BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS | BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE | CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Publication in the Official Journal ~~Yes~~ / No

File Number: T 717/89 - 3.3.2

Application No.: 82 304 515.8

Publication No.: 0 075 395

Title of invention: Products displaying the antigenicity of hepatitis B virus E antigens and methods of producing those antigens

Classification: C12P 21/06

D E C I S I O N
of 25 March 1992

Applicant: Biogen, Inc.

Headword: Hepatitis B virus E antigens/BIOGEN

EPC Article 56

Keyword: "Inventive step - (no)"

Headnote

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number : T 717/89 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 25 March 1992

Appellant : Biogen, Inc.
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Decision under appeal : Decision of Examining Division of the European Patent Office dated 26.05.89 refusing European patent application No. 82 304 515.8 pursuant to Article 97(1) EPC.

Composition of the Board :

Chairman : A.J. Nuss
Members : U.M. Kinkeldey
R.L.J. Schulte

Summary of Facts and Submissions

I. European patent application No. 82 304 515.8, published under No. 0 075 395, was refused by the Examining Division. The refusal was based on six claims. Claim 1 reads as follows:

"1. A process for producing at least one polypeptide displaying the antigenicity of hepatitis B virus e antigens comprising the steps of:

a) preparing an extract of a microbial host characterized by the expression of a polypeptide displaying the antigenicity of hepatitis B virus core antigen; and

b) digesting said extract with a reducing agent resistant protease in the presence of a reducing agent to convert the polypeptide displaying the antigenicity of hepatitis B virus core antigen into a polypeptide displaying the antigenicity of hepatitis B virus e antigens."

II. The refusal of the application was based on the ground that the application did not meet the requirements of Article 56 EPC. The arguments can be summarised as follows:

(a) Based on the disclosure of the following prior art documents:

(1) Journal of Immunology, Vol. 123, No. 3, (1979), pages 1415-1416
(2) Nature, Vol. 291, (June 1981) pages 503-506

the technical problem of the present application was to provide at least one polypeptide displaying the

antigenicity of the hepaptitis B virus e antigen (HBeAg). As a solution the applicants proposed a process which was characterised by the features of a) and b) of Claim 1.

The expression in feature b) "to convert the polypeptide displaying the antigenicity of HBcAg into a polypeptide displaying the antigenicity of HBeAg" was not considered to constitute an additional characterisation of the process since this expression merely defined the feature of the process by the result to be achieved.

(b) A process for producing polypeptides displaying the antigenicity of HBeAg by treating hepatitis core antigen particles which displayed the antigenicity of HBcAg by chemical means especially by the use of pronase and 2-mercaptoethanol was known from document (1), in particular from page 1415 in the chapter "Material and Methods". The process according to Claim 1 differed from the process described in document (1) only in that HBcAg was produced by recombinant DNA technique, whereas in document (1) the respective core particles were purified from other sources.

(c) Document (2) described the synthesis of HBcAg in a bacterial host cell like E.coli by expressing the cloned gene for HBcAg. The use of HBcAg produced by recombinant DNA technique according to the disclosure of document (2) instead of purified core particles as described in document (1) was considered as an obvious solution for the underlying technical problem within the meaning of an analogous use. In fact, once the HBcAg was available in "purer" form i.e. produced by genetic engineering, it presented itself for the use in

the known process. Thus, not only could the skilled person successfully apply the known process to purer HBcAg but rather would have applied this known process to that purified HBcAg.

III. The Appellants appealed against this decision and paid the corresponding fee. Further, a written statement setting out the grounds for appeal was filed.

IV. Together with their statement of grounds the appellants filed a new set of claims which replace the rejected claims. Claim 1 reads as follows:

"1. A process for producing at least one polypeptide displaying the antigenicity of hepatitis B virus e antigens comprising the steps of:

(a) preparing an extract of a microbial host characterised by the expression of a polypeptide displaying the antigenicity of hepatitis B virus core antigen; and

(b) digesting said extract with a reducing agent resistant protease in the presence of a reducing agent to convert the polypeptide displaying the antigenicity of hepatitis B virus core antigen into a polypeptide displaying the antigenicity of hepatitis B virus e antigens; **wherein the polypeptide displaying the antigenicty of hepatitis B virus e antigens is essentially free of primate serum polypeptides and primate liver polypeptides.**"

(The emphasised part of the claim represents the amendment made in the appeal stage).

Claim 5 was amended respectively.

V. The arguments put forward by the Appellants during the appeal proceedings can be summarised as follows:

(a) The amendment of Claim 1 and 5 respectively to recite that the polypeptides displaying HBeAg antigenicity, which were produced by the processes of this invention, were essentially free of primate serum polypeptides and primate liver polypeptides was inherent in the present invention, due to the fact that the processes employed to produce HBeAg polypeptides utilised recombinant DNA techniques. Prior to the present invention, preparations of HBeAg were derived from natural sources, for example primate serum or liver, and, therefore, they were invariably contaminated with primate serum or liver polypeptides.

(b) The technical problem facing the applicants was how to produce HBeAg by recombinant DNA means. None of the cited documents, taken alone or in combination, taught or suggested how to solve this problem. This mechanism of production was important in that it allowed, for the first time, the production of commercially feasible quantities of HBeAg; it further enabled the production of HBeAg essentially free of primate serum polypeptide and primate liver polypeptides and finally it identified the portion of the HBV genome which encoded HBeAg. In this connection it was critical to distinguish the term "HBcAg", referring solely to the individual hepatitis B virus core antigen polypeptide from the term "core particle" which denoted a structure containing HBcAg on its surface and any of a number of other polypeptides inside of this structure. The authors of document (1) improperly used these terms interchangeably and actually in a confusing manner. This confusion might have led the Examining Division to an erroneous judgment of the inventive step.

A critical feature of the present invention was the demonstration, for the first time, that HBcAg could be converted to HBeAg. Prior to the present invention, the question of whether HBeAg was released from the core particle or constituted a degradation/denaturation product of one of its components remained unanswered. Therefore, the expression "to convert ...", which was said by the impugned decision to not constitute an additional characterisation of the process of Claim 1 was not just that but rather was a key technical feature of this invention.

(c) It was agreed with the impugned decision to the extent that the process of document (1) and the present invention employed digestion with a reducing agent resistant protease in the presence of a reducing agent or dissociation in the presence of a reducing agent. However, the question of inventive step could not be determined without viewing the process as a whole. This included not only an examination of specific process steps, but additionally the starting material and the final product of the overall process period. Both of these were essential to the invention as a whole and neither was disclosed or suggested in document (1). Rather, the starting material employed in the process of document (1) was drastically different from that used by the applicants. Actually, in document (1) it is stated that the analysis of the degradation product besides of the core protein showed the presence of any number of minor polypeptides not detectable above the background variation which must await further clarification. Therefore, it was impossible to determine whether the HBeAg prepared according to the process of document (1) was a degradation product of HBcAg, and a degradation of one of the other

polypeptides, or merely one of the several polypeptides, other than HBcAg, present in their core particle preparation. In contrast, a HBcAg preparation by recombinant DNA techniques did not contain any other hepatitis B virus proteins (except some HBeAg resulting from in vivo conversion). As a result of employing this starting material the recombinant production of HBeAg was able and conclusively it was proved that HBeAg was derived from HBcAg.

(d) The Examining Division's contention that the use of recombinant hepatitis B virus core antigen as disclosed in document (2) instead of core particles used for the process in document (1) was "an obvious solution for the underlying technical problem (analogous use)" was contested, because the core particle comprised a polypeptide shell which encapsulated other polypeptides and nucleic acids. The shell was composed of hepatitis B virus core antigen. Cryptically located within the shell were components such as viral DNA, DNA polymerase and, according to belief of those skilled in the art prior to applicants' invention, HBeAg. Thus, core particle shell and the sole component that made up the shell are not analogous. It was repeatedly emphasised that the application of the inventive process was the only way to definitely clarify the connection of HBcAg and HBeAg on a molecular level.

(e) As to the Examining Division's question in its impugned decision "whether the skilled person once having the possibility to prepare HBcAg in pure form would apply the known (conversion) process to said purified HBcAg", the answer was "no". Nothing in document (1) suggested that their process converts HBcAg (or any other polypeptide present in their core particle preparation) to HBeAg. None of the data presented in document (1)

contradicted the prevalent view prior to the present invention that HBeAg was a polypeptide present inside of the core particle, separate and distinct from HBcAg and encoded by its own gene. Neither the exposure of HBeAg after digestion/denaturation of core particles, nor the loss of HBcAg antigenicity following those treatments suggested that HBeAg derived directly from HBcAg. It seemed highly unlikely that one of ordinary skill in the art would have suspected that treatment of HBcAg with 2-mercaptoethanol and pronase or 2-mercaptoethanol and SDS, would convert one known HBV antigen (HBcAg) to another HBV antigen (HBeAg). Taking all remarks about the relationship between HBeAg and HBcAg into account which were contained in document (1) there was no motivation to apply the technique disclosed in document (1) to a HBcAg prepared by recombinant DNA techniques. If anything, document (1) taught extraction of HBeAg from the core particle. Thus, the Examining Division's conclusion was based on a hindsight approach, working backwards from the disclosure of the present invention.

As it was demonstrated that the core particles described in document (1) were contaminated with other polypeptides and in view of the amendments in the newly filed claims, patentability over the documents cited by the Examining Division was evident.

VI. The Appellants request that the decision be set aside and a patent be granted on the basis of the set of claims filed together with the statement of grounds for the appeal. Auxiliarily they request the case to be remitted to the Examining Division for further prosecution.

Reasons for the Decision

1. The appeal is admissible.

2. Amendments (Article 123(2) EPC)

The new feature having been added in newly filed Claims 1 and 5, characterising the polypeptide displaying the antigenicity of hepatitis B virus e antigens by their being essentially free of primate serum polypeptides and primate liver polypeptides is not described explicitly in the originally filed patent application. However, as a matter of fact, it is self-evident and unequivocal that polypeptides produced by recombinant DNA technique cannot be contaminated with primate serum or liver polypeptides. The new features in Claims 1 and 5 represent a technical effect which, although not spelled out literally in the application, is unambiguously derivable from the whole disclosure of the application. Thus, the new set of claims is allowable with regard to Article 123(2) EPC.

3. Novelty (Article 54 EPC)

None of the prior art documents cited in the proceedings describe a process as claimed and thus the question of novelty is not at issue.

4. Problem and Solution

4.1 To investigate the problem underlying the patent application the Board considers document (1) to be the closest prior art. This document describes the identification of two HBeAg subspecifities revealed by chemical treatment and enzymatic digestion of liver-derived HBcAg. The HBcAg was isolated by a known method from human liver and the purified HBcAg produced a distinct precipitin line when tested by immunodiffusion against standard human

anti-HBc. When separate samples of HBcAg were treated with SDS and 2-mercaptoethanol or digested with pronase and subsequently examined by immunodiffusion, HBeAg specificity was found in both samples, whereas HBcAg specificity was no longer present. In this study the cryptic localisation of HBeAg in the core particle was confirmed. The teaching of document (1), addressed to the skilled person, is that HBeAg can be prepared by using HBcAg as starting material and digesting or treating it as described (see page 1415, right column, chapter "Results and Discussion", first paragraph).

4.2 If it is desired to use the HBeAG protein in compositions and methods for the detection of antibodies to HBeAgs in human blood serum and for the preparation of antibodies to these HBeAgs for use in the detection of HBeAgs in the blood serum or liver of potentially infective carriers of HBV, the man skilled in the art is confronted with the drawbacks of the known process to isolate HBeAg as described in document (1), namely that the desired protein is contaminated by hundreds of other undesired proteins derived from natural sources like primate serum or liver.

Starting from document (1) the problem underlying the patent application thus can be seen in the preparation of HBeAg unaccompanied by contaminating primate serum or primate liver polypeptides.

4.3 This problem is solved in the patent application as described in Claim 1 by preparing an extract of a microbial host characterised by the expression of a polypeptide displaying the antigenicity of hepaptitis B virus core antigen and digesting said extract with a reducing agent resistant protease in the presence of a reducing agent to convert the polypeptide displaying the antigenicity of HBcAg into a polypeptide displaying the antigenicity of HBeAg.

The description of the patent application, in particular the chapter "Recombinant Plasmids" on page 9, from line 15 and examples 1 and 2 provide evidence that the stated problem was actually solved by the applicants.

5. **Inventive step (Article 56 EPC)**

5.1 The question is whether or not, starting from document (1), the claimed process was obvious to a skilled person with regard to the knowledge disclosed by document (2).

5.2 When trying to find a solution to the above stated problem, the man skilled in the art would certainly have noticed that document (2) describes the production of HBcAg free of serum and liver contamination by recombinant DNA technique in a bacterial host cell like E.coli by expressing the cloned gene for HBcAg, because it is self-evident that this method of production does not lead to products contaminated by primate serum polypeptides and primate liver polypeptides. In view of this advantage, he would not have hesitated to use the known recombinant technique for preparing products displaying HBeAg antigenicity instead of the method of preparation described in document (1). Consequently, although the claimed process differs from the closest prior art method in that it ensures that the polypeptide displaying the antigenicity of HBeAg is essentially free of primate serum polypeptides and primate liver polypeptides, as it is now expressively mentioned in both Claims 1 and 5, this features is to be considered as obvious for the reason that it is nothing else than the unavoidable effect resulting from another requirement expressed in the claims, namely that HBeAg is prepared by recombinant DNA techniques which the man skilled in the art would have tried to apply in order to obtain products free of contaminating primate serum and liver polypeptides.

5.3 The Board agrees with the Appellants' argument that the teaching of document (1) does not provide clear knowledge about the relationship between HBcAg and HBeAg on a molecular level. Actually in document (1), on page 1416, left column, paragraph 2 it is stated that the difference between the two HBeAgs, described in that document, exposed by the two procedures presented there, suggested that serum HBeAg may consist of polypeptides of HBcAg released from hepatocytes rather than of degradation products of core particles.

However, what matters in the present case is whether or not the man skilled in the art needs precise knowledge to arrive at the idea to replace the starting material for the preparation of HBeAg, being HBcAg, derived from natural sources like serum and liver by that prepared by recombinant DNA technique.

5.4 When investigating the question whether the lack of the detailed knowledge about the true relationship between the starting product and the derived product on a molecular level could possibly be a decisive factor inasfar as it could represent a serious bar to the skilled person, one has to take into account that the priority year of the present patent application was 1981. This was a time when admittedly the recombinant DNA technique was still in its infancy. It might not have been the most desired method to provide the starting material by recombinant DNA technique because of the known amount of effort to prepare a protein by that technique. If, however, as in the present case, the problem to be solved was to avoid any contamination by undesired polypeptides derived from serum or liver the method of preparing the polypeptide by recombinant DNA technique was the promising alternative.

It is further decisive that the treatment of HBcAg to obtain HBeAg is identically the same in document (1) and the present application. Thus, while applying the same means in both cases the same results are obtained independently of any knowledge of a relationship between HBcAg and HBeAg on a molecular level.

5.5 Under these circumstances it was mere routine work for a skilled person to try with a reasonable expectation of success the replacement of the HBcAg purified from serum or liver by this polypeptide derived from recombinant DNA technique.

5.6 It is appreciated by the Board that, as stressed by the Appellants, in fact it was only by the inventors of the present patent application that the correct molecular relationship between the two polypeptides being here in discussion was clarified by applying the method described in document (1) to the polypeptides prepared according to the technique described in document (2). According to the latter teaching a gene is constructed, coding for a polypeptide displaying the antigenicity of HBcAg; when treating a polypeptide prepared by this method according to the method described in document (1), which is the same as described in Claim 1(b), the question of molecular relationship between the two hepatitis antigens in question is answered, since the result of the claimed method is in fact identically the same as that described in document (1). However, said new technical insight has to remain without effect on the assessment of inventive step, if otherwise the solution of the problem was obvious to the man skilled in the art.

The Board is well aware of the danger of hindsight approach when working backwards from the disclosure of an invention. As can be seen from the preceeding paragraphs, this is however not the way the Board has proceeded. In the present case the Board cannot see any evidence on which the argument could be based that a skilled person, confronted with the above defined problem, starting from document (1), with the knowledge of the teaching of document (2) would not have replaced a starting material having known disadvantages by another known starting material not having such disadvantages. Otherwise expressed, the Board is convinced that not only could the skilled person have combined the teachings of documents (1) and (2) but that he would indeed have done so because there was for the man skilled in the art a reasonable expectation of success.

5.7 Thus, the subject-matter of Claim 1 lacks an inventive step. Claims 2 to 6 which relate to preferred embodiments fall with non-allowability of Claim 1.

Order

For these reasons, it is decided that:

The appeal is dismissed.

The Registrar The Chairman

P. Martorana A. Nuss

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