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D E C I S I O N
of 17 October 2000

Case Number: T 0637/97 - 3.3.4

Application Number: 89903593.5

Publication Number: 0406272

IPC: C12N 15/12

Language of the proceedings: EN

Title of invention:
Production of Insulin-Like Growth Factor Binding Protein

Patentee:
GENENTECH, INC., et al

Opponent:
Celtrix Pharmaceuticals, Inc.

Headword:
Binding protein/GENENTECH

Relevant legal provisions:
EPC Art. 114(2), 56

Keyword:
"Late-filed documents - not admitted"
"Inventive step (yes)"

Decisions cited:
T 0386/94, T 0412/93, T 0296/93

Catchword:
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Case Number: T 0637/97 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 17 October 2000

Appellant: (Proprietor of the patent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 16 April 1997 revoking European patent No. 0 406 272 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: L. Galligani
S. C. Perryman

Summary of Facts and Submissions

I. The appeal lies from the decision of the opposition division issued on 16 April 1997 whereby the European patent No. 0 406 272, which had been opposed under Article 100(a) and (b) EPC, was revoked pursuant to Article 102(1) EPC on the grounds that the subject-matter of claims 1 and 26 lacked an inventive step and that no enabling disclosure was provided in respect of the subject-matter of claims 26 and 37.

Claims 1, 26 and 37 read as follows:

"1. An isolated DNA sequence comprising a sequence that encodes insulin-like growth factor binding protein BP53, wherein said DNA sequence is selected from the group consisting of:

(a) the DNA sequence set forth in Fig. 3; and

(b) DNA sequences that hybridize under stringent conditions to the DNA sequences defined in (a)."

"26. Insulin-like growth factor binding protein BP53 that is unaccompanied by associated native glycosylation, that has at least about 80% homology with the amino acid sequence of the mature protein shown in Fig. 3, and that possesses one or both of the biological properties of (a) binding insulin-like growth factor (IGF), or (b) cross-reacting immunologically with an antibody raised against at least one epitope of the corresponding native binding protein."

"37. A method for producing insulin-like growth factor binding protein BP53, which comprises culturing cells transformed with DNA encoding a protein having at least about 80% homology with the amino acid sequence of mature IGF-BP depicted in Figure 3, and which possess one or both of the biological properties of (a) binding insulin-like growth factor (IGF), or (b) cross-reacting immunologically with an antibody raised against at least one epitope of the corresponding native binding protein."

Claims 2 to 6, 13 to 18 concerned embodiments of the DNA sequence of claim 1. Claims 7 and 19 were directed to an expression vector comprising the DNA sequence of claim 1. Claims 8 to 12 and 20 to 21 were directed to host cells transformed with the vector. Claims 22 to 25 concerned a method for producing IGF-binding protein by culturing the said cells. Claims 27 to 29 were directed to embodiments of the protein of claim 26, claims 30 to 36 compositions containing it. Claim 38 concerned an embodiment of the method according to claim 37.

II. With the statement of grounds of appeal, the appellants (patentees) filed amended claims and a new document (61). The respondents (opponents) submitted comments thereto.

III. On 20 December 1999, the board issued a communication with an outline of the points to be discussed at oral proceedings scheduled to take place on 28 March 2000. These were postponed in consequence of a joint request of both parties.

IV. On 25 February 2000, the appellants filed a new main request and an auxiliary request, together with new

documents (62) to (66).

V. On 15 September 2000, the respondents made new submissions and filed a new document (68).

VI. The appellants filed on 6 October 2000 comments on the respondents' submissions and new documents (69) to (76).

VII. On 12 October 2000, the appellants filed a new first auxiliary request and a second auxiliary request together with written submissions and new documents (77) to (81).

VIII. Oral proceedings took place on 17 October 2000. The appellants withdrew all previous requests and filed as a sole request claims 1 to 27 submitted on 12 October 2000 as second auxiliary request, together with amended description pages. Claims 1 to 25 were identical to claims 1 to 25 as granted. Claim 26 was identical to claim 37 as granted except for the qualification "eukaryotic" which was added between the terms "culturing" and "cells".

IX. The following documents are referred to in the present decision:

(1) J. Biol. Chem., Vol. 261, No. 19, 5 July 1986, pages 8754 to 8760;

(2) Biochem. Biophys. Res. Comm., Vol. 147, No. 1, 31 August 1987, pages 408 to 415;

(22) EP-A-0 093 619;

(59) WO-A-90/06950 (date of filing: 21 December 1989; date of priority: 22 December 1988)

X. The appellants submitted essentially that at the time of the invention the prior art information about protein BP53 was still incomplete and uncertain. In fact, documents (1) and (2) left the skilled person in doubt as to relationship between two closely migrating IGF-binding proteins and provided only limited amino acid sequence data which did not allow the designing of suitable probes for DNA libraries screening. Under these circumstances, the skilled person could not be confident that the isolation of a DNA sequence encoding the protein would be a straightforward project. As confirmed by the Dr Wood's declarations on file, the task was not an easy one and unusual measures (eg use of internal sequences and combination of several probes simultaneously) had to be taken in order to achieve the goal. This justified the acknowledgement of an inventive step.

XI. The respondents argued that in 1988 the isolation of a DNA sequence encoding IGF-binding protein BP53 falling under the terms of claim 1 did not involve an inventive step. This was because purified homogeneous BP53 protein (cf document (1)) was available, and thus the cloning of a DNA encoding it was achievable in a straightforward manner by the skilled person by means of the classical cloning techniques, which also included the design of pools of probes of the lowest degeneracy based of the amino acid sequence of internal tryptic fragments of the molecule, as described, for example, in document (22) (cf the declarations of Drs K. A. Ward, G. W. Both and D. Mascarenhas, see documents (26)-(29)). In this

respect, the fact that the appellants had achieved their result by taking a tortuous route did not matter because the claims were not centred on the method of cloning, but on the DNA as such. The obviousness of the project was also confirmed by the fact that the respondents' team, which did not have access to rich resources as the appellants' team, achieved in a very short time the same result by following the straightforward route dictated by the prior art (cf document (59)). The case of decision T 386/94 (OJ EPO 1996, 658) in which inventive step was denied was the closest to the circumstances of the present one.

XII. The appellants requested as sole request that the decision under appeal be set aside and that the patent be maintained on the basis of: Claims 1 to 27 submitted on 12 October 2000 as second auxiliary request; pages 3, 4 and 5 of the description as submitted at the oral proceedings on 17 October 2000; pages 6 to 23 of the description as granted; the figures as granted.

The respondents requested that the appeal be dismissed.

Reasons for the Decision

Late-filed documents

1. Documents (77) to (81), which include three expert declarations, were filed by the appellants three working days before the oral proceedings as a reply to the respondents' submissions of 15 September 2000. In the appellants' view, these documents, although late-filed, should be admitted into the proceedings as they

do not change the framework of the case, they constitute a supplement to earlier submissions, and were filed in reply to the respondents' criticism of previous submissions.

2. The board decides to disregard under Article 114(2) EPC the documents in question for the reasons that they were filed at a very late stage and, admittedly, they are not of any particular relevance. They were merely meant as counter-comments to comments which had been submitted by the respondents within the time limit (one month before oral proceedings) fixed by the board in its communication dated 20 December 1999. In the board's judgment, it is not appropriate to allow the continuous filing of supplemental documents of marginal relevance in reply to comments made by the other party as this would render obsolete the setting of a final date for making submissions.

Inventive step

3. The most appropriate starting point for the evaluation of inventive step is represented by the knowledge about human IGF-binding protein BP53 such as that represented by documents (1) and (2). These can be read in combination as the latter makes reference to the first and both are concerned with the structural and functional characterisation of the protein. What was known about the protein can be summarised essentially as follows: a single protein peak with a molecular weight of 45-50 kD had been isolated by high performance reverse-phase and gel permeation chromatography; however, this single peak had been resolved on SDS-PAGE electrophoresis, both reduced and unreduced, into a major (43 kD and 53 kD, reduced and

unreduced, respectively) and minor band (40 kD and 47 kD, reduced and unreduced, respectively), both of which stained for protein and carbohydrate. For the presence of the minor band the following possibilities requiring further exploration were put forward: either a difference in glycosylation, or contamination, or a possible association of two components into a complex (cf discussion in document (1)). For the two protein components an identical amino-terminal region was suggested, a sequence of 15 amino acids being reported in Figure 4 of document (2).

4. Having regard to the said knowledge about human IGF-binding protein BP53, the underlying technical problem can be defined as the provision of means for producing this protein in pure form.

5. The solution proposed by the claims at issue is the specific DNA sequence set forth in Figure 3 and DNA sequences which hybridise thereto under stringent conditions as well as vectors and host cells containing said sequences and the corresponding methods for expressing the protein.

6. The relevant question is whether the skilled person faced with the stated technical problem, in consideration of other relevant prior art findings and/or common general knowledge, would arrive at a DNA sequence falling under the terms of claim 1.

7. The respondents drew a parallel between the technical circumstances of the present case and those of decision T 386/94 (supra) in which inventive step was denied.

The board does not agree with this view because the

technical circumstances of the said case were quite different from those of the present one. In fact, there the prior art had already provided a DNA molecule encoding 80% of the prochymosin and thus the task of cloning the full-length DNA encoding prochymosin and chymosin was considered to be greatly facilitated. In the present case, no knowledge whatsoever was available concerning any DNA encoding the protein.

8. The respondents relied also on the argument that their team, which did not have at its disposal large resources as did the appellants' team, succeeded in the cloning effort shortly afterwards by following a simpler route. In their view, this is indicative of the obviousness of the result.

In the board's view, these considerations have no bearing on the evaluation of inventive step because the obviousness or otherwise of a given subject-matter cannot be judged on the basis of whether or not one or more teams were working in parallel at the same project or whether or not a team was working under more favourable conditions than another team (cf T 296/93 of 28 July 1994, see point 7.4.4 of the reasons).

9. While it is true that in 1988 the art of sequencing a given known protein and that of cloning and expressing the corresponding gene encoding it was more advanced than in the early 1980s (the time of filing of the patent application of case T 386/94, supra), it is also a fact that the inventive step of a given subject-matter has always to be examined in each case on its own merits by carefully evaluating the particular technical circumstances of the case. In this respect, it should be kept in mind that in 1988 the situation

was not "one cloning strategy fits all". Thus, the following consideration made in T 412/93 of 21 November 1994 (see point 142 iv) of the reasons), is considered to be applicable in the present analysis: "working according to the precise recipe of a particular piece of prior art relating to another gene to show lack of inventive step in this particular field of genetic engineering is only of limited value, because of the unique characteristic of each and every gene which make extrapolations highly speculative."

10. When the particular technical circumstances of the present case are taken into account, it is observed that, although human IGF-binding protein BP53 had to some extent been structurally and functionally characterised, its complete amino acid sequence was still unknown and, moreover, the exact relationship between the major and minor band components had not yet been clarified. Under these circumstances, it cannot be reasonably maintained that the skilled person had an unclouded starting point for preparing suitable probes necessary for the screening of DNA libraries and that cloning work with other genes, eg human tissue plasminogen activator (cf document (22)), would have provided a "ready-to-use" and reliable strategy. Moreover, the available sequence of 15 amino acids was admittedly useless for designing suitable probes in view of its high level of degeneracy (cf declaration of D. Mascarenhas).

11. In the board's judgement, the skilled person, faced with the technical situation as depicted above, would have concluded that the task of isolating a DNA encoding IGF-binding protein BP53 was not a routine one as it required inter alia the preliminary clarification

of those unsolved questions. Moreover, the skilled person would simply not have been able to anticipate, for example, whether the further elucidation of the amino acid sequence of either components would have revealed sequences of internal fragments of a lower level of degeneracy suitable for producing adequate probes. The skilled person would have considered the successful conclusion of the endeavour to be dependent not so much on the technical skill in performing the different steps of known cloning protocols, but more importantly on the ability of devising a successful experimental protocol by introducing, if necessary, appropriate modifications in known protocols or even on the ability of taking, if needed, a different approach. Under these circumstances, the skilled person would not have had a reasonable expectation of success and for this reason would not have regarded the solution proposed by the claims at issue as an obvious achievement.

12. The board notes that this view is consistent with what is said in document (59), which is the respondents' patent application dealing also with the isolation of a DNA encoding IGF-binding protein, wherein *inter alia* the following statements are made (emphasis added):

- on page 11: "Many proteins and polypeptides have been produced by use of recombinant DNA techniques. There is no published report of production of carrier protein-like polypeptide in this manner. **There are numerous obstacles to using the techniques of recombinant DNA technology to clone and express a carrier protein-like polypeptide gene. Obtaining a gene encoding a carrier protein-like polypeptide is difficult for**

a variety of reasons".

- On page 50: "In the case of carrier protein, the screening problem was further exacerbated by the lack of a sufficiently purified sample of carrier protein mRNA or DNA, or portion thereof, to act as a screening probe for the identification of the desired clone. The only available probes were those based on the limited N-terminal protein molecule information. **Therefore, the screening process for the carrier protein clones is very time-consuming and difficult.**"

13. In sum, the board judges that the subject-matter of the claims at issue involves an inventive step.

The adaptation of the description

14. As regards the adaptation of the description, the respondents objects that, in addition to the amendments carried out on pages 3 to 5, other passages in relation to the expression of a DNA encoding IGF-binding protein in prokaryotes need to be deleted in consequence of the fact that granted claim 26 relating to the unglycosylated protein is no longer pursued.

15. The board observes that, while the amendments carried out on pages 3 to 5 are directly in response to the deletion of claim 26 from the claim request at issue, the passages of the description of which the respondents request the deletion are in relation to the subject-matter claims 9 and 15 (identical to claims 9 and 15 as granted) which are inter alia concerned, respectively, with prokaryotic host cells transformed with a vector comprising the DNA sequence of claim 1

and with a DNA sequence of claim 1 comprising a signal sequence recognized by prokaryote cells. These claims had been challenged by the respondents only under Article 100(a) EPC (lack of inventive step), **not** under Article 100(b) (sufficiency of disclosure). As an inventive step has now been recognised by the board for the claims at issue, the board finds no reasons for deleting the passages in question from the description as they provide the necessary support in the description for the subject-matter of these claims.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent on the basis of the appellants sole request.

The Registrar: The Chairwoman:

U. Bultmann U. Kinkeldey