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Bezeichnung der Erfindung: DNA transfer vector, host transformed with it, vaccine, and their production
Title of invention:
Titre de l'invention :

Klassifikation / Classification / Classement : C12N 15/00

ENTSCHEIDUNG / DECISION

vom / of / du 29 August 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 : Hepatitis B Virus/UNIVERSITY OF CALIFORNIA

EPÜ / EPC / CBE Articles 83, 84; Rule 29

Schlagwort / Keyword / Mot clé : "Sufficiency (yes) - claimed plasmids and unclaimed plasmids"
"Clarity (yes) - wording in terms of problem/solution - no obligation"

Leitsatz / Headnote / Sommaire

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Case Number : T 181/87

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 29 August 1989

Appellant : The Regents of the University of California
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Decision under appeal : Decision of Examining Division of the European Patent Office dated 02.12.86 refusing European patent application No. 80 400 722.7 pursuant to Article 97(1) EPC

Composition of the Board :

Chairman : P. Lançon

Members : U. Kinkeldey
P. Rotter } Co-Rapporteurs
E. Persson
R. Schulte

Summary of Facts and Submissions

I. European patent application 80 400 722.7 was filed on 23 May 1980 and published on 10 December 1980 with publication No. 20251. Priority was claimed from US-applications 41 909 and 107 267 filed on 24 May 1979 and 26 December 1979 respectively. The application was refused on the basis of Claims 1-4, 7, 12, 16 and 21 by the decision of the Examining Division of the European Patent Office dated 2 December 1986. All relevant claims are worded as follows:

1. A DNA transfer vector comprising at least a portion of the nucleotide sequence encoding the hepatitis B surface antigen and being substantially free of the nucleotide sequence encoding the hepatitis B core antigen.

6. The transfer vector of Claim 5 wherein the vector is pEco-63 and the host is E. coli HB 101.

7. A method for maintaining, replicating, and expressing the DNA transfer vector of Claim 1 comprising, isolating the genetic material comprising at least a portion of the nucleotide sequence encoding hepatitis B surface antigen,

recombining the genetic material with a DNA transfer vector, forming a recombinant transfer vector,

transforming a host cell with the recombinant transfer vector,

selecting a host cell strain capable of maintaining, replicating, and expressing the recombinant transfer vector, and

growing the selected host cell under conditions favouring its proliferation, thereby maintaining,

replicating, and expressing at least a portion of the nucleotide sequence encoding hepatitis B surface antigen.

10. A vaccine according to Claim 9 wherein the protein comprises HB_SAg protein.

12. A method of making a vaccine against hepatitis B virus comprising the steps of

(a) transforming a microorganism with a DNA transfer vector of Claim 1, said nucleotide sequence being inserted in a region of the transfer vector controlled by an expressible operon, in reading frame phase and orientation such that translation expression of said operon results in translation expression of said nucleotide sequence,

(b) growing said microorganism under growth conditions that allow expression of said operon, thereby making said immunology active protein constituent of the surface antigen of hepatitis B virus,

(c) purifying the protein made in step b, and

(d) mixing the purified protein with a sterile, physiologically acceptable diluent, thereby making a vaccine against hepatitis B virus.

15. An antigenic protein comprising the amino acid sequence of the surface antigen of hepatitis B virus and being substantially free of the amino acid sequence of

hepatitis core antigen, synthesised by a micro-organism and capable of eliciting antibodies cross-reactive with an immunologically reactive component of hepatitis B virus.

16. A microorganism containing and replicating a DNA transfer vector of Claim 1.

17. A micro-organism according to Claim 16 comprising the bacterial strain Escherichia coli HB101pEco-63.

II. The first ground for refusal was that the subject-matter of the claims cited above represent nothing but professional paraphrasing of a technical problem already known in the state of the art (Nature, Vol. 279) and thus were not allowable regarding the problem/solution concept (Rule 27(1)(d), first half sentence in connection with Article 84, first sentence and Rule 29(1), first sentence EPC). There was no real technical difference between the said underlying technical problem and the definitions given in the claims by way of solution.

The second ground for refusal was that the procedure described in the published patent application, which led to the chemical compounds pEco-3, pEco-63, pBam-69 and pBam-132, the structure of which was unknown, could not be repeated, since the starting material referred to on page 17, lines 3-5 of the application as certain individual Dane particles was not sufficiently described there. Apparently, the use of different starting material would lead to different plasmidic chemical compounds and thus there was no certainty that the procedure in question repeatedly would lead to the individual plasmids pEco-3, pEco-63, pBam-69 and pBam-132 as required by Article 83 EPC.

Further questions were left undecided in the decision, namely whether or not

(a) the non-repeatability of the procedure described on pages 17-21 of the published patent application which leads to the chemical compounds pEco-3, pEco-63, pBam-132 and pBam-69 affects the validity of the present claims and, if so, to what extent;

(b) certain requested corrections of the priority documents can be allowed;

(c) the new vector of Claim 6 and the new microorganism of Claim 17 are available either on the basis of a proper deposition according to Rule 28 EPC or by chemical synthesis;

(d) Claim 22 is allowable under Article 56 EPC;

(e) the subject-matter of Claims 9 and 10 is the same; if so, one of those would have to be deleted;

(f) Claim 18 lacks novelty;

(g) Claims 10 and 15, which relate to the "S protein", enjoy the first priority date and, if not, whether or not they are allowable under Article 56 EPC with regard to an intervening prior art document Nature, Vol. 280, page 815; and

(h) Claims 11, 13, 19 and 20 enjoy the first priority and, if not, whether or not they are allowable under Article 56 EPC with regard to intervening prior art documents (Nature, Vol. 280, page 815 and Nature, Vol. 281, page 646, which were mentioned in a communication of 14 November 1985).

III. A notice of appeal was filed on 2 February 1987 together with payment of the appeal fee, and a statement of grounds was submitted on 7 April 1987 together with new Claims 23-31.

On 15 February 1988 an alternative set of Claims 1-27 was filed by the Appellant.

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

(1) The problem underlying the claimed invention was the provision of the hepatitis B surface antigen without the hepatitis B core antigen. The solution of this problem was provided by the DNA transfer vector claimed in Claim 1, comprising at least a portion of the nucleotide sequence encoding the hepatitis B surface antigen and being substantially free of the nucleotide sequence encoding the hepatitis B core antigen. The means to solve the problem were thus clearly stated in the main claim and therefore the claim was not a mere paraphrasing the problem.

Further, the estimation of the above mentioned prior art document Nature Vol. 279 as already solving the above cited problem was not correct. Said document described the cloning of all hepatitis B virus DNA including HB_CAg DNA and HB_SAg DNA. There was no evidence nor suggestion that the product obtained was essentially free of HB_CAg and could have been used as a vaccine. These vaccines were often mentioned as a desired goal but there was no encouraging result in said document. Rather the possibility to obtain HB_SAg seemed to be very doubtful by the described experiments.

Thus, neither the prior art document Nature Vol. 279 described the invention as claimed in Claim 1 nor was this claim paraphrasing only the problem underlying the invention.

(2) The four plasmids pEco-3, pEco-63, pBam-132 and pBam-69 were examples illustrating the invention and were not claimed as such. It was not the requirement of Article 83 EPC that a certain example has to be reproducible identically. Rather, the requirement was that the European patent application must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. This requirement was fulfilled in the present case because there was described in the application the starting material for preparing vectors as claimed and a detailed procedure how to prepare the vectors as claimed. The starting material in the present case could be identified without any problem as Dane particles which had been known since 1970 (Dane et al., Lancet 695, 1970).

In the case that said Dane particles differ from each other because they were of different serotypes, the skilled worker nevertheless would be able to prepare vectors as claimed by following the sufficiently clear and complete disclosure of the present application, although the resulting plasmids might not be identical with the four individual plasmids described in preferred examples in the present application.

IV. As to the issues left undecided by the Examining Division, the Appellant offered to delete Claim 10 but otherwise contested the views of the Examining Division on the points referred to under paragraph II(a)-(h) above.

V. The Appellant requests that the decision be set aside and the application be allowed on the basis of the refused Claims 1-22 and additional Claims 23-31 filed with Statement of Grounds, or remitted to the Examining Division.

With letter of 12 February 1988, an alternative set of claims was filed; oral proceedings have also been solicited regarding questions not clearly formulated in the decision.

Reasons for the Decision

1. The appeal complies with Articles 106-108 and Rule 64 EPC and is, therefore, admissible.

2. Article 123(2) EPC

The claims upon which the refusal of the application were based were said to be allowable under Article 123(2) EPC in the impugned decision. The Board agrees with this opinion. New Claims 23-31, filed together with the grounds of appeal are also in accordance with Article 123(2) EPC, because they relate to micro-organisms (Claims 23-29) or vaccines (Claims 30-31), which are either defined by features of foregoing claims (Claims 23-25, 27-31) or (Claim 26) of the description (page 29, line 19 et sequ.).

3. Clarity (Article 84 and Rules 27(1)(d) and 29(1) EPC).

One reason for the refusal was that the application was not allowable under the above-mentioned Article and Rules.

The features of the refused Claim 1 are

(a) a DNA transfer vector,

(b) comprising at least a portion of the nucleotide sequence encoding the hepatitis B surface antigen and

(c) being substantially free of the nucleotide sequence encoding the hepatitis B core antigen.

The mentioned terms represent structural and functional features which are to be understood as "technical features of the invention" in the sense of Rule 29 EPC. For the skilled man it is clear that a DNA transfer vector consists of nucleotides which are rowed in a sequence and may comprise nucleotide sequences encoding proteins. In the present case, the character of the DNA sequence is clearly stated in the main claim. In a number of previous decisions the Board held that functional features in claims are allowable under certain conditions (inter alia T 292/85 "Polypeptide expression" of 25 January 1988, published in OJ EPO 7/1989, 275). The Board can thus not follow this part of the decision of the Examining Division stating that the objected claims do not define the matter for which protection is sought.

4. As to the "problem/solution" problem the Examining Division concluded non-allowability under Article 84 EPC of the refused claims because the problem underlying the claims was already known in the prior art as represented by the reference Nature, Vol. 279, 1979, page 43.

When analysing Article 84 in connection with Rule 27(1)(d) EPC one cannot find an **expressis verbis** obligation for a wording of the claims in terms of the problem and the solution. The requirements of Rule 27 EPC

relate to the description only and not to the claims. Connection to Article 84 which states the requirements of the wording of the claims is presented by the second sentence of Article 84 saying that the claims shall be clear and concise and be supported by the description. This does not mean that a desirable presentation of the problem underlying the invention and the technical solution of this problem in the description has to be repeated in the claims. The "problem/solution" system has been developed by the jurisprudence of the Boards of Appeal as a basis for answering the question of inventiveness. In this context, it is to be understood that the "problem" is defined in relation to the closest prior art and the "solution" represents the claimed invention.

5. Whether or not the description fulfils the requirement of Rule 27(1)(d) EPC has to be examined by analysing the description in the light of the prior art.

6. The only prior art reference, Nature, Vol. 279, 1979, page 43, analysed by the Examining Division in its decision, relate to the preparation of hepatitis B DNA containing vectors in general; cloning and expressing of hepatitis B DNA encoding only at least a portion of the nucleotide sequence of the hepatitis B surface antigen and being substantially free of the nucleotide sequence for hepatitis B core is not subject-matter and not envisaged by the said reference. Therefore, in the Board's opinion, the problems to be solved in said reference and the present patent application are different. As a conclusion of all the above statements, the Board therefore holds the refused claim to be not in conflict with Article 84 and Rule 27(1)(d) EPC.

7. Sufficiency (Article 83 EPC).

7.1 The second ground for the refusal of the patent application was that four definite plasmids, named pEco-3, pEco-63, pBam-69 and pBam-132, whose preparation is described in the description, were not reproducible identically. It has to be pointed out here that among the mentioned plasmids the plasmid pEco-63 is subject-matter of two claims, either as such (Claim 6) or incorporated into a host bacterium (Claim 17).

7.2 The requirement of reproducibility in the sense of Article 83 that the European patent application must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art may have different effects on the identical reproducibility of specific plasmids if claimed or if described in certain examples falling under the claim.

If a plasmid is the invention, demonstrated by the fact that it is claimed, reproducibility of this definite plasmid has to be demonstrated in the European patent application.

If, however, the invention as claimed is broader than one certain example, describing the preparation of a definite plasmid, the requirements of Article 83 EPC are not such, that this example has to be reproducible identically, as long as there is evidence that the disclosure of the preparation of the specific plasmid leads reliably to plasmids which may differ from the definite mentioned plasmid but nevertheless falls under the broad term of the claim. This view has already been expressed by the Board in earlier decisions (T 292/85, Ibid.; T 281/86 "Preprothaumatin", OJ EPO 1989, 202).

7.3 As far as plasmid pEco-63 is concerned, which is the subject-matter of Claims 6 and 17, the requirement of Article 83 EPC, is considered by the Board to be satisfied by the disclosure of the patent application providing sufficient information to a person skilled in the art in order to enable him to reproduce this very plasmid.

7.4 In cases like the present one where the invention concerns a microbiological process or the product thereof, involving the use of a micro-organism, Rule 28 EPC only applies if the micro-organism is not available to the public and cannot be described in the European patent application in such a manner as to enable the invention to be carried out by a person skilled in the art. In the present case it has thus to be examined whether or not possibly the written disclosure of the patent application may enable the invention to be carried out by a person skilled in the art, or, if not, a valid deposition of the claimed micro-organism has been made. Actually, as becomes evident from the description of the published application, page 7, lines 21 to 30, the transfer vector of Claim 6 and the micro-organism, carrying the said transfer vector (Claim 17), have been deposited with a recognised depositary institution, namely the American Type Culture Collection, before the filing date of this application with the assession numbers ATCC 40009 and 31518 respectively.

7.5 The Appellant, in response to certain questions during the examination proceedings concerning the formal aspects of the depositions made, submitted that the preparation of the transfer vector and the micro-organism as claimed in Claims 6 and 17 respectively has been described in such detail in the specification that it can be carried out by a person skilled in the art. The Board has examined this question.

7.6. In example 1 of the description the preparation of the transfer vector pEco-63, being subject-matter of Claim 6, has been described. A double-stranded circular HBV-DNA was isolated from so-called Dane particles as described in the literature. It is clear from the description that this HBV-DNA contains a single site recognised by the restriction enzyme EcoRI. If a circular DNA has only one recognition site for a certain restriction enzyme the result of cleaving that circular DNA is one single strain of linear DNA. This fact is expressed in the description by stating that after treatment of the isolated DNA from Dane particles with EcoRI endonuclease resulted in a single sharp band corresponding to about 3,200 base pairs (bp) length. This linear DNA was incorporated in a well known and, in the literature, well described plasmid, named pBR325 which equally contains only one single cleavage site for the restriction enzyme EcoRI. By ligating this plasmid, cleaved by EcoRI and the equally cleaved DNA, isolated from Dane particles as described in the description on pages 17-20, line 26, recombinant hybrid plasmids like the one, named pEco-63, result. The Examiner, during the examining procedure, correctly stated that the DNA, isolated from Dane particles, may vary; it is, however, the Board's opinion that in the specific present case it is very likely that without undue burden DNA from a Dane particle can be isolated which has just one single cleavage site for the EcoRI restriction enzyme which then can be ligated to the well-known plasmid pBR325, having equally only one EcoRI restriction enzyme recognition site. It is acknowledged that even in cases like the present one which can be evaluated as a relatively simple one in the otherwise often very complicated genetic engineering procedures, there will certainly be some trial and error for obtaining a plasmid having the characteristics of the plasmid pEco-63. The Board nevertheless is of the opinion that working according to the instructions given in the specification in view of

the fact of the relatively simpleness of this specific process will reliably lead to a plasmid having the same characteristics as the claimed plasmid pEco-63.

The bacterial strain E. coli HB-101, which is also subject-matter of Claim 6, has already been described in the literature in detail and is known since 1969 (see pages 18 and 19 of the published application, lines 26-35). This particular strain is one of the most used host strains in the field of genetic engineering.

7.7 Claim 17 relates to a micro-organism comprising the bacterial strain Escherichia coli HB-101 pEco-63. Thus, the subject-matter of this claim is the mentioned definite bacterial strain, containing the plasmid pEco-63. The transformation of this known and frequently used bacterial strain with the plasmid pEco-63 also is a procedure which can be carried out by a skilled person according to the description of this application. Therefore, the requirements of Article 83 EPC are met also for the definite micro-organism claimed in Claim 17.

7.8 There are three further plasmids, plasmids pEco-3, pBam-69 and pBam-132, which, according to the impugned decision, were not identically repeatable and therefore do not fulfil the requirements of Article 83 EPC. These plasmids are not claimed but rather their production is described in the specification in certain examples. As far as plasmids pEco-3 is concerned, the facts on file provide evidence for reproducibility of these plasmids in the same way as for the claimed plasmids pEco-63, discussed above, since the plasmids pEco-63 and pEco-3 have been prepared according to the same procedure and therefore the same reasons for both plasmids apply.

7.9 Plasmids pBam-69 and pBam-132 were prepared by combining Dane-particle-DNA cleared by the restriction enzyme BamHI with equally cleared plasmid pBR322. According to the description (page 17, first paragraph), cleavage of the circular HBV-DNA, obtained from Dane particles by BamHI, produces two fragments which infer that HBV-DNA contains two BamHI recognition sites. The two BamHI fragments were separately cloned into the BamHI recognition site of the plasmid pBR322, resulting in two hybrid plasmids, one of which contained an about 2,100 bp BamHI fragment and was designated pBam-132; the other one contained a smaller fragment of about 1,100 bp, which was designated pBam-69. The plasmid, used as vector for the construction of the named hybrid plasmids, the plasmid pBR322 is the definitely most used plasmid in the field of genetic engineering and had been described at the priority date of the present application in the literature and was freely available. Again the Board believes that a skilled person would be able, without inventive skill and undue burden to prepare the plasmids in question.

It has further to be mentioned here that even if the plasmids described in the examples would not have been reproducible identically this would not necessarily, as discussed earlier result in a conflict with the requirement of Article 83 EPC as far as working according to the examples would lead to products falling under claims being broader than the specific embodiments of the examples is concerned.

8. Conclusions

8.1 It follows from the above considerations that the decision under appeal has to be set aside and the case remitted to the first instance for further prosecution. As far as the questions left undecided in that decision (cf. paragraph

II, page 4 above) the Board draws attention to the fact that the questions under (a) and (c) have been dealt with in the reasons given above for the Board's decision.

8.2 For the further examination of this application the Board also draws attention to the decision T 269/87 "Prochymosin" of 24 January 1989 (unpublished in OJ EPO) regarding claims comprising the term "pEco-63".

9. Request for oral proceeding.

According to Article 116 EPC oral proceedings shall take place at the request of any party to the proceedings. The Appellant requested that the Board should allow the application in the amended form or remit the application to the Examining Division. With letter dated 12 February 1988 the Appellant pointed out that oral proceedings were requested due to the great number of questions which had not been clearly formulated in the impugned decision. It is true that the decision under appeal mentions a number of issues which were left undecided. But these issues are no subject-matter of the decision under appeal and consequently they cannot be dealt with in the appeal proceedings. Under these circumstances and having regard to the fact that the present decision fully concurs with the case put forward by the Appellant, the Board has refrained from appointing oral proceedings.

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