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**Datasheet for the decision
of 29 June 2012**

Case Number: T 1374/09 - 3.3.08
Application Number: 05018141.1
Publication Number: 1627919
IPC: C12N 15/40, C12N 15/86,
C12N 5/10
Language of the proceedings: EN

Title of invention:

An infectious cDNA clone of North American porcine reproductive and respiratory syndrome (PRRS) virus and uses thereof

Applicant:

Pfizer Products Inc.

Headword:

Infections PRRSV/PFIZER

Relevant legal provisions:

EPC Art. 54, 56, 83, 123(2)

Keyword:

"Main request:
Added matter (no)
Sufficiency of disclosure, novelty, inventive step (yes)"

Decisions cited:

G 0001/03

Catchword:

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Case Number: T 1374/09 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 29 June 2012

Appellant: Pfizer Products Inc.
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Groton, CT 06340 (US)

Representative: Markus, Marc A.
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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 18 December 2008
refusing European patent application
No. 05018141.1 pursuant to Article 97(2) EPC.

Composition of the Board:

Chairman: M. Wieser
Members: B. Stolz
J. Geschwind

Summary of Facts and Submissions

- I. The appeal lies against the decision of the examining division to refuse European patent application EP 05018141 pursuant to Article 97(2) EPC.
- II. The examining division found that the request before it, claims 1 to 22 filed with letter received on 26 May 2008, met the requirements of Articles 123(2), 84 and 54 EPC, but did not meet the requirements of Article 56 EPC.
- III. The applicant (appellant) lodged an appeal and requested that the decision of the examining division be set aside and a patent be granted on the basis of the main request received on 26 May 2008. Oral proceedings were requested should the board not be able to grant the main request.
- IV. The appellant was summoned to oral proceedings. A communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) annexed to the summons, informed the parties of the preliminary non-binding opinion of the board on some of the issues of the appeal proceedings.
- V. With letter dated 23 April 2012, the appellant submitted its comments to the board's communication as well as auxiliary requests I to IV.
- VI. Oral proceedings were held on 24 Mai 2012. In the course of these proceedings, the appellant filed a new main request and withdrew all its other requests.

VII. Claims 1 to 7 of the main request are identical to claims 1 to 6, and 8 of auxiliary request III submitted with letter dated 23 April 2012, and read:

1. An isolated polynucleotide molecule comprising a DNA sequence encoding an infectious RNA molecule wherein said DNA sequence is at least 85% identical to the sequence of SEQ ID NO.1.

2. An isolated infectious RNA molecule encoded by an isolated polynucleotide molecule according to claim 1, which infectious RNA molecule encodes a North American PRRS virus.

3. An isolated polynucleotide molecule according to claim 1 in the form of a plasmid.

4. A transfected host cell comprising a DNA sequence encoding an infectious RNA molecule, wherein said DNA sequence is at least 85% identical to the sequence of SEQ ID NO.1.

5. A plasmid capable of directly transfecting a suitable host cell and expressing a Nidovirales virus from the suitable host cell so transfected, which plasmid comprises a) a DNA sequence encoding an infectious RNA molecule encoding the Nidovirales virus said DNA sequence having a sequence with at least 85% sequence identity to the sequence of SEQ ID NO: 1 and b) a promoter capable of transcribing said infectious RNA molecule in said suitable host cell.

6. A method for generating a Nidovirales virus, which method comprises transfecting a suitable host cell with

a plasmid according to claim 5 and obtaining virus generated by the transfected host cell.

7. An isolated polynucleotide molecule comprising a DNA sequence encoding an infectious RNA molecule encoding a North American PRRS virus that is genetically modified so that it lacks a detectable antigenic epitope, wherein said DNA sequence is at least 85% identical to the sequence of SEQ ID NO.1 but lacks one or more DNA sequences encoding a detectable antigenic epitope.

VIII. The following documents are referred to in this decision:

D4: Meulenberg et al., Journal of Virology 72(1): 380-387, 1998

D5: EMBL U87392 version 4

D6: EMBL AF046869 version 1

D8: Nelsen et al., Journal of Virology 73(1): 270-280, 1999

D11: K.S. Faaberg and G. Liu, CRWAD, Proceedings of the 82nd Annual meeting, November 11, 12, and 13, 2001, abstract No. 176

D12: K.S. Faaberg et al., IXth International Symposium on Nidoviruses, 24 - 29 May 2003, abstract P.6.6.

IX. Appellant's arguments as far as relevant to the present decision can be summarized as follows:

Regarding sufficiency of disclosure, there was no undue burden to obtain infectious PRRSV clones with 85% homology. Standard techniques such as described in paragraph [0028] could be used to modify Seq. ID no. 1 of the patent application, and the resulting sequences could be readily tested for infectivity by one of the assays disclosed in the examples.

Regarding inventive step, starting from document D5 as closest prior art, the technical problem could be defined as the provision of an infectious clone of a North American PRRSV isolate. The sequence of the North American isolate disclosed in document D5 lacked nucleotide sequence at its 5' end and did not encode an infectious RNA molecule. The skilled person would not have arrived at the claimed solution by modifying the sequence disclosed in document D5 with reference to document D4. The sequence disclosed in document D5 not only lacked sequence at its 5' end but, as shown in documents D11 and D12, required further modifications to become infectious. Document D11, published in 2001, was co-authored by a scientist of document D5 and showed that attempts to generate an infectious clone from the virus RespPRRS continued to fail. Document D12 provided additional evidence that the sequence disclosed in document D5 could not be readily translated into an infectious clone. The required modifications to the sequence of document D5 could not be readily derived from document D4.

- X. The appellant requested that the decision under appeal be set aside and a patent be granted on the basis of its main request.

Reasons for the Decision

Admissibility of the main request

1. The claims of the main request were filed at the oral proceedings after discussion of the requests previously on file. During this discussion, the board had directed appellant's attention to issues arising under Article 83 EPC. These issues could not be derived from the decision under appeal and had not all been explicitly mentioned in the communication attached to the summons to oral proceedings. In order to address this situation, the appellant requested an opportunity to submit a new main request which consisted of claims 1 to 6, and 8 only of previous auxiliary request III, filed with letter of 23 April 2012.
2. Under Article 13(1) RPBA, any amendment to a party's case after it has filed its grounds of appeal or reply to a communication from the board may be admitted and considered at the board's discretion.

Although the filing of the main request must be regarded as late, the board has decided to admit it in view of the fact that it was filed as a reaction to objections which in their entirety could not have been recognised by the appellant and that the amendment consisted merely of deleting claims from an auxiliary request already on file.

Articles 123(2), 84 and 54 EPC

3. Basis for the feature "85% identical to the sequence of Seq ID NO. 1" can be found in the claims as originally

filed in combination with paragraph 36 of the description. Thus the requirements of Article 123(2) are met.

4. The genomic North American PRRSV sequences disclosed in documents D5 and D6 both lack a complete 5' end sequence which is necessary for infectivity (cf. document D4, p. 382, left column, last paragraph; document D11). Thus, despite being more than 85% identical with the sequence of Seq ID No. 1, they do not anticipate the claimed subject matter. The claimed subject matter is novel.

5. The board has no evidence and sees no reason to deviate from the findings of the examining division, and is thus satisfied that the requirements of Articles 123(2), 84 and 54 EPC are met.

Article 83 EPC

6. Claims 1, 2, 5, and 7 are product claims defined by reference to Seq ID No. 1 and are functionally restricted to those sequences which encode an infectious RNA molecule.

In a case where a technical effect is expressed in a claim, in the present case the infectivity of the encoded RNA, the issue whether this effect is achieved across the whole scope of the claim is a question of sufficiency of disclosure (Decision of the Enlarged Board of Appeal, G 001/03, OJ 2004, 413, Reasons 2.5.2).

It remains thus to be established whether the skilled person, taking into account the disclosure of the

patent application and its general knowledge, was in a position to perform the claimed invention readily and without undue burden across essentially the entire breadth of the claims.

7. The cloning of a cDNA encoding an infectious RNA of a North American PRRS virus is described in detail in Example I. Cloning of the indispensable 5' and 3' ends is disclosed in [0127] and [0129], respectively. The creation of a full-length infectious cDNA clone included the assembly of overlapping PCR fragments as well as the correction of multiple mutations resulting from the cloning procedures (cf. [0130], line 53; [0132], line 16; [0133], line 20; [0134], line 25; [0135], line 33). A plaque test for assessing infectivity of the assembled full-length clone is disclosed in [0138]. Further tests are described in Examples IV (e.g. [0153]), and V to VII.

8. The present application thus provides a detailed procedure for the cloning of one particular infectious full-length clone, pT7P129A, and the board has no doubts that the skilled person was in a position to readily derive further sequences from Seq ID No. 1 by conventional means such as those mentioned in paragraph [0028] of the description. Any full-length clone derived from Seq ID No. 1 could then readily be tested by one of the tests disclosed in the patent application.

9. The isolated polynucleotide molecule of claim 7 encodes an infectious RNA molecule encoding a North American PRRSV virus that is genetically modified so that it lacks a detectable antigenic epitope.

Example II of the patent application discloses a modified virus with a deletion of ORF 7 and the production of infectious virions in a helper cell. Antibodies to the ORF 7 protein are commonly found in the sera of PRRS virus infected pigs ([0141], last sentence), and although there is no experimental proof on file, it seems plausible that, as also stated in [0141], pigs vaccinated with an ORF7 deleted PRRS virus would lack antibodies to this virus. Moreover, there is no evidence against it and the board has no doubts that the skilled person was in a position to readily produce and test modified virus with deletions of antigenic epitopes on the basis of the disclosed nucleic acid sequence and the above-mentioned test for infectivity.

10. The board is thus satisfied that the requirements of Article 83 EPC are met.

Article 56 EPC

11. The closest prior art document for the assessment of inventive step is document D5, database entry U87392 (Rel. 57 of 19 November 1998) from the EMBL Nucleotide sequence database which discloses 15409 base pairs of nucleotide sequence of the North American PRRSV isolate VR-2332 with 92% sequence identity with Seq ID 1. Due to the absence of a complete 5' sequence, the disclosed cDNA encodes a non-infectious RNA molecule. Document D5 (section "5' UTR", "misc_features") makes reference to primer extension studies suggesting that there are 20 additional nucleotides at the 5' end.

12. Starting from D5, the technical problem is defined as the provision of a cDNA molecule encoding an infectious RNA of a North American PRRS virus.

13. The solution to this problem proposed by claim 1 is an isolated polynucleotide molecule comprising a DNA sequence encoding an infectious RNA molecule having at least 85% sequence identity with Seq ID No. 1.

14. Example 1 of the application describes the assembly of cDNA clone pT7P129A which is capable of infecting MARC-145 cells in vitro and of producing the symptoms of a PRRSV infection in pigs. The cDNA sequence of this clone differs from the consensus sequence of Seq ID 1 derived from viral isolate P129A in two positions.

The board is convinced that the skilled person, based on the teaching of the patent application, was in a position to readily derive further infectious clones having at least 85% sequence identity with Seq ID No. 1 (cf. points 7 and 8 above), and is therefore satisfied that the technical problem, as defined above, has been solved.

15. It remains to be established whether this solution involved an inventive step.

16. In its decision, the Examining Division held in essence that the claimed solution was obvious in view of document D5, explicitly mentioning that "there are 20 nucleotides at the 5' end", and of document D4 disclosing the cloning of an infectious European PRRSV isolate. Document D4 (page 382, left column, last para.) stated that "it is generally admitted that the entire

viral sequence, including the 5' and 3' ends, are required to obtain infectious clones". The examining division concluded that the skilled person would have used the method outlined in document D4 in order to obtain the missing 5' end of isolate VR-2332 and would thus have arrived at the claimed solution in an obvious way.

17. The appellant had argued that the sequence disclosed in document D5 contained errors which would most likely abolish infectivity of the clone. The Examining division considered this argument not pertinent because the appellant had not provided sufficient evidence to prove its point.

18. In the grounds for appeal, the appellant further argued that the sequence disclosed in document D5 was the result of assembling multiple short sequences obtained by sequencing small portions of viral strain VR-2332. This could be derived from document D8 which described the work leading to the sequence disclosed in document D5. Assembling small fragments on paper was however not the same as providing a full-length infectious cDNA clone because the cloning process was error prone for multiple reasons.

In response to the board's communication annexed to the summons to oral proceedings, the appellant filed new document D11 to further support this argument.

19. Document D11 is a conference abstract from November 2001, reporting on difficulties when trying to obtain recombinant infectious clones of North American PRRSV strains. The document states that "no infectivity was

seen on BHK-21 cell transfection with an in vitro derived RNA representing our full-length cDNA copy of RespPRRS". Sequence comparison showed that the cloning procedure resulted in multiple amino acid substitutions which "may be a reason for the lack of infectivity of the RespPRRS full-length clone", and a deletion "which may also affect infectivity of the cDNA clone". Document D11 further states that "[t]he difficulty in deriving infectious copies of North American PRRSV strains suggests that the genome is unstable in bacteria, even under conditions shown to result in infectious transcripts of the European strain, Lelystad" (note: the cloning of the Lelystad strain is disclosed in document D4). Document D11 concludes that "novel approaches to rapid development and manipulation of PRRSV genomes may need to be established".

20. The board takes from document D11 that even two years after the priority date of the present application, one of the authors of document D5, Kay S. Faaberg, could not obtain cDNA clones encoding infectious RNA molecules of North American PRRSV isolates by simply combining the teaching of document D5 with that of document D4. One of the reasons for these difficulties seems to have been the instability of the cloned DNA sequences. Document D5 is silent in this respect and the solution to this problem was apparently not derivable from document D4 in an obvious way.

21. Thus, as the claimed solution to the technical problem defined in point 12 above was not obvious to an expert in the technical field, such as one of the authors of document D5, even two years after the priority date of the present application, the same must have been all

the more true for the average skilled person at the relevant date.

22. Therefore, claim 1 involves an inventive step, and the same applies to claims 2 to 7.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the department of first instance with the order to grant a patent in the following version:
 - claims 1 to 7 of the main request filed during the oral proceedings of 24 May 2012, and
 - the description to be adapted thereto.

The Registrar:

The Chairman:

A. Wolinski

M. Wieser