D22, D42, D48 and D49, all published after the priority date of

- the patent, as evidence for the successful application of the "naked RNA" approach to the recovery of chimeric non-segmented negative-strand RNA viruses.
29. In documents D19, D20, D42 and D48, rescue of synthetic "minigenomes" (also referred to as "minireplicons") consisting of the CAT (chloramphenicol acetyl transferase) gene flanked by 5' and 3' non-coding sequences derived from the genome of Sendai virus (D19), respiratory syncytial virus (D20 and D48) or measles virus (D42) is reported. The minigenomes, which are fairly small in size (less than 1 kb) and do not contain any coding sequences from the viral genome, can replicate only in host cells infected with the corresponding wild-type virus, which provides for the viral proteins necessary for replication and packaging of the recombinant minigenome in the host cell. Thus, contrary to the appellant's view, the board does not consider documents D19, D20 and D42 as conclusive evidence for a successful rescue of chimeric **infectious** non-segmented negative-strand RNA **viruses** using naked recombinant RNA.
30. Document D22 discloses the recovery of infectious Sendai virus by transfecting host cells with the complete viral genome in its "naked" form. To support replication and transcription, the viral L, P and NP proteins must be supplied in the host cells at a certain stoichiometric ratio which may be determined by using a synthetic minigenome analogue containing the luciferase gene as reporter gene. Recovery of **chimeric** infectious Sendai virus is however not reported in this document.

31. Document D49 describes the rescue of a synthetic (recombinant) analogue of the genomic negative-strand RNA of respiratory syncytial virus (RSV). This synthetic analogue, which is 7502 nucleotides in length, i.e. nearly half of the complete RSV genome, includes part of the viral genome and the heterologous CAT gene under the control of RSV gene-start and gene-end signals (cf. abstract). Upon transfection of RSV-infected host cells with the defective analogue, CAT expression is observed, though the efficiency of the recombinant RNA analogue in expressing CAT is said to be much lower than that of the minigenome described in document D20.

32. The appellant has admitted that transfection of host cells with the recombinant viral analogue described in document D49 does not lead to the rescue of infectious (non-defective) chimeric virus. However, in its view the suggestion that an absolute restriction against the encapsidation of large preformed RNAs analogous to viral RNA does not exist (cf. D49, page 256, last sentence of the left column), allows the skilled person to draw the conclusion that chimeric viruses containing the full-length viral genome could be obtained upon transfection of host cells with "naked" recombinant RNA.

33. In view of the results reported in document D49, the board believes that this conclusion cannot be drawn. Compared to the 8-fold smaller minigenome described in document D20, the synthetic recombinant analogue disclosed in D49 is 119- to 347-fold less efficient in expressing CAT upon transfection (cf. last sentence of the abstract in D49). According to the authors of the article, the difference in the CAT expression can be

explained by a lower efficiency of the chimeric analogue in the initial process of entering the replicative cycle, which might be due to its eight-fold larger size. As possible causes for the drastic reduction in the replication efficiency, various factors associated with the size of the viral RNA, such as a reduced efficiency of transfection, an increased sensitivity of the RNA to degradation, or a reduced efficiency of encapsidation of the "naked" RNA, have been suggested (cf. page 254, right column, second full paragraph).

34. If one extrapolates the low efficiency of replication for the construct described in document D49 to the much longer genome of paramyxoviruses, the suggestion made by the authors of D49 appears to be rather speculative. Therefore, the board cannot accept document D49 as conclusive evidence that recovery of chimeric infectious paramyxoviruses containing the **full-length** genome can be achieved with "naked" RNA.
35. For the reasons stated above, none of the documents cited by the appellant provides convincing evidence for the successful recovery of chimeric infectious non-segmented negative-strand RNA viruses containing the genetic information for all viral functions necessary for replication of the virus in the absence of a wild-type helper virus.
36. The board thus concludes that, in the absence of technical details and experimental evidence in the patent, the skilled person could not obtain chimeric non-segmented negative-strand RNA viruses without an undue burden of experimentation and, possibly,

application of inventive skills. The subject-matter of claims 26 and 45 not being sufficiently disclosed over the whole range claimed, maintenance of the patent on the basis of the main request, of which claims 26 and 45 are part, is not justified.

First auxiliary request - Claims 25 and 40 - Sufficiency of disclosure

37. The subject-matter of claims 25 and 40 of the first auxiliary request (cf. Section XI above) filed during the oral proceedings before the board, which correspond to claims 26 and 45 as granted, has been limited to chimeric viruses derived from influenza virus or respiratory syncytial virus. Whereas chimeric influenza virus can be recovered using the methods disclosed in the patent, the board is of the view that, for the reasons given in connection with the main request (cf. points 30 and 32 to 34 above), the patent does not provide the skilled person with sufficient and adequate guidance for recovering chimeric infectious (i.e. non-defective) RSV. Consequently, the subject-matter of claims 25 and 40 does not fulfil the requirements of Article 83 EPC.

Second auxiliary request

38. Whether or not additional claim requests filed at a very late stage of the appeal, e.g. during the oral proceedings, are admitted into the proceedings is a matter of discretion of the concerned board, the decision being taken in each case in the light of the particular circumstances. The boards of appeal of the EPO have developed a substantial body of case law

concerning the criteria for taking late-filed claim requests into consideration (cf. "Case Law of the Boards of Appeal of the European Patent Office", 4th edition 2001, chapter VII.D.14.2). The time of filing, the reason why the request has been filed late and its *prima facie* allowability are relevant criteria. If compliance of the request with the requirements of Articles 123 and 84 EPC can be quickly checked, and the amendments introduced to the claims are necessary and appropriate to meet a ground for opposition, "the chances of such a request being accepted even at a very late stage are much improved" (cf. decision T 794/94 of 17 September 1998, point 2.2.1 of the Reasons).

39. The second auxiliary request (cf. Section XII above) was filed at a late stage of the oral proceedings before the board, allegedly in order to overcome objections raised by the board under Articles 123(2) and 84 EPC to previous auxiliary requests which were later withdrawn or replaced by new requests.

40. Preliminary examination of the amended claims revealed deficiencies under Article 123 and 84 EPC arising from the introduced amendments. In particular, the amendment to claims 1 and 38 by replacing the feature "*...comprising a binding site specific for an RNA-directed RNA polymerase of a negative strand RNA virus, ...*" by the feature "*... comprising a 3' non-coding flanking sequence containing a binding site specific for an RNA-directed RNA polymerase of the negative strand RNA virus, ...*" offends against Article 84 EPC, as it introduces an ambiguity which was not present in the claims as granted.

41. Whereas in claims 1 and 38 as granted it is clear that the heterologous RNA sequence and the binding site specific for an RNA-directed RNA polymerase are operatively linked, the language of the amended claims leaves open whether the heterologous RNA sequence is operatively linked to the 3' non-coding flanking sequence or the binding site for the RNA polymerase, these two sequences not being necessarily identical. This lack of clarity may be relevant also for the assessment as to whether the requirements of Article 123(2) and (3) are fulfilled.
42. Also amended claims 40 to 43, which derive from claims 46 to 49 as granted and read "*The chimeric influenza comprising virus...*", are considered to be unclear within the meaning of Article 84 EPC, because the use of the term "*comprising*" in this context does not allow a clear definition of the matter for which protection is sought.
43. As for claims 25 and 39 (derived from claims 26 and 45 as granted), amendments similar to those of claims 1 and 38 have been introduced. These claims having been restricted to chimeric **influenza** viruses, it is not apparent to the board which ground for opposition is intended to be met by the introduction of the amendment (cf. Rule 57a EPC), particularly having in mind that the opposition has been withdrawn in so far as it concerned subject-matter relating to influenza virus.
44. It can be inferred from the remarks above that, having regard to the provisions of Articles 123 and 84 and Rule 57a EPC, the amended claims of the second auxiliary request are *prima facie* not clearly allowable.

Consequently, the board decided to not admit the claim request into the proceedings.

Allowance of further auxiliary requests into the proceedings

45. Article 111(1) EPC empowers the boards of appeal to disregard claim requests which are late-filed. Exercising this discretionary power, this board, having regard to the exceptional problems sometimes involved in patents in the field of genetic engineering that can make formulation of a suitable request difficult (cf. decision T 794/94, *supra*), has been often prepared to allow new claim requests filed during oral proceedings.
46. In the present case, the granted claims included numerous independent claims directed to different subject-matter, as well as claims related to similar subject-matter differing solely in the terminology used. During the appeal proceedings, various attempts were made by the appellant to bring its claim requests in conformity with the requirements of the EPC. At oral proceedings, the appellant was several times given the opportunity of filing new claim requests which were then considered by the board, a provisional opinion as to their allowability being expressed in each case (cf. Section X above). After having refused to allow the second auxiliary request into the proceedings for the reasons indicated in points 39 to 43 above, the board then announced that it would not accept any further auxiliary requests that the appellant might have intended to file subsequently.

47. The proprietor of the patent cannot rely on the board's discretion being exercised in its favour. As stated by Board 3.3.4 in decision T 794/94 (*supra*): *"The boards take a conservative view on what amendments are appropriate, in order to avoid an unnecessary multiplication of the issues in dispute and lengthening of the procedure. While the proprietor might wish to completely reformulate the claims in order to bring out what is considered to be the invention, such free formulation is only possible when drafting the application text originally, with a more limited opportunity during examination. It is not appropriate in appeal proceedings in inter partes proceedings. Clarity is not a ground for opposition, so it cannot by itself be a ground for changes by the proprietor. The general legal presumption is that a change in terminology implies a change in meaning. In inter partes proceedings if the terminology is changed this should be to avoid a ground of opposition. If no different meaning is intended, the wording of the granted claims should be changed as little as possible to avoid new issues being raised unnecessarily."*
48. In the absence of an allowable claim request, the appellant's request that the decision under appeal be set aside cannot be granted.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

A. Wolinski

L. Galligani