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Datasheet for the decision of 17 July 2006

Case Number: T 0331/07 - 3.3.08

Application Number: 95201936.2

Publication Number: 0702085

IPC: C12N 15/86

Language of the proceedings: EN

Title of invention:
Recombinant infectious non-segmented negative strand RNA virus

Patentee:
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Opponents:
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Institut Pasteur
Adams, Harvey Vaughan John
BERNA BIOTECH AG

Headword:
Negative-strand RNA virus/CONZELMANN

Relevant legal provisions:
EPC Art. 87, 88, 54, 56

Relevant legal provisions (EPC 1973):
-

Keyword:
"All requests - priority rights - no"
"Main request - novelty - no"
"Auxiliary requests I to III - novelty - no"
"Auxiliary requests IV and V - inventive step - no"

Decisions cited:
G 0002/98

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0331/07 **-** 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 17 July 2006

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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 6 December 2006 concerning maintenance of European patent No. 0702085 in amended form.

Composition of the Board:

Chairman: L. Galligani
Members: F. Davison-Brunel
C. Rennie-Smith

Summary of Facts and Submissions

I. European patent No. 0 702 085 with the title "Recombinant infectious non-segmented negative strand RNA virus" and claiming priority from the European patent application 94202089 of 18 July 1994 was granted with 18 claims on the basis of the European patent application No. 95201936.2 filed on 14 July 1995.

Claims 1, 8 and 11 read as follows:

"1. A genetically manipulated infectious replicating non-segmented negative-stranded RNA virus mutant comprising an insertion and/or deletion in an open reading frame, a pseudogene region or an intergenic region of the virus genome.

8. A virus mutant according to claims 1-6, characterized in that the virus mutant belongs to the family of rhabdoviridae.

11. A virus mutant according to claim 8, characterized in that the virus mutant is rabies virus."

II. Five oppositions were filed under Article 100(a) to (c) EPC for lack of novelty and inventive step, insufficiency of disclosure and added subject-matter. The opposition division considered that the subject-matter of the main, first and second auxiliary requests then on file did not enjoy priority as of the filing date of the priority document and, therefore, lacked novelty over the teachings of documents (10) and (11) (see infra) which were published in the priority interval. The patent was maintained on the basis of the

third auxiliary request then on file. Claims 1 and 7 of this request read as follows:

"1. A genetically manipulated infectious replicating rabies virus mutant comprising an insertion or deletion in an open reading frame, a pseudogene region or an intergenic region of the virus genome.

7. A genetically manipulated infectious replicating rabies virus mutant comprising an insertion and/or deletion in an open reading frame, a pseudogene region or an intergenic region of the virus genome, characterized in that the virus mutant carries a heterologous nucleic acid sequence encoding an epitope or polypeptide of a pathogenic virus or microorganism."

Claims 2 to 6 and 8 to 13 respectively related to further features of the viruses of claims 1 or 7. Claim 14 was directed to a vaccine comprising a rabies virus mutant according to the preceding claims 1 to 13. Claim 15 related to a process for the preparation of a genetically manipulated infectious replicating rabies virus and claims 16 and 17 related to further features of the process of claim 15.

III. The appellant (patentee) filed an appeal, paid the appeal fee and submitted a statement of grounds of appeal together with a new main and three auxiliary requests. The third auxiliary request was the request accepted by the opposition division.

IV. Respondents I to V (opponents 1 to 5) submitted replies thereto.

V. The board sent a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal, indicating its preliminary, non binding-opinion.

VI. The appellant and respondents I to III replied to this communication. The appellant's submissions were accompanied by the same main request as filed with the grounds of appeal and new auxiliary requests I, II and V, the pending auxiliary requests I to III being renumbered auxiliary requests II, IV and VI respectively - the sixth auxiliary request thus being the request accepted by the opposition division, see II, supra.

Claim 1 of the **main request** and of the **first auxiliary request** read as follows:

"1. A genetically manipulated infectious replicating non-segmented negative-stranded RNA virus mutant comprising an insertion or deletion in an open reading frame, a pseudogene region or an intergenic region of the virus genome."

Claim 1 of the **second** and **third auxiliary requests** read as follows:

"1. A genetically manipulated infectious replicating non-segmented negative-stranded RNA virus mutant comprising an insertion or deletion in an open reading frame, a pseudogene region or an intergenic region of the virus genome, characterized in that the virus mutant belongs to the family of rhabdoviridae."

Claim 1 of the **fourth** and **fifth auxiliary** requests read as follows:

"1. A genetically manipulated infectious replicating rabies or vesicular stomatitis virus comprising an insertion or deletion in an open reading frame, a pseudogene region or an intergenic region of the virus genome."

VII. Oral proceedings took place on 17 July 2008. Although duly summoned, respondent IV did not take part in the proceedings. At the end of the oral proceedings, the appellant withdrew auxiliary request VI - the claim request accepted by the opposition division - as it was redundant.

VIII. The documents on file which are mentioned in this decision are the following:

(2): Conzelmann, K-K and Schnell, M., J. of Virology, Vol.68, No.2, pages 713 to 719, February 1994;

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

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

(26): Rose, J.K., Proc.Natl.Acad.Sci.USA, Vol.94, pages 14998 to 15000, December 1996.

IX. The appellant's arguments in writing and during oral proceedings insofar as relevant to the present decision may be summarized as follows:

All requests
Articles 87 and 88 EPC; priority rights

The claimed subject-matter enjoyed priority rights as of the filing date of the priority document because this document taken as a whole left no doubt that the invention was to be carried out with any kind of infectious replicating non-segmented negative-stranded RNA viruses, including rhabdoviridae, vesicular stomatitis virus (VSV) and rabies virus.

- On page 1 of the priority document, the title of the invention, "Recombinant infectious non-segmented negative strand RNA virus" already made it clear that the disclosure was not limited to rabies viruses. In fact, rabies viruses were shortly thereafter identified "as an example of a non-segmented negative-stranded RNA virus of the Rhabdoviridae family." Other species were also identified as belonging to this family such as VSV. From page 6, line 22 to page 7, line 9, it was taught that all non-segmented, negative-stranded RNA virus replicated by the same mechanism which necessarily involved the formation of a ribonucleoprotein complex (RNP). On page 13, the reason was given why earlier attempts at multiplying them in vivo in a recombinant manner had failed: the positive-stranded messenger RNAs encoding the viral proteins hybridized to the negative-stranded genomic RNA and, thus, interfered with the crucial encapsidation step. Then, the priority document gave extensive information as to how to multiply rabies viruses (as an example of non-segmented, negative-stranded RNA virus) by circumventing the above mentioned problem due to RNA/RNA hybridisation using an

antigenomic approach. Since the problem with encapsidation was common to all non-segmented negative-stranded RNA virus and its solution was described for one of them, the skilled person would take it as a matter of fact that this solution was equally applicable to all of them.

- Document (2) on file taught that, using earlier techniques, attempts at encapsidating negative-stranded RNA transcripts were only successful when these transcripts were of a relatively short size. On the contrary, the priority document showed that full length rabies genomic RNA such as rabies viral RNA could be made into infectious particles. The skilled person would, thus, be all the more inclined to use the technique therein described with other RNA viruses of the same type.
After the antigenomic approach to non-segmented, negative-stranded RNA virus replication had become known, many groups working with different species of such viruses had made use of it, which was a clear indication that the teaching established with rabies viruses was recognized by the scientific community as generally applicable to all of them.

- There were two declarations on file, namely that of Prof. Baltimore of 2 July 1997 and of Dr. Schnell of 1 July 1997, to the effect that the positive results obtained with rabies viruses would not necessarily be/had not been reproducible with other negative-stranded RNA viruses. However, the first one did not provide any scientific basis for its allegations. As for the second one, it was of limited credibility inasmuch as before its author's reported failure to use the

antigenomic approach for the multiplication of VSV, another group had succeeded to do so.

In accordance with the practice of the EPO as reflected in the Guidelines for Examination, the implicit as well as explicit disclosures of the priority document had to be taken into account when assessing priority. Here, there was no doubt that the concept of the "antigenomic approach to negative-stranded RNA viruses recombinant replication" was at least implicitly disclosed in the priority document as being applicable to all these viruses. The priority date was, thus, valid.

Articles 54 and 56 EPC; novelty

As the subject-matter of the main request enjoyed priority rights, documents (10) and (11) published in the priority interval were not relevant to novelty or inventive step and the request fulfilled the requirement of Art.54 and 56 EPC. This was also true of auxiliary requests I to V for the same reason.

X. The respondents' arguments in writing and during oral proceedings insofar as relevant to the present decision may be summarized as follows:

All requests
Articles 87 and 88 EPC; priority rights

- The Enlarged Board of Appeal's decision G 2/98 (OJ EPO 2001, 413) established the principles to be followed when assessing the validity of a priority document. In particular, it was stated in point 6.8 of the decision that a narrow and strict interpretation of the concept

of "the same invention" should be applied. Reading the priority document made it absolutely clear that its teaching only related to rabies viruses. Its title, "Recombinant infectious non-segmented negative strand RNA virus", had no legal value and, besides, the word "virus" was used in the singular, which certainly did not convey the information that the invention was meant to be covering more than the rabies virus itself. On page 1, the rabies virus was put in its phylogenetic context (page 1), its clinical effects, its genomic organisation and the problems associated with its use as a vaccine were then described (pages 2 to 5). On pages 6 and 7, a somewhat broader disclosure of the ways to manipulate viral genomes in general was given with a specific passage on page 7 dealing with negative-stranded viruses. From page 8 onwards, only rabies viruses were mentioned. Even in the passage on page 16 which related to future lines of investigation, there was no mention at all of applying the technique to further non-segmented negative-stranded viruses. Neither the generic invention as claimed in claim 1 of the main request and auxiliary requests I to III nor the invention as claimed in auxiliary requests IV and V relating to VSV viruses were even as much as hinted at in the priority document which, therefore, was not suitable for establishing priority rights.

- Post-published document (26) (see page 14998, right-hand column) mentioned that, because of low efficiency, it was not obvious that the antigenomic approach would work with other viruses than rabies virus, eg. with VSV. There was, thus, evidence on file that the scientific community did not regard it as a matter of fact that the teachings of the priority document could be extended. In

this respect, it ought to be kept in mind that the examples provided by the priority document all concerned rabies viruses with alterations in the intergenic region and that not all non-segmented, negative-strand viruses had such a region in their genome.

- The appellant's argument as regards scientific groups having immediately understood the antigenomic approach also to be applicable to other non-segmented, negative stranded viruses than rabies virus may have reflected a possible lack of inventive step of further inventions. Yet, it did not amount to evidence that these further inventions were comprised in the priority document, even in an implicit manner.

- There were two declarations on file, namely that of of Prof. Baltimore of 2 July 1997 and of Dr. Schnell of 1 July 1997, expressing the view that, at the priority date, the skilled person would not have expected that the antigenomic approach for the recombinant production of rabies viruses would necessarily work with other non-segmented negative-stranded RNA viruses.

In accordance with G 2/98 (supra), common general knowledge could be taken into account when assessing the content of a priority document and, indeed, it would have been a matter of common general knowledge that rabies viruses were part of the family of non-segmented, negative-stranded viruses and that their replication required the formation of the RNP complex (as indicated in the priority document). Yet, in accordance with the case law, common general knowledge could be used to interpret a disclosure but not to broaden it. Here, there was nothing to interpret, the disclosure of the

priority document being, as already explained, strictly limited to rabies viruses. For this reason, neither of the main request and auxiliary requests I to V enjoyed priority.

Articles 54 and 56 EPC; novelty and inventive step

As documents (11) and (10) published in the priority interval respectively disclosed the claimed invention and the antigenomic approach applied to VSV, novelty or inventive step must be denied to claim 1 of the main request and auxiliary requests I to III whereas claim 1 of auxiliary requests IV and V lacked inventive step.

XI. The appellant requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request filed on 16 April 2007 or auxiliary requests I to V filed on 17 June 2008.

The respondents requested that the appeal be dismissed.

Reasons for the decision

All requests; claim 1
Articles 87 and 88 EPC; priority rights

1. The main issue to be decided in the present case is whether the invention relating to non-segmented negative-stranded RNA virus mutants (main and first auxiliary requests), to rhabdoviridae virus mutants (auxiliary requests II and III) and to vesicular stomatitis virus mutants (auxiliary requests IV and V) enjoys priority rights as of the filing date of the

European patent application No. 94 202 089.2 (priority document). Indeed, a negative conclusion in this respect would have the consequence that documents (10) and (11) published in the priority interval would become relevant for novelty and/or inventive step.

2. When assessing priority, guidance is found in the Enlarged Board's decision G 2/98 (supra). There, the principle to be applied is defined as follows:

"The requirement for claiming priority of the "same invention", referred to in Article 87(1)EPC, means that a priority of a previous application in respect of a claim of a European patent application in accordance with Article 88 EPC is to be acknowledged only if the skilled person can derive the subject-matter of the claim directly and unambiguously, using common general knowledge, from the previous application as a whole."

As for the meaning of the expression "the same invention", it is explained in point 6.8 of the decision:

"It seems, therefore, that a narrow or strict interpretation of the concept of "the same invention" referred to in Article 87(1) EPC, equating it with the concept of "the same subject-matter" referred to in Article 87(4) EPC (cf. point 2 supra) is perfectly consistent with paragraphs 2 to 4 of Article 88 EPC."

The question to be answered is, thus, whether the subject-matter disclosed in the European application 94 202 089.2 is the same as that now claimed.

3. On page 1 of the priority document, the invention is entitled "Recombinant infectious non-segmented negative strand RNA virus" and the description starts with the sentence:

"The present invention is concerned with a genetically manipulated infectious replicating rabies virus mutant and a process for the preparation of such a mutant."

Then, on pages 2 to 5, the phylogenic background, clinical effects and genomic organisation of rabies viruses are explained and anti-rabies vaccines are discussed. On pages 6 and 7, recombinant production of viruses in general (including DNA viruses, positive- or negative- stranded RNA viruses) is briefly reviewed with a specific passage dealing with the hitherto encountered difficulties in obtaining infectious non-segmented negative-stranded viruses by recombinant means. On page 8, it is once more mentioned that:

"The present invention provides a genetically manipulated infectious replicating rabies virus mutant, ...".

From there on to the end of the general section, the information provided solely concerns rabies viruses, ways to mutate them, to produce them recombinantly by the antigenomic approach and ways to use them as vaccines. Most importantly, when mention is made on page 16 of possible future developments, applying the antigenomic approach to the recombinant viral production of other non-segmented, negative stranded RNA viruses is not one of them. The examples are all carried out with rabies viruses wherein mutations are inserted in a

portion of the genome (the intergenic region) which is not common to all non-segmented, negative-stranded RNA viruses.

4. In the board's judgment, the title of the invention , if taken into account at all, does not suggest that the invention is intended to be carried out with more than one virus because the term virus is used in the singular. As for the following technical contribution, it does not warrant acknowledging priority to all non-segmented, negative-stranded virus mutants, rhabdoviridae virus mutants or vesicular stomatitis virus mutants (main request, auxiliary requests I to V). Applying the antigenomic approach to the recombinant viral production of these viruses is certainly not the explicit subject-matter of the priority document; the possibility of doing so is not even hinted at. It is also not an implicit teaching, even taking into account common general knowledge which discloses that non-segmented negative-stranded RNA viruses, including rabies viruses, have certain features in common - eg. their mode of replication, patent in suit [0016] - but also that they are distinct entities - eg. their overall genomic organisation is "comparable", patent in suit [0004]. Unless the skilled person would be prompted to do so, he/she would have no reason to expect that a method set up with one of the negative-stranded RNA viruses would necessarily be applicable to the others. Indeed, this is reflected in post-published document (26) (page 14998, right-hand column) where it is mentioned that:

"Because of the low efficiency *[of rabies viruses recovery],* it was not obvious that this would work with other viruses..."

To argue to the contrary - as the appellant did - is to use only as much of the common general knowledge as is favourable to its own purpose (the similarities existing between negative stranded viruses) to extend the content of the priority document artificially and in an unwarranted manner. The simple fact is that the claimed subject-matter cannot be derived from the priority document directly and unambiguously using common general knowledge.

5. The appellant also argued that the skilled person would in any case be inclined to apply the antigenomic approach to viruses other than rabies viruses - once it was known - because of the negative outcome of all methods hitherto tried to encapsidate long recombinant RNAs (document (2), page 718, right-hand column)). This may well be true but it is not a suggestion which is contained in the priority document which, in accordance with the Enlarged Board's decision G 2/98 (supra), must relate to the subject-matter for which priority is claimed if priority is to be acknowledged.

6. Finally, the appellant commented on the shortcomings of two declarations on file to the point that the skilled person had no technical reasons to expect that the antigenomic approach to recombinant production would work in a "generic manner". These comments need not be reviewed here insofar as a negative conclusion on priority can be reached without assessing their validity.

7. For the reasons explained in points 2 to 4, supra, it is concluded that the subject-matter of the main request and of auxiliary requests I to V enjoys priority as of

the filing date of the patent in suit namely, 14 July 1995.

Articles 54 and 56 EPC; novelty and inventive step

8. The respondents objected to claim 1 of each of the main request and auxiliary requests I to V on file for lack of novelty or inventive step over the teachings of documents (11) or (10) published before 14 July 1995.

9. Document (11) is the scientific publication corresponding to the teachings of the priority document: it discloses a genetically manipulated infectious replicating non segmented negative stranded rabies virus mutant comprising a deletion in the intergenic region of the viral genome (see abstract). Rabies virus being non-segmented negative-stranded viruses of the rhabdoviridae family, this teaching is novelty destroying for the subject-matter of claim 1 of the main request and auxiliary requests I to III.

10. Document (10) is a scientific publication describing the recovery of vesicular stomatitis virus from animal cells using the antigenomic approach (page 4477, right-hand column). The viruses carry a mutation in the 5' or 3' non coding regions of the glycoprotein gene (page 4479, "Identification of Sequence Tags"). This mutation is a substitution (a deletion followed by an insertion) aimed at facilitating the identification of the viruses which are recovered. It is, thus, different from those mutations carried by the claimed virus. However, it is a feature which has no bearing on the scientific achievement per se which, as already above mentioned, is

the antigenomic approach applied to VSV recombinant production. Thus, document (10) discloses all of the features of the VSV viruses of claim 1 of auxiliary requests IV and V which would be relevant for inventive step. For this reason, claim 1 of auxiliary requests IV and V - insofar as it relates to VSV viruses - lacks inventive step over the teachings of document (10) and, therefore, does not fulfil the requirements of Article 56 EPC.

Order

For these reasons, it is decided that:

The appeal is dismissed.

The Registrar The Chairman

A. Wolinski L. Galligani