

Internal distribution code:

- (A) [] Publication in OJ
(B) [] To Chairmen and Members
(C) [X] To Chairmen
(D) [] No distribution

D E C I S I O N
of 12 November 2003

Case Number: T 0608/00 - 3.3.8

Application Number: 91901026.4

Publication Number: 0502976

IPC: C12N 15/00

Language of the proceedings: EN

Title of invention:

Production of recombinant polypeptides by bovine species and transgenic methods

Patentee:

Pharming Intellectual Property BV

Opponent:

PPL Therapeutics (Scotland) Ltd

Headword:

Transgenic bovine/PHARMING

Relevant legal provisions:

EPC Art. 123(2)

Keyword:

"Main and auxiliary requests: allowability of amendments (no)"

Decisions cited:

-

Catchword:

-



Case Number: T 0608/00 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 12 November 2003

Appellant: Pharming Intellectual Property BV
(Proprietor of the patent) Niels Bohrweg 11-13
NL-2333 CA Leiden (NL)

Representative: Williams, Richard Andrew Norman
Hepworth Lawrence Bryer & Bizley
Merlin House
Falconry Court
Bakers Lane
Epping, Essex CM16 5DQ (GB)

Respondent: PPL Therapeutics (Scotland) Ltd
(Opponent) Roslin
Edinburgh EH25 9PP (GB)

Representative: Sheard, Andrew Gregory
Andrew Sheard, Patent Attorney
P.O. Box 521
Berkhamsted, Herts. HP4 1YP (GB)

Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 30 March 2000
revoking European patent No. 0502976 pursuant
to Article 102(1) EPC.

Composition of the Board:

Chairman: L. Galligani
Members: T. J. H. Mennessier
S. C. Perryman

Summary of Facts and Submissions

- I. The patentee (appellant) lodged an appeal against the decision of the opposition division given at oral proceedings on 10 February 2000 with written reasons posted 30 March 2000 revoking the European patent No. 0 502 976. The patent was granted on European application No. 91 901 026.4 which originated from an international application published as WO 91/08216 (to be referred to in the present decision as the application as filed).
- II. Whereas two parties (opponents 1 and 2) had opposed the patent, one of them (opponent 2) withdraw its opposition on 8 February 2000 before the decision of the opposition division and, thereby, ceased to be a party to the opposition proceedings. Opponent 1 is the present respondent.
- III. The patent had been opposed on the grounds as set forth in Articles 100(a) and (b) EPC that the invention was not new (Article 54 EPC), did not involve an inventive step (Article 56 EPC) and was not sufficiently disclosed (Article 83 EPC) and on the ground as set forth in Article 100(c) EPC that the patent contained added matter (Article 123(2) EPC).
- IV. Reasons for the revocation were presence of added matter with respect to granted claim 1 (to which the main request was directed), lack of inventive step of claim 1 of the first auxiliary request filed on 10 February 2000 then on file, and lack of clarity of claim 1 of the second auxiliary request filed on the same date.

- V. The appellant filed an appeal, paid the appeal fee and submitted a statement of grounds of appeal. Reimbursement of the appeal fee was requested in view of the absence in the written decision of any reference to certain verbal statements made by the opposition division at the oral proceedings, which absence was alleged to amount to a substantial procedural abuse justifying a refund of the appeal fee.
- VI. In the statement of grounds of appeal the appellant indicated that its claim requests were the main request and the first auxiliary request on which the decision of the opposition division was based. New documents were filed.
- VII. The respondent filed observations as well as new documents in reply to the statement of grounds of appeal submitting *inter alia* that both requests on file offended against Article 123(2) EPC.
- VIII. A communication under Article 11(2) of the Rules of Procedure of the Boards of Appeal presenting some preliminary and non-binding views of the board was then sent to the parties. It was in particular indicated therein that the issues to be considered at oral proceedings were, in the order, those of Articles 123(2), 83 and 56 EPC.
- IX. With a letter of 11 September 2003 the respondent withdrew its request for oral proceedings.
- X. On 6 October 2003 the respondent filed a CD-ROM containing a digital version of a videotape already on

file. The appellant objected to the admission of this CD-ROM into the proceedings.

XI. On 29 October 2003, the appellant informed the board that it would not be represented at the scheduled oral proceedings and requested that the decision be taken on the basis of the written submissions.

XII. The oral proceedings took place on 12 November 2003 in the absence of the parties.

XIII. Claim 1 of the **main request** read:

"1. The use of in vitro maturation of a bovine oocyte in the production of a transgenic bovine species of desired phenotype."

XIV. Claim 1 of the **auxiliary request** read:

"1. The use of in vitro maturation of a bovine oocyte in the production of a transgenic bovine species capable of producing a recombinant polypeptide in the milk of lactating females of said species, wherein the transgene is heterologous to its promoter and is under the control of expression regulation sequences which are derived from a gene which is expressed primarily in the mammary gland."

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

Main and auxiliary requests (Article 123(2) EPC)

The application as filed dealt in general with transgenic bovine species and in particular with methods "*for producing transgenic non-human mammals having a desired phenotype*" (see page 1, lines 4 and 5). The sentence starting at line 18 on page 11 taught generally about introducing a transgene into an embryonal target cell of the animal of choice. As shown by the sentence starting at line 18 on page 15 which recommended that generally appropriate expression regulation sequences be derived from genes "*that are expressed primarily in the tissue or cell type chosen*", the application as filed clearly envisaged expression other than in the mammary gland, i.e. effectively any phenotype, in the context of introducing a transgene into an embryonal target cell.

The question for the skilled person, therefore, was how in detail to introduce the transgene into the embryonal target cell. Relevant description was to be found in the passage starting at line 13 on page 28. This passage dealt with the question of introducing transgenes into embryonal target cells, and specifically referred to the microinjection of the transgene into the pronuclei of fertilized oocytes of the non-human animal.

Accordingly, the next question for the skilled reader was how to provide the fertilised oocytes in question.

On this question the specification provided a clear teaching in Example 6. It was quite true that reference was made therein to microinjection into *in vitro*

matured oocytes of a transgene encoding for the expression and secretion of human lactoferrin, but there was no question of the skilled person believing or considering of necessity that this was the only possible application of *in vitro* matured oocytes. It would have been clearly apparent to the skilled person that the general description by reference to *in vitro* maturation of the oocytes and to *in vitro* fertilisation which followed, not to mention the subsequent description of *in vitro* culture of the fertilised oocytes, contained nothing which was specific to a human lactoferrin-encoding transgene. In this respect, all the Examples which involved introduction of a transgene used the same *in vitro* maturation technique.

The skilled reader knew from the application as filed that in order to perform the transgene microinjection he had to obtain a supply of fertilised oocytes. As bovine oocytes could only be matured *in vivo* or *in vitro*, the use of *in vitro* matured oocytes as one possible technique would have been apparent **implicitly** to the skilled person **even in the complete absence of Example 6**.

The skilled person when considering the application as filed could determine that at least the possibility of the use of *in vitro* maturation of bovine oocytes was contemplated for the production of a bovine transgenic species of any phenotype. This was enough to establish implicit disclosure and enough to meet the requirements of Article 123(2) EPC.

XVI. The respondent's arguments in writing, insofar as they are relevant to the present decision, may be summarised as follows:

Main and auxiliary requests (Article 123(2) EPC)

The application as filed disclosed *in vitro* maturation in Examples 6 and 7, and by implication in Example 10. Examples 6 and 7 related exclusively to how human lactoferrin might be produced in transgenic cattle, and Example 10 related to the potential production of human serum albumin.

All that was derivable directly and unambiguously from the application as filed was the production of human lactoferrin and human serum albumin from transgenic cattle produced from *in vitro* matured oocytes. There was no disclosure of the use of *in vitro* maturation of oocytes in relation to the preparation of transgenic cattle capable of producing any other protein.

The application as filed did not disclose the combination of *in vitro* maturation of oocytes and the production of any protein in transgenic cattle. In contrast, it was certainly ambiguous as to whether an individual feature of the embodiment of Examples 6, 7 and 10 was broadly applicable, in the complete absence of any generalising language.

There was nothing in the general part of the application as filed that even mentioned *in vitro* maturation of oocytes, let alone gave it any significance.

XVII. The appellant requested in writing that the decision under appeal be set aside and that the patent be maintained as granted or, auxiliarily, on the basis of the auxiliary request filed on 10 February 2000. It also requested the reimbursement of the appeal fee.

XVIII. The respondent requested that the appeal be dismissed.

Reasons for the Decision

Main request

Claim 1 (Article 123(2) EPC)

1. Claim 1 is directed to the use of ***in vitro* maturation of a bovine oocyte** in the production of **a transgenic bovine species of desired phenotype**. Thus, protection is sought for transgenic bovine species of **any** desired phenotype obtained as the result of a process initiated by the use of **any** protocol of *in vitro* maturation of bovine oocytes.
2. As accepted by the appellant, the general part of the description of the application as filed does not explicitly disclose the *in vitro* maturation technique.
3. In its reasoning the appellant relies essentially only on a passage of the application which is part of a paragraph beginning at line 12 of page 28 and finishing at line 16 of page 29. The paragraph contains general comments on methods of introducing transgenes into embryonal target cells of **the non-human animal** and more specifically refers in general terms to **microinjection**

- of the transgene into the pronuclei of fertilised oocytes** and the subsequent *in vitro* culture of those oocytes until a pre-implantation embryo is obtained which is thereafter transferred to an appropriate female to permit the birth of a transgenic animal.
4. The board notes that the place in the application as filed where reference is made to *in vitro* maturation (IVM) of oocytes is in Examples 6 and 7 where the microinjection of a transgene encoding human lactoferrin (hLF) into bovine oocytes, matured and fertilised *in vitro*, is described. The protocol used for IVM is given in Example 6 with reference to the experimental study of Sidard et al. (1988), Biol. Reprod., Vol. 39, pages 546 to 552 (D4).
 5. Neither the general part of the description as filed nor any one of the sixty-two claims as originally filed make any reference in general to IVM as the technique to be used in order to obtain the oocytes to be fertilised. Neither is any particular significance accorded to IVM in the particular examples in question so as to make their teaching go beyond the specificity of the protocol used or of the transgene introduced. The passage of the description on page 28 referred to by the appellant merely refers to fertilised oocytes and is totally silent as to the manner in which the oocytes are obtained.
 6. In the board's judgement, the fact that it was known in the art that oocytes could be obtained by either *in vivo* or *in vitro* maturation does not allow a generalisation of the specific teaching of Examples 6 and 7 (specific protocol for IVM, specific gene

microinjected) to the use of **any** IVM protocol in the production of a transgenic bovine species of **any** desired phenotype. This is because the description of the application as filed fails to give any indication that the concept of having the oocytes recovered from the ovaries matured *in vitro* is indeed at the basis of any invention, and thus the unemphasized use of a specific IVM protocol in Examples 6 and 7 is to be seen as an experimental detail which cannot support the generalisation proposed in claim 1 of the main request.

7. Nor is the board convinced by the appellant's argument (see bottom of page 13 of the statement of grounds of appeal) that "all the Examples which involve introduction of transgene use the same IVM". As it may be inferred from the passages referred to by the appellant (namely, page 68, lines 20 to 23 and page 79, lines 14 to 18), the further Examples which are meant in that statement are Examples 10 and 16 which describe each the construction of a transgene, one encoding human serum albumin (hSA) (Example 10) and one encoding human protein C (Example 16). The afore-mentioned passages are no more than mere statements respectively indicating that the transgene of Example 10 is used "to produce transgenic bovine species producing hSA in their milk **in a manner analogous to that used to produce hLF in the milk of bovine species**" (emphasis added by the board) and that the transgene of Example 16 "is used to **generate transgenic bovine species as previously described**" (emphasis added by the board). Such statements cannot be equated with an unambiguous disclosure showing that said transgenes are to be microinjected into *in vitro* matured bovine oocytes.

8. For the above reasons, the board finds that the subject-matter of claim 1 has no support in the application as filed and, thus, offends against the provisions of Article 123(2) EPC. The request as a whole is therefore not allowable.

Auxiliary request

Claim 1 (Article 123(2) EPC)

9. Claim 1 of this request in comparison to claim 1 of the main request is limited to the use of IVM in the production of transgenic female bovine species capable of producing in their milk **any** desired polypeptide, this being achieved by expression of a gene heterologous to its promoter and under the control of expression regulation sequences derived from a gene which is expressed primarily in the mammary gland.
10. For the reasons given above in respect of claim 1 of the main request, the board considers that the content of the application as filed does not allow a generalisation of the specific teaching of the Examples 6 and 7, where a specific IVM protocol was used for producing fertilised bovine oocytes into which a transgene encoding hLF is microinjected, to a general use of IVM producing **any** polypeptide in the milk of transgenic female bovine species.
11. Thus, also claim 1 of this request is considered not to have support in the application as filed and, consequently, to offend against the provisions of

Article 123(2) EPC. The request as a whole is therefore not allowable.

Reimbursement of the appeal fee (Rule 67 EPC)

12. In its submissions the appellant requested a refund of the appeal fee consequent upon omissions in the written decision being viewed as a substantial abuse justifying a refund. According to Rule 67 EPC a reimbursement may only be ordered in the event that the Board of Appeal deems an appeal to be allowable. This is not the case. Thus the request for reimbursement is refused. The board would add that the alleged omissions were not relevant to the reasoning of the opposition division in revoking the patent, so that there was no non-compliance with Rule 68 EPC or any other substantial procedural violation.

Order

For these reasons it is decided that:

1. The appeal is dismissed.
2. The request for reimbursement of the appeal fee is refused.

The Registrar:

The Chairman:

A. Wolinski

L. Galligani