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Veröffentlichung im Amtsblatt	Ja/Nein
Publication in the Official Journal	Yes/No
Publication au Journal Officiel	Oui/Non

Aktenzeichen / Case Number / N° du recours : T 283/86 - 3.3.2

Anmeldenummer / Filing No / N° de la demande : 81 303 824.7

Veröffentlichungs-Nr. / Publication No / N° de la publication : 0 047 600

Bezeichnung der Erfindung: Bovine pre-growth and growth hormone
Title of invention:
Titre de l'invention :

Klassifikation / Classification / Classement : C12N 15/00

ENTSCHEIDUNG / DECISION

vom / of / du 17 March 1989

Anmelder / Applicant / Demandeur : The Regents of the University of California

Patentinhaber / Proprietor of the patent / Titulaire du brevet :

Einsprechender / Opponent / Opposant :

Stichwort / Headword / Référence :

EPÜ / EPC / CBE Art. 83

Schlagwort / Keyword / Mot clé : "sufficient disclosure - yes"

Leitsatz / Headnote / Sommaire

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Case Number : T 283/86 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 17 March 1989

Appellant : The Regents of the University of California
2199 Addison Street
Berkeley
California 95616
USA

Representative : De Minvielle-Devaux, Ian Benedict Peter
CARPMAELS & RANSFORD
43, Bloomsbury Square
London WC1A 2RA
GB

Decision under appeal : Decision of Examining Division 023 of the European Patent Office dated 16 January 1986, posted on 12 March 1986, refusing European patent application No. 81 303 824.7 pursuant to Article 97(1) EPC

Composition of the Board :

Chairman : P. Lançon

Members : G. Szabo
O. Bossung
G.D. Paterson
P. Rotter

Summary of Facts and Submissions

I. European patent application no. 81 303 824.7, filed on 21 August 1981 and published on 17 March 1982 with publication number 47600 was refused by the decision of the Examining Division of the European Patent Office given on 16 January 1986 and notified on 12 March 1986 on the basis of 21 claims according to the main request and 18 claims according to an auxiliary request. Claims 1, 4 and 5 of the main request are worded as follows:

"1. A DNA transfer vector comprising a deoxynucleotide sequence coding for bovine pre-growth hormone, said deoxynucleotide sequence comprising a plus strand having the sequence:

5′ - ATG ATG GCT GCA GGC CCC CGG ACC TCC CTG
CTC CTG GCT TTC GCC CTG CTC TGC CTG CCC TGG ACT CAG GTG
GTG GGC GCC TTC CCA GCC ATG TCC TTG TCC GGC CTG TTT GCC
AAC GCT GTG CTC CGG GCT CAG CAC CTG CAC CAG CTG GCT GCT
GAC ACC TTC AAA GAG TTT GAG CGT ACC TAC ATC CCG GAG GGA
CAG AGA TAC TCC ATC CAG AAC ACC CAG GTT GCC TTC TGC TTC
TCC GAA ACC ATC CCG GCC CCC ACG GGC AAG AAT GAG GCC CAG
CAG AAA TCA GAC TTG GAG CTG CTT CGC ATC TCA CTG CTC CTC
ATC CAG TCG TGG CTT GGG CCC CTG CAG TTT CTC AGC AGA GTC
TTC ACC AAC AGC TTG GTG TTT GGC ACC TCG GAC CGT GTC TAT
GAG AAG CTG AAG GAC CTG GAG GAA GGC ATC TTG GCC CTG ATG
CGG GAG CTG GAA GAT GGC ACC CCC CGG GCT GGG CAG ATC CTC
AAG CAG ACC TAT GAC AAA TTT GAC ACA AAC ATG CGC AGT GAC
GAC GCG CTG CTC AAG AAC TAC GGT CTG CTC TCC TGC TTC CGG
AAG GAC CTG CAT AAG ACG GAG ACG TAC CTG AGG GTC ATG AAG
TGC CGC CGC TTC GGG GAG GCC AGC TGT GCC TTC TAG- 3′

wherein
A is deoxyadenyl,
G is deoxyguanyl,

C is deoxycytosyl and
T is thymidyl.

4. The DNA transfer vector of Claim 1 wherein said transfer vector is the plasmid pBP348, or a plasmid differing therefrom only in the length of the poly(A) and/or poly(C) portions thereof.

5. A microorganism transformed by the transfer vector of any of Claims 1 to 4.

II. The ground for the refusal was that:

(1) The process for the production of the specific plasmid pBP348 of Claim 4 as described on original and published pages 20 to 21, line 2 was not exactly repeatable, since the starting materials, mentioned on page 20, lines 3 to 4, namely the pituitaries of an individual female bovine animal were not described in a way as to suffice the requirements of Article 83 EPC. When using a different donor for the pituitaries as starting material to produce the specific plasmid claimed in Claim 4 same plasmid might not be reproducible in an identical way because of the allelic variation phenomenon. Further the exact length of the poly G/C stretches flanking the cDNA transcript was not disclosed either. Therefore Claim 4 and pages 20-22 of the specification were not allowable under the said Article.

(2) Claim 5 of the main request was not allowable under Article 83 EPC because the scope of the broadly and generally drafted Claim 5, defining a "microorganism" per se, includes embodiments which at the date of filing the application could not be prepared by a man skilled in the art without practising inventive skill or undue experimentation.

(3) Said reasons for the non-allowability of Claims 4 and 5 of the main request applied correspondingly to the auxiliary request.

III. A Notice of Appeal was filed on 10 May 1986 together with payment of the appeal fee, and a Statement of Grounds was submitted on 28 June 1986.

The Appellant submitted substantially the following arguments in support of the appeal:

(1) The basis for the Examining Division's finding that the processes described in examples 1, 10(A) and (B) are not repeatable - a finding which leads to non-allowability of Claim 4 and thus implicitly of Claim 1 -, was the assertion that the use of a different animal donor in the procedure of example 1 would not necessarily lead to the defined plasmid pBP348, which is a unique chemical compound because of "the allelic variation phenomenon". It was denied explicitly that allelic variations in the bovine growth hormone gene did exist, and it was further submitted that even if allelic variations existed, it would be most surprising if there were more than a very small number of differences in the sequences of growth hormone genes between individuals of the same species, which differences, if any, would not affect the coding function of the gene.

The Examining Division had not provided any evidence for the existence of allelic variations of the bovine growth hormone.

(2) For supporting the view about the extent of the burden of proof in the case of objections under Article 83

EPC, objections should be supported specifically by a published document.

(3) Article 83 was to be understood as requiring that the application as a whole was to "disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art", rather than that all the specific examples should be exactly repeatable. An application did not fail to describe how to carry out the invention, if an attempt by a skilled person to reproduce a particular example actually produced an embodiment of the invention which might differ in some insignificant respect from the one which was specifically described in the respective example.

A DNA-sequence representing a putative allelic variant would be substantially the same as the recited sequence and thus would form part of the present invention.

(4) Also any variations of the DNA-sequence of the plasmid pBP348, claimed in Claim 4, for example poly G/C stretches of varying length, were equally immaterial with respect to the reproducibility of the claimed invention, in this case the claimed plasmid.

IV. In response to a Communication of the Board pursuant to Article 110(2) EPC, issued on 22 March 1988, suggesting that the Board was not convinced that Claim 5 was allowable, the Appellant requested that the claims on file be amended such that in Claims 5, 6 and 7 of the main request and the auxiliary request respectively, the words "microorganism" and "bacterial, yeast or animal cell" respectively should be changed to the word "bacterium".

V. The Appellant requests that the decision of the Examining Division to refuse this application be set aside, and that a patent be granted on the basis of the claims of the main request, or, in the alternative on the basis of the auxiliary claims, amended as set out above under paragraph IV, respectively.

Reasons for the Decision

1. The appeal is admissible.

2. No formal objections according to Article 123(2) can be raised against the present wording of the claims, i.e. limitation to "bacterium", which are adequately supported by the disclosure (cf. Examples 10A and 10B).

3. Claim 4 of the main request relates to a DNA transfer vector of Claim 1 wherein said transfer vector is the plasmid pBP348 or a plasmid differing therefrom only in the length of the poly (A) and/or poly (C) portions thereof. Claim 4 comprises by reference to Claim 1 a deoxynucleotide sequence coding for bovine pre-growth hormone, having a sequence which is exactly defined and consists of 218 codons or 654 nucleotides defined by the respective capital letters. The DNA-sequence claimed in Claim 1 and contained by reference in the plasmid pBP348, claimed in Claim 4, provides complete genetic information for the expression of the bovine pre-growth hormone, and thus by definition is called a "gene". In nature within a defined systematical entity, usually a species, the phenomenon "gene" may exist in variants. There are two types of variants; either the DNA-sequence differs from the original gene while the proteins are nevertheless identically the same, - this phenomenon is a consequence of the genetic code being degenerate - or there are some differences in the DNA-sequences which code for proteins

which have different molecular structures but still function equally or very similarly in use. Genes of the latter type are called "allelic" genes or "alleles". It is known in some cases that certain genes occur in a degenerated or allelic form. In man, for example, there are three alleles governing the blood type, namely A, B and O. In the large majority of cases it is not known whether or not a natural protein, and thereby the corresponding gene, exists in allelic variations.

4. According to the present patent application it is apparently possible to repeatedly produce by recombinant DNA technique bovine growth pre-hormone cDNA. According to example 1 (page 20) of the specification female bovine pituitaries were collected and total RNA was prepared from these pituitaries. Starting from this crude source of RNA the known schedule of preparing the desired DNA coding for bovine re-growth hormone was followed, including the selection of polyadenylated RNA, transcribing this RNA into cDNA using reverse transcriptase. The cDNA was then combined with one of the usual expression plasmids for the final production of bovine pre-growth hormone coded by the isolated cDNA. According to Example 2, the cDNA sequence was analysed and the result is represented by the DNA-sequence claimed in Claim 1. According to Examples 3 to 10 of the specification in which variations of Example 1 are described, relating for example to different expression vectors or different host organisms, reference is made to Example 1, as far as the isolation of the RNA from bovine pituitaries and the following isolation preparation of the respective cDNA and to Example 2 as far as the sequence analysis of the latter is concerned. This implies already that according to the specification the isolation, preparation and analysis of the DNA sequence claimed in Claim 1 has been done repeatedly and in all cases resulted in the same, namely the claimed, DNA-sequence.

5. In the absence of evidence to the contrary it is the Board's view that the unique character of the hormone is prima facie established. Under these circumstances requirements for reproducibility of the preparation of a defined DNA-sequence is not to doubt. There seems to be no room for objections under Art. 83 EPC based on unsupported and possibly speculative knowledge.

6. Claim 4 relates to a recombinant plasmid, namely pBP348, comprising the DNA-sequences of Claim 1 and thus reproducibility in the sense of Article 83 EPC is also given as far as the said DNA-sequence is concerned. The claimed plasmid comprises, however, further defined DNA-sequences, sufficient disclosure of which has to be examined.

7. According to Example 1 of the application plasmid pBP348 was constructed using the plasmid pBR322, which is well known in the art as being one of the most used plasmids. This basic plasmid is freely available in many laboratories and depositories all over the world and described and sequenced in detail (Bolivier et al., Gene 2, 1977). The combination of this well known plasmid and the DNA-sequence defined in Claim 1, will always necessarily lead to the plasmid pBP348 as claimed in Claim 4 or to a plasmid differing therefrom only in the length of the poly (A) and/or poly (C) portions thereof. Tailing cDNAs and plasmids with one of the four nucleotides and its complement, respectively, improves the annealing process between the cDNA and the plasmid DNA. It is described for instance on page 13, lines 2-12 in general and in Example 1 (page 21, lines 7, 8 and 14) in detail, how to prepare dC-tailed double-stranded cDNA for the insertion of that cDNA into a cleaved and complementary dG-tailed plasmid pBR322. A dA-tailing may be in some cases more convenient and can be carried out in an analogous way to dC-tailing. The choice depends on the

circumstances and can be made by using common general knowledge, as can the variation of the length of the poly A-and/or poly C-portions. Plasmid pBR348 as claimed is thus a derivative of commonly known plasmid pBR322, which is evident for the skilled person by the nomenclature "pBR". It has previously been decided by a Board of Appeal that an invention is sufficiently disclosed if at least one way is clearly indicated enabling the person skilled in the art to carry out the invention (T 292/85, Polypeptide expression/GENENTECH I, dated 27 January 1988, to be reported in the O.J. EPO). According to Examples 1 and 2 of the present application one way to prepare the plasmid pBP348 is disclosed. In the Board's judgement, the requirements of Article 83 EPC are thus fulfilled with regard to the subject-matter specified in Claim 4.

8. As to the grounds of refusal of the application presented under point 4.1 of the impugned decision, to the effect that examples in a specification have to be identically repeatable, reference is made to another decision of the Board of Appeal (T 281/86 of 27 January 1988, Preprothaumatin/UNILEVER, to be reported in the O.J. EPO) in which the Board came to the conclusion that "there is no requirement under Article 83 EPC to the effect that a specifically described example of the process must be exactly repeatable. Variations in the constitution of an agent (here: Genetic precursors) used in a process are immaterial to the sufficiency of the disclosure provided the claimed process reliably leads to the desired product". For the reasons stated above there is no evidence in the present case that a skilled man working according to Examples 1 and 2 could not reliably produce a plasmid having the features of plasmid pBR348 or variants thereof as claimed. Thus in the Board's judgement no insufficiency under Article 83 EPC arises on account of the preparation of plasmid pBR348 according to the examples.

9. By restricting Claims 5, 6 and 7 to a "bacterium" there are no longer objections to these claims under Article 83 EPC, which are thus also allowable in this respect.

10. The Examining Division accepted the novelty of the refused claims, but it appears that there has not yet been a substantive examination as far as inventiveness is concerned. The Board therefore remits the case to the Examining Division for further prosecution, on the basis of the claims of the present requests.

Order

For these reasons, it is decided that:

1. The decision of the first instance is set aside.

2. The case is remitted to the Examining Division for further prosecution.

The Registrar: The Chairman:

F.Klein P.Lançon