Case Number: T 0506/02 - 3.3.8
Application Number: 95112559.0
Publication Number: 0780475
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Language of the proceedings: EN

Title of invention:
cDNA corresponding to the genome of negative-strand RNA viruses, and process for the production of infectious negative-strand RNA viruses

Patentee:
SCHWEIZ. SERUM- & IMPFINSTITUT BERN

Opponent:
Akzo Nobel N.V.
Conzelmann, Karl-Klaus Prof. Dr.

Headword:
Measles virus/IMPFINSTITUT

Relevant legal provisions:
EPC Art. 54, 56, 123(2)
EPC R. 88

Keyword:
"Main request - novelty (no)"
"First auxiliary request - in breach of Article 123(2) (yes)"
"Second auxiliary request - inventive step (yes), sufficiency (yes)"
"Correction according to Rule 88 EPC (yes)"

Decisions cited:
G 0001/03, G 0002/03

Catchword:
Case Number: T 0506/02 - 3.3.8

DECISION
of the Technical Board of Appeal 3.3.8
of 18 January 2005

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Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted
on 15 March 2002 concerning maintenance of
European patent No. 0780475 in amended form.

Composition of the Board:
Chairman: F. L. B. Davison-Brunel
Members: M. R. Vega Laso
S. C. Perryman
Summary of Facts and Submissions

I. European patent No. 0 780 475 (European application No. 95 112 559.0) with the title "cDNA corresponding to the genome of negative-strand RNA viruses, and process for the production of infectious negative-strand RNA viruses" was granted with 25 claims for all Designated Contracting States.

II. Two oppositions were filed relying on the grounds of Article 100(a) and (b) EPC, in particular lack of novelty (Article 54 EPC), lack of inventive step (Article 56 EPC) and lack of sufficient disclosure (Article 83 EPC). In an interlocutory decision posted on 15 March 2002, the opposition division found that the subject-matter of claim 1 of the main request (claims filed as first auxiliary request on 20 September 2001) lacked novelty over document D8: EP 0 702 085 A1.

As for the first auxiliary request filed during the oral proceedings held on 20 November 2001, the opposition division decided that the disclaimer introduced into claim 1 in order to delimit the claimed subject-matter against the disclosure of document D8, offended against Article 123(2) EPC. The amended claims 1 to 22 of the second auxiliary request as filed in the oral proceedings were however considered to fulfil the requirements of Articles 83 and 56 EPC. The patent was maintained on the basis of the second auxiliary request and a description amended accordingly.
III. Claim 1 of the main request read as follows:

"1. A method for the production of an infectious non-segmented negative-strand RNA virus of the family Paramyxoviridae comprising

(a) introducing a cDNA molecule comprising the entire (+)-strand sequence of said negative-strand RNA virus operatively linked to an expression control sequence, which allows the synthesis of antigenomic RNA transcripts bearing the authentic 3'-termini, into a helper cell expressing an RNA-polymerase, preferable T7 RNA-polymerase, an N and a P protein, preferably of the virus to be rescued, and, further, an L protein, preferably of the virus to be rescued, encoded by a cDNA comprised by a plasmid either transiently or stably introduced into said cell; and

(b) recovering the assembled infectious non-segmented negative-strand RNA virus.

Dependent claims 2 to 22 related to various embodiments of the method of claim 1. Independent claims 23 and 24 were directed to an infectious non-segmented negative-strand RNA virus of the family Paramyxoviridae, and a vaccine comprising the virus, respectively.

IV. Claim 1 of the first auxiliary request was identical to that of the main request, except that it included the negative feature "wherein said polymerase is not expressed from a recombinant vaccinia virus" referring to the RNA polymerase produced in the helper cell.
V. Claim 1 of the second auxiliary request differed from that of the main request in the limitation "...a helper cell expressing an RNA-polymerase, preferable T7 RNA-polymerase, an N and a P protein, preferably of the virus to be rescued, wherein said proteins are expressed from stably transfected expression plasmids and, further, ..." (introduced limitation emphasized by the board).

VI. Dependent claims 2 to 22 of the first and second auxiliary requests were identical to the corresponding claims of the main request. Independent claims 23 and 24 of the main request were deleted.

VII. The patent proprietor (appellant I) and opponent 02 (appellant II) each lodged an appeal against the interlocutory decision of the opposition division. With its statement setting out the grounds of appeal, appellant I filed three sets of claims which were identical to the main request and the first and second auxiliary requests considered by the opposition division, except that in claim 20 of all requests the phrase "the plasmid as defined in any one of claims 4 to 20" was replaced by "the plasmid as defined in any one of claims 4 to 19". Both parties requested oral proceedings according to Article 116 EPC.

VIII. Opponent 01, which was party to the appeal proceedings as of right, did not file any observations.

IX. 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 sent with the summons, the board expressed its provisional opinion on...
substantial matters in connection with Articles 123(2), 84, 54 and 56 EPC.

X. The following documents are mentioned in the present decision:

D1: Schnell, M.J. et al., The EMBO Journal, Vol. 13, No. 18, September 1994, pages 4195 to 4203;


D8: EP 0 702 085 A1;


XI. Appellant I's arguments, as far as they are relevant to the present decision, can be summarized as follows:

Main request, claim 1 - novelty

It was clear and unambiguous from the wording of claim 1 that the T7 polymerase is expressed from a plasmid (whether stably or transiently), but not from a vaccinia virus. Therefore, for this reason alone, it must be concluded that the claim was novel over document D8. In any case, the examples of document D8 related exclusively to rabies virus, a member of the family Rhabdoviridae, and a method for obtaining a virus of the family Paramyxoviridae was not unambiguously and directly derivable from document D8. Furthermore, the teaching of document D8 did not provide sufficient information for the skilled person to be able to obtain an infectious paramyxovirus in a straightforward manner. For this reason, document D8 did not affect the novelty of claim 1.
**First auxiliary request, claim 1 - allowability of disclaimer**

Although the disclaimer in claim 1 of the first auxiliary request was not literally disclosed in the application as filed, in the bridging paragraph on page 12 to 13 of the original application it was described that the use of a vaccinia virus-based expression system was to be avoided because of its drawbacks. The drawbacks of the use of helper viruses and in particular of vaccinia virus were also extensively discussed in the introduction to the state of the art. Taking this into account, it had to be considered unambiguously and directly derivable from the application as filed that the use of vaccinia virus based expression of T7 polymerase should be avoided.

Even if it was considered that the disclaimer had not been disclosed in the application as filed, it was nonetheless allowable under Article 123(2) EPC, as it properly disclaimed subject-matter disclosed in document D8, and also fulfilled the requirements established by the case law of the boards of appeal. Document D8 did not unambiguously and directly disclose means other than vaccinia virus as a source for T7 polymerase expression. Moreover, this document provided no information to the person skilled in the art which would enable him/her to put the invention into practise, in particular as regards to plasmids. For these reasons, the introduction of the disclaimer in claim 1 was allowable under Article 123(2) EPC.
Second auxiliary request - inventive step

Document D1 or D2 could be regarded as the closest prior art. D1 was concerned with the generation of infectious rabies virus, a member of the family of Rhabdoviridae, based on the entire viral genome. The process disclosed in D1 required expression of N, P and L protein of rabies virus from a plasmid, and that of T7 RNA polymerase from a co-transfected helper vaccinia virus. N, P and L proteins were produced under the control of T7 polymerase. Document D2 disclosed the rescue of vesicular stomatitis virus (VSV), another member of the family of Rhabdoviridae, based on an approach similar to the approach taken in D1.

The technical problem underlying the subject-matter claimed in the patent was to provide a method for the production of recombinant viruses of the family Paramyxoviridae, most preferably of measles virus, and a system for the recovery of such viruses with reasonable efficiency. The drawbacks of the methods disclosed in documents D1 and D2 were indicated in column 8, second full paragraph of the patent.

Neither document D1 nor document D2 was concerned with Paramyxoviridae or contained a pointer towards the use of an expression system other than vaccinia virus. There was no suggestion or motivation whatsoever provided by these documents that the teaching could be applied to Paramyxoviridae. The method disclosed in D1 had to be seen in its context as described, ie as a method for rescuing rabies virus. As for document D2, the skilled person would merely consider the teachings of said document for rhabdoviruses, ie VSV, but
certainly not for all negative-strand RNA viruses. Neither D1 or D2 even speculated that the disclosed methods could be used for other negative-strand RNA viruses. The lack of such a statement was particularly important since at the relevant priority date the provision of a generally applicable method for virus rescue was highly desired. If the disclosed methods had been regarded as generally applicable by the authors of D1 and D2, they would have mentioned this in their articles. Consequently, it was not obvious to try to apply the expression system of D1 or D2 to Paramyxoviridae.

There was absolutely no motivation to combine the disclosure content of either D1 or D2 with any of the documents D3 to D6. Both D1 and D2 used the vaccinia virus system for the expression of the T7 polymerase, and the authors did not even consider changing the system when problems with the recovery of infectious rabies virus arose. In view of D2, the skilled person would not expect that the large genomic sequences of the members of the family Paramyxoviridae could be rescued with reasonable efficiency.

The person skilled in the art would not have considered any of documents D3 to D6 because they related to a different technical field. Moreover, in the light of the problems discussed in, eg document D4, even when trying to combine the teaching of any of these documents with that of documents D1 or D2, there would have been no reasonable expectation of success. Consequently, although the person skilled in the art could have exchanged these systems, he/she would not have done so. Inventive step could thus be acknowledged.
Sufficiency of disclosure

In the opposition proceedings not a single piece of evidence had been submitted in order to substantiate the alleged lack of sufficiency of disclosure. Evidence filed in appeal proceedings had to be deemed as late filed and, thus, not admissible.

XII. The arguments submitted by Appellant II, both in writing and at oral proceedings, were as follows:

Main request, claim 1 - novelty

The wording of claim 1 did not specify how the coding sequences for the T7 RNA polymerase and the N and P proteins were introduced into the cells. Thus, the claim covered also methods in which these proteins were introduced by way of a vaccinia virus as in document D8. For this reason, document D8 was novelty destroying.

First auxiliary request, claim 1 - disclaimer

The negative feature included in claim 1 did not fulfil the requirements established in the case law for allowability of a disclaimer under Article 123(2) EPC, as it did not exclude the whole subject-matter of document D8 comprising the expression of T7 RNA polymerase from other sources than the vaccinia virus. In fact, the use of vaccinia virus for expression of the enzyme was merely an example.
Second auxiliary request - inventive step

Both D1 and D2 described the use of the antigenome approach for the generation of a negative-strand virus, in particular rabies virus (RV) and VSV. Moreover, document D1 explicitly stated that the approach may be applicable to other negative-strand viruses. The antigenome approach having already been shown to function in two different viruses, the skilled person would have expected it to be applicable also to measles virus. The small size difference of RV and VSV compared to MV was not significant. There was no indication in document D1 that the length, or the presence of an additional cistron would have an effect on the recovery of virus from cDNA using vaccinia virus. Even if a 34% increase in length would affect recovery, a reduction in the range of approximately one third would easily be sufficient for the recovery of measles virus.

Claim 1 required that stably transfected plasmids were used for the expression of T7 polymerase, N and P proteins. This feature was widely known at the filing date and even suggested in documents D1 and D2. The disclosure of document D1 was not restricted to the vaccinia virus expression and did not specify how the RNA polymerase had to be produced. The use of vaccinia virus was not the only option at the filing date. Problems associated with the use of vaccinia virus were generally known from prior art documents D3, D4, D5, D6 and D10. The skilled person would have used stably transfected plasmids in order to express the necessary genes. Thinking of ways how to avoid the use of vaccinia virus, the possibility to use a helper cell line stably expressing the RNA polymerase and the N and
P proteins would have readily come to the mind of the skilled person taking into account the teachings of document D10.

The opposition division held that documents D3 to D6 would not be considered by the skilled person as they related to a different field. This was not true, as the person skilled in the art interested in using mammalian cells as hosts cells for expression would necessarily consider all documents relating to expression in mammalian cells. The skilled person would then, by combining document D1 or document D2 with any of documents D3 to D6, arrive at the method as claimed. Therefore, the subject-matter of claim 1 did not involve an inventive step.

Sufficiency of disclosure

Document D23 showed that the method according to the patent worked only with the Edmonton strain as used in the examples of the patent. Thus, the requirements of Article 83 EPC were not fulfilled in relation to the subject-matter of claim 1 over the whole scope of the claim.

XIII. Opponent 01, who was a party as of right in the appeal procedure, endorsed the arguments of appellant II.

XIV. Appellant I (patentee) requested that all the claim requests in the proceedings be amended under Rule 88 EPC by amending claim 20 to read "... defined in any of claims 3 to 19 ...", and as main and first auxiliary requests that the decision under appeal be set aside and that the patent be maintained on the
basis of the main request or the first auxiliary request refused by the opposition division, or as second auxiliary request that the appeal of opponent 02 be dismissed.

Appellant II (opponent 02) requested that the decision under appeal be set aside and that the patent be revoked.

The other party (opponent 01) supported the request of appellant II.

Reasons for the Decision

Main request, claim 1 - Novelty

1. Much controversy arose all through the proceedings with regard to the way claim 1 should be construed. Although Article 84 EPC is not a ground of opposition, it is manifest that the meaning of claim 1 must be ascertained, as the decision on novelty will depend upon it. The issue is whether or not the feature "encoded by a cDNA comprised by a plasmid either transiently or stably introduced into said cell" applies to the RNA polymerase, ie whether the cDNA encoding this enzyme is intended to be introduced into the helper cell solely by means of a plasmid.

2. The claim as such requires that the cDNA comprising the entire (+)-strand sequence of the negative-strand RNA virus be introduced "into a helper cell expressing an RNA-polymerase, ... , an N and a P protein, ... , and, further, an L protein, ... , encoded by a cDNA..."
comprised by a plasmid either transiently or stably introduced into said cell". In the board's judgement, this feature is to be broadly interpreted, meaning that the limitation "encoded by ..." applies only to the L protein, whereas location (plasmid, helper virus or insertion into the genome of the helper cell) and expression (transient or stable) of the genetic information encoding the RNA polymerase and proteins N and P are not subjected to any limitation. It is on this understanding of the claimed subject-matter that the assessment of novelty over document D8 has been made.

3. Document D8, which constitutes relevant prior art under Article 54(3) and (4) EPC, discloses a two-step method for the preparation of an infectious replicating non-segmented negative-strand RNA virus. In the first step, a DNA molecule comprising the cDNA of the non-segmented negative-strand RNA virus, and one or more DNA molecules encoding the virus N, P and L proteins are introduced into a host cell expressing a RNA polymerase, and in the second step, the viruses produced by the cells are isolated (cf. column 11, line 13 and claim 13 of D8). In column 12, lines 26, 27, it is mentioned that in the host cell the T7 RNA polymerase "is expressed for example cytoplasmatically from vaccinia virus recombinant". The method is also said to be applicable to the obtention of any infectious non-segmented negative-strand RNA virus, in particular viruses of the family Paramyxoviridae or Rhabdoviridae (cf. claims 17 and 18). In a preferred embodiment, the cDNA derived from the genome of rabies virus is contained in a plasmid including appropriate transcription initiator and terminator sequences.
recognizable by the polymerase co-expressed by the transfected cells (cf. column 12, lines 17-22).

4. The teachings of document D8 are exemplified using the pSAD L16 plasmid which contains cloned cDNA spanning the entire genome of rabies virus strain SAD B19, including the genomic 3' and 5' ends (cf. column 13, lines 25-30), and flanked by the T7 RNA polymerase promoter on the one side (cf. column 13, lines 39-41) and the hepatitis delta virus (HDV) antigenome ribozyme sequence on the other side, this sequence being followed immediately by a T7 transcription terminator sequence (cf. column 13, lines 48-51 and legend to Figure 2 on column 22, lines 3-25). Host cells infected with a recombinant vaccinia virus (vTF7-3) expressing T7 RNA polymerase are co-transfected with pSAD L16 and three further plasmids (pT7-T-N, pT7-T-P and pT7-T-L) which contain sequences encoding rabies virus proteins N, P and L under the control of the T7 promoter. After cultivation, infectious rabies virus is recovered (cf. column 14, line 53 to column 15, line 15).

5. Because of this example the board is unable to accept the further argument presented by appellant I that document D8 does not teach the requirement of antigenomic paramyxovirus RNA transcripts bearing the authentic 3'-termini as specified in claim 1. Indeed, a person skilled in the art, being conservative and cautious, would not depart from the detailed instructions given in this example. In particular, when attempting to obtain paramyxoviruses he/she would take care that the construct would carry a precise and authentic 3' end.
Thus, the method disclosed in document D8 falls within the scope of claim 1, ie is detrimental to novelty.

The examples of document D8 relate exclusively to rabies virus. Yet, it is clear from the description as a whole and from the claims that document D8 also relates to a method for obtaining a virus of the family Paramyxoviridae. The description of document D8 begins with the following statement: "The present invention is concerned with a genetically manipulated infectious replicating non-segmented negative-stranded RNA virus mutant and a process for the preparation of such mutant" (cf. column 1, lines 3-6). In the next paragraph, several species belonging to the family of Rhabdoviridae are listed, rabies virus being cited as an example of a virus of this family. The description then goes on to introduce other families of non-segmented negative-strand RNA viruses, emphasizing their similarity with regard to genome organization: "Beside the family of Rhabdoviridae also viruses belonging to the Paramyxoviridae (e.g. ...) and Filoviridae, and several viruses not assigned to a family (e.g. ...) have a non-segmented negative-stranded RNA genome. The overall genomic organisation in the non-segmented negative-stranded RNA viruses of the various families is comparable. Especially between the paramyxoviridae and the rhabdoviridae, there are only minor differences in the overall genomic organisation..." (cf. column 1, lines 14-27). Thus, it is apparent already from the introductory remarks of document D8 that a method for the production of non-segmented negative-strand RNA viruses in general, ie not restricted to rabies virus was envisaged. Moreover, later in the description it is stated: "More
specifically the invention provides non-segmented negative-stranded RNA viruses of the paramyxo- and rhabdovirus family" (cf. column 5, lines 9-11; emphasis added by the board). Finally, as already mentioned in point 3 supra, claim 17 of document D8 is specifically directed to a method in which the non-segmented negative-strand RNA virus genome is obtained from the family of Paramyxoviridae.

8. On this account, the board is convinced that the skilled person in the technical field of genetics of non-segmented negative-strand RNA viruses will clearly understand from the passages cited above that the method disclosed in document D8 is applicable to the obtention not only of infectious rabies virus, but also of other non-segmented negative-strand RNA viruses, in particular viruses of the family Paramyxoviridae.

8.1 Three declarations were also presented to the effect that the disclosure of document D8 was not enabling with regard to obtaining paramyxoviruses. However, these declarations contain no conclusive evidence that allows the board to conclude that an infectious non-segmented negative-strand RNA virus of the family Paramyxoviridae could not be obtained using a method as disclosed in document D8.

9. In a Memorandum (D29) by Prof. Billeter, one of the inventors designated in the patent in suit, the opinion is expressed that the method disclosed in document D8 would only be suitable for the rescue of robust viruses which grow to high titers and are not appreciably impaired in their replication by vaccinia helper virus. In order to obtain pure rescued virus using the method
of D8, further measures would have to be taken, for instance, physical separation of the helper vaccinia virus by filtration or partial inhibition of the replication of this virus by Ara C. Prof. Billeter states that, because of vaccinia virus-mediated recombination, it proved to be extremely difficult, and in some cases impossible, to rescue viruses containing debilitating mutations in the N, P and L genes of the antigenomic plasmid. Furthermore, the method of D8 allowed the detection of rescued virus only after amplification by several replication cycles.

10. The board cannot accept Prof. Billeter's arguments as conclusive. It should be noted that step (b) in claim 1 of the patent in suit does not specify any level of titre or degree of purity of the virus to be obtained, but requires only recovery of the virus. Thus, whether additional steps are necessary or not in order to **purify** a recovered virus is irrelevant for the assessment of sufficiency, the decisive issue being that the disclosure of document D8 allows the **recovery** of the desired virus. The fact that amplification might be necessary prior to the detection of the **rescued** virus is also of no relevance; nevertheless, passaging of the recovered virus to increase the titre is described on column 15, lines 16-27 of document D8.

11. As for the alleged difficulties encountered when rescuing certain mutants, the burden of proof was upon appellant I to establish on the basis of verifiable data that, despite following the conditions given in document D8, infectious virus could not be recovered. However, no data has been submitted to support this allegation.
12. A further declaration by Dr Kolakovsky states that Sendai virus, a member of the paramyxovirus family, was not recovered using the method disclosed in document D8. A different method is said to have been applied for the recovery of Sendai virus, this method employing:
1) embryonated eggs that allow enrichment of Sendai virus instead of helper vaccinia virus, and 2) Ara C to inhibit vaccinia virus production. Reference is made to document E1, authored by inter alia Dr Kolakovsky, in which the recovery of Sendai virus is reported.

13. In the introductory chapter of document E1, the authors review various approaches to rescuing infectious non-segmented negative-strand RNA viruses. After referring to the publications of Schnell et al. (1994) and Lawson et al (1995) (documents D1 and D2 in the present proceedings) as a successful approach to the recovery of rhabdoviruses from full-length cDNA, the authors state: "Here we report the recovery of infectious Sendai paramyxovirus (15 kb) from cDNA using this approach" (cf. page 6088, left column, line 2-4). In this respect, it should be noted that document D1 is the scientific publication of the method disclosed in D8, and that essentially the same method as disclosed in D8 for rabies virus is used in E1 for the recovery of Sendai virus, additional passages in embryonated eggs and Ara C being used in order to enrich the recovered virus. However, no evidence is provided in document E1 that the method disclosed in D8 would not work for Sendai virus.
14. As for the declaration of Dr Schnell, the board notes that all the statements contained therein relate to the obtention of vesicular stomatitis virus (VSV), a virus of the family of Rhabdoviridae. This evidence is therefore not suitable for supporting the allegation that a virus of the family of Paramyxoviridae cannot be obtained following the method disclosed in document D8.

15. In conclusion, there are no convincing arguments or evidence on file that support appellant I's allegations with respect to novelty. Since document D8 discloses in an enabling manner a method with all the features of claim 1, the subject-matter of this claim lacks novelty over D8. The main request must therefore fail.

First auxiliary request, claim 1 - Article 123(2) EPC

16. Claim 1 of this request differs from claim 1 of the main request by the presence of the disclaimer "wherein said polymerase is not expressed from a recombinant vaccinia virus". This disclaimer is meant to exclude from the scope of the claim the teachings of document D8 which is relevant to novelty under Article 53(3)(4) EPC. Its allowability under Article 123(2) EPC needs to be investigated.

17. The passage on page 5, lines 33 to 35 of the published application was argued to provide the information that vaccinia virus should not be used to introduce the polymerase-encoding DNA in the helper cells. This passage reads:
"Since the rescue system now developed, in contrast to the one used for rescue of RV (Schnell et al., 1994), VSV (Lawson et al., 1995) and very recently also for SeV (D. Kolakofsky, personal communication), does not rely on any helper virus,...".

18. In the board's judgement, neither the wording in the cited passage of the application provides a literal support for the wording of the introduced negative feature, nor does there exist a direct correspondence between the subject-matter excluded by the introduced negative feature (rescue system using a recombinant vaccinia virus to produce RNA polymerase) and the disclosure in the passage of the application indicated by appellant I (rescue system not relying on any helper virus). Thus, the application as filed, and in particular the passage cited by appellant I fails to provide a clear and unambiguous disclosure that could serve as a basis for the negative feature in claim 1 of the first auxiliary request.

19. In the absence of a disclosure in the application, the negative feature has to be considered as an undisclosed disclaimer and its allowability falls to be examined applying the criteria established in decisions G 1/03 and G 2/03 (OJ EPO 2004, 413 and 448). In these decisions, the Enlarged Board of Appeal held that a disclaimer may be allowable in order to inter alia restore novelty by delimiting a claim against state of the art under Article 54(3) and (4) EPC. In the present case, the disclaimer introduced into claim 1 of the first auxiliary request aims at restoring novelty by delimiting the claim against document D8, which
constitutes prior art under Article 54(3) and (4) EPC for the claimed subject-matter.

20. However, according to the same decisions, a disclaimer which is or becomes relevant for the assessment of inventive step is to be considered to add subject-matter contrary to Article 123(2) EPC (cf. Headnote II.3 in decision G 1/03, supra). In the present case, document D1, which constitutes prior art under Article 54(2) EPC, discloses the same method for the production of infectious, non-segmented negative-strand RNA virus as document D8. The only reason why it was not taken into account when assessing novelty is that it does not explicitly mention that the method allows the obtention of infectious virus of the family of Paramyxoviridae. Yet, the same disclaimer which excludes the teachings of document D8 also excludes the teaching of document D1. Because it provides essentially the same information as document D8, document D1 is relevant for inventive step (see points 21 to 26 below) and therefore cannot be excluded. The amendment in claim 1 of the first auxiliary request to introduce the disclaimer at issue is therefore in breach of Article 123(2) EPC. For these reasons, the first auxiliary request is rejected.

Second auxiliary request, claim 1 - Inventive step

21. Document D1, which is considered to be the closest prior art, discloses a method for the production of infectious, non-segmented negative-strand RNA virus, namely rabies virus, in which helper cells expressing T7 RNA polymerase from recombinant vaccinia virus vTF7-3 are transfected with plasmid pSAD L16. This
plasmid includes the entire antigenomic cDNA sequence of rabies virus flanked by the T7 polymerase promoter and the hepatitis delta virus antigenomic ribozyme sequence (cf. paragraph bridging pages 4196 and 4197, as well as the legend to Figure 1). The cells are co-transfected with plasmids pT7T-N, pT7T-P and pT7T-L encoding the N, P and L proteins (cf. page 4197, left column, lines 1 to 16 of the paragraph under the heading "Recovery of authentic infectious RV"). Transcription of the antigenomic sequence by the T7 RNA polymerase should produce transcripts with a precise 3' end (cf. page 4197, left column, lines 16 to 18). Infectious rabies virus is recovered from the cells by subjecting the same to three cycles of freezing and thawing. Cleared of cellular debris by centrifugation, the extract is used to inoculate fresh cells. Infection by rabies virus is demonstrated by direct immunofluorescence staining of the cells (cf. page 4197, left column, last six lines from the bottom).

22. The final goal of the authors of document D1 is – as in the patent in suit – to establish a system that allows the genetic manipulation of non-segmented negative-strand RNA viruses to be used inter alia for the preparation of vaccines. The method is said to be potentially applicable also for other negative-strand viruses (cf. last sentence of the Abstract). Paramyxoviruses are mentioned among other non-segmented negative-strand RNA viruses (cf. page 4195, right column, third full paragraph).

23. Thus, starting from document D1 as the closest prior art, the objective technical problem to be solved may be defined as the provision of a method for the
production of yet another non-segmented negative-strand RNA virus, in particular a virus of the family of Paramyxoviridae. No inventive step can be recognized in the formulation of the problem because, as just mentioned, the potential applicability of the method of document D1 to other negative-strand viruses is explicitly recognized in the same document.

24. The solution given in claim 1 is to express the RNA polymerase and the N and P proteins in the helper cells from stably transfected expression plasmids, ie in the method according to claim 1 helper cells are employed in which the sequences encoding the RNA polymerase and the N and P proteins are stably inserted into the genome. As for the sequence encoding the L protein, it can be either inserted in the genome or present on a plasmid. The advantages of this method over the prior art reside not only in avoiding the use of vaccinia virus, but also in providing a "ready-to-use" helper cell line which only needs, in order for infectious non-segmented negative-strand RNA virus to be produced, to be transformed with the plasmid including the viral cDNA and, optionally, a plasmid encoding the L protein.

25. In document D10, the difficulties associated with the use of helper viruses are discussed and, as a solution, a stable helper cell line producing the NP, P and L proteins of Sendai virus under the control of the human cytomegalovirus promoter-enhancer region is proposed. However, the board notes that the cell line described in D10 performs the replication and encapsidation of viral RNA only when the RNA is provided in the form of nucleocapsid-like particles. The possibility to achieve replication using viral antigenomic cDNA under the
control of an RNA polymerase promoter as disclosed in D1 is not even mentioned, although document D1 had already been published and its teaching, a major advance in the field of genetics of non-segmented negative-strand RNA viruses, was well known in the art. Thus, it appears doubtful whether the skilled person would have considered combining the teachings of D1 and D10 in order to obtain infectious paramyxoviruses.

26. But, even if it is assumed that the skilled person would have done so, there remains that document D10 does not provide any guidance with respect to the RNA polymerase. Documents D3 to D6 were cited in this context as suggesting to the skilled person that the RNA polymerase should be expressed from the helper cells genomic DNA. However, none of these documents relate to the field of genetics of negative-strand RNA viruses, documents D3, D4 and D6 being rather concerned with the optimization of protein expression in mammalian cells, and document D5 aiming at understanding the role of an internal ribosomal entry site in translation by hepatitis A virus. In the board's view, the skilled person had no motivation to seek guidance in a different technical field. Thus, alone the substitution of the vaccinia virus-encoded RNA polymerase as disclosed in document D1, by an RNA polymerase stably expressed in the helper cell as in claim 1 required already inventive skills.

27. For these reasons the board concludes that the subject-matter of claim 1 of the second auxiliary request involves an inventive step.
Sufficiency of disclosure (Article 83 EPC)

28. In the board's judgement, document D23 filed in appeal proceedings does not provide convincing evidence to support the allegation that the method of claim 1 works solely with the viral strain used in the patent (Edmonton strain). It is true that D23 shows that, when the cell line 293-3-46 described in the patent is used, no measles virus from the IC-B strain is produced, unless the 293-3-46 cells are overlaid with B95a cells. This appears to be due to the fact that the human embryonic kidney-derived 293-3-46 cells are not susceptible to **B95a cell-isolated** measles virus, including the IC-B strain (cf. D23, page 6645, first sentence of the last paragraph).

29. However, it should be noted that, although the cell line 293-3-46 is used as helper cell in the examples of the patent in suit, claim 1 is not restricted to a method employing this cell line. Moreover, the results reported in document D23 do not preclude that measles virus of the IC-B strain which has not been passaged in B95a cells could be obtained using 293-3-46 cells, nor that measles virus of the IC-B strain can be obtained using any helper line other than 293-3-46 cells, for instance B95a cells expressing a T7 RNA polymerase and N, P and L protein from measles virus.

Claim 20 - Request for correction under Rule 88 EPC

30. It is immediately evident that the reference to "a plasmid as defined in any one of claims 4 to 20" in claim 20 of the second auxiliary request filed on 20 November 2002 is incorrect, and that nothing else
could be intended than to refer to claims in which such a plasmid is defined, ie claims 3 to 19. Therefore, the request of appellant I for correction of claim 20 pursuant to Rule 88 EPC must be granted.

Order

For these reasons it is decided that:

1. The second auxiliary claim request filed on 20 November 2002, on the basis of which the opposition division maintained the patent is to be amended pursuant to Rule 88 EPC so that claim 20 reads "... defined in any of claims 3 to 19 ...".

2. The appeals of the patentee and of opponent II are dismissed.

The Registrar:                        The Chairman:

A. Wolinski                           F. Davison-Brunel