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BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

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File Number: T 157/90 - 3.3.2

Application No.: 82 303 667.8

Publication No.: 0 070 675

Title of invention: Human calcitonin precursor polyprotein structural gene

Classification: C12N 15/00

D E C I S I O N
of 12 September 1991

Applicant: CELLTECH LIMITED

Headword: Human calcitonin structural gene/CELLTECH

EPC Article 123(2) EPC

Keyword: "Inadmissible generalisation"

Headnote

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number : T 157/90 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 12 September 1991

Appellant : CELLTECH LIMITED
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Decision under appeal : Decision of Examining Division of the European Patent Office dated 7 September 1989, posted on 5 October 1989 refusing European patent application No. 82 303 667.8 pursuant to Article 97(1) EPC.

Composition of the Board :

Chairman : P.A.M. Lançon
Members : U.M. Kinkeldey
E.M.C. Holtz

Summary of Facts and Submissions

I. European patent application No. 82 303 667.8, relating to a human calcitonin precursor polyprotein structural gene, was published with number 0 070 675 with 17 claims. Claims 1 and 7 read as follows:

"1. A structural gene encoding a polypeptide comprising the amino acid sequence of human calcitonin, in which said polypeptide is processable to produce human calcitonin.

7. A polypeptide containing the amino acid sequence of human calcitonin which is processable to produce human calcitonin."

II. In response to notifications issued by the Examining Division the Applicants (Appellants) filed new sets of claims on different occasions.

Finally, with a letter of 18 May 1988, a set of claims was filed whose Claim 1 reads as follows:

"1. A vector including a structural gene encoding a polypeptide comprising the amino acid sequence of human calcitonin and an additional amino acid at the C-terminus of the amino acid sequence of human calcitonin, wherein the polypeptide is processable to authentic human calcitonin by enzymically processing the said additional amino acid to form an amide group at the C-terminus of the amino acid sequence of human calcitonin".

(Emphasis added).

New Claim 8, relating to a fusion polypeptide was amended correspondingly.

III. The application was refused by the Examining Division with a decision given at the end of oral proceedings held on 7 September 1989. The refusal was based on the grounds that the subject-matter of Claims 1 and 8 filed with the letter dated 18 May 1988 did not meet the requirements of Article 123(2) EPC.

The reasons for the refusal were essentially that the application as originally filed was broadly concerned with the production of human calcitonin by recombinant DNA techniques, in particular with the construction of fusion proteins comprising a host protein (at the N-terminus) in combination with the peptide comprising the amino acid sequence of human calcitonin. A particular, secondary embodiment of the original application was the preparation of calcitonin-glycine fusions, i.e. of proteins comprising the sequence of human calcitonin (also in the form of fusion proteins) in which an additional glycine residue was present at the C-terminus of the calcitonin sequence, this additional glycine serving as amidation signal. This was in line with the suggestion of the prior art of the possible role of a C-terminal glycine residue for the in vivo amidation of the adjacent C-terminal amino acids in proteins.

Claims 1 and 8 on file represented a generalisation of the teaching to calcitonin having at the C-terminus any amino acid. The replacement of the disclosed specific feature, being glycine as amidation signal, by a broader general expression being any amino acid as amidation signal, constituted an amendment inadmissible under Article 123(2) EPC because the original application gave no indication whatsoever to the skilled person that any additional amino acid at the C-terminus could be used as amidation signal in the processing of recombinant calcitonin. On the contrary, the application made clear that glycine was

required for the amidation of the C-terminus proline residue. Thus, the generalisation to any amino acid must be regarded as new information for the skilled person. Also two prior art references, namely

(I) Breddam, et al. (Carlsberg Res. Commun., Vol. 45, 1980, pp. 237-247) and

(II) Breddam, et al. (Carlsberg Res. Commun., Vol. 45, 1980, pp. 361-367)

which were cited in the patent application and thus were said to be incorporated into the disclosure by reference, did not constitute an implicit teaching that any additional amino acid placed at the C-terminus of calcitonin could be used as amidation signal.

IV. The Appellants appealed against the decision of the Examining Division and paid the appeal fee on the same day. Further, they filed a written statement setting out the grounds for appeal on 6 February 1990. Together with the grounds for appeal, they filed two new sets A and B of claims to be considered as two auxiliary requests. The main request was based on the claims as rejected.

Claim 1 of set A reads as follows:

"1. A vector including a structural gene encoding a polypeptide comprising the amino acid sequence of human calcitonin, wherein said polypeptide is enzymically processable to produce human calcitonin using the C-terminal modification activity of the yeast enzyme carboxypeptidase Y."

A corresponding process Claim 10 was amended accordingly.

Claim 1 of set B reads as follows:

"1. A vector including a structural gene encoding a polypeptide comprising the amino acid sequence of human calcitonin-glycine wherein said polypeptide is enzymically processable to authentic human calcitonin."

Oral proceedings were held on 12 September 1991.

V. The appeal was essentially substantiated as follows:

Main Request

The Appellants conceded that there was no expressive basis for the claims in the application as originally filed. This, however, was not required for an allowable amendment within the meaning of Article 123(2) EPC. Rather, the specification must be interpreted as if read and understood by the skilled person at the filing date.

As early as 1964, the structure of the peptide hormone human calcitonin was found to be a polypeptide having 32 amino acids and it was discovered that an amide group at the C-terminus of the polypeptide was essential for biological activity. When preparing the cDNA for human calcitonin it was discovered that calcitonin was located in the middle of a large precursor protein flanked by other amino acid sequences. The invention described in the present application allowed for the first time the production of authentic human calcitonin by recombinant DNA technique which required for full activity and therefore utility an amidation at the C-terminus. The specification of the present application as originally filed identified this problem and taught the skilled person broadly how the problem of C-terminus amidation

might be solved, namely by the enzymically processing of a suitably modified calcitonin precursor polypeptide. The application described a method for the production of human calcitonin comprising processing a polypeptide in the broad meaning. On page 16, lines 22 to 28, of the originally filed application, reference was made to the need for a C-terminal additional amino acid and specifically to glycine. The skilled person reading this passage would immediately appreciate that the circumstances discussed were those which prevail in vivo and were thus not limiting upon the process that could, with equal facility, be conducted in the in vitro processes of recombinant DNA technology. Although the mentioned passage indicated that glycine was an important consideration, this had to be interpreted only in view of the fact that it had been recognised that glycine was involved in vivo in the amidation of the C-terminal proline residual. The reference to glycine thus had to be interpreted as a reference to a specific example set forth in the present application but not limiting on the overall content in teaching to the skilled person. Further, one had to note that the glycine extension was mentioned as an alternative to proline as the C-terminal amino acid. The skilled person faced with the teaching in the specification that conversion of the liberated peptide into authentic calcitonin was possible through the use of C-terminal modification activity of yeast carboxypeptidase Y would go to references (I) and (II) and would find in these papers the information necessary to work the invention. The choice of glycine as the additional amino acid at the C-terminus was arbitrary and made simply because this was the amino acid next to the C-terminus in nature and along with the other amino acids in the flanking sequence was implicated in post-translational modification in vivo.

The content of the specification as originally filed, included the skilled person's interpretation of references (I) and (II), read in the context of the reference to them made in the patent specification. Precisely because references (I) and (II) did not spell out what to do, the skilled person had to study the reactions discussed and extract the information he required as he was specifically directed to do by the specification. In doing this he would inevitably derive, directly and unambiguously, the subject-matter now claimed.

Reference was made to decisions T 194/84 (OJ EPO 1990, 59) and T 159/86 of 27 October 1987 (not published in OJ EPO) which were said to deal with comparable facts and with the question whether a generalisation of a specific feature constituted added matter within the meaning of Article 123(2) EPC.

According to decision T 6/84 (OJ EPO 1985, 238) it was allowed to incorporate a specific means of a disclosure in a patent specification by reference to prior art documents.

Auxiliary Request A

The set of claims according to this auxiliary request limited the scope of protection to those polypeptides susceptible to C-terminal modification with the yeast carboxypeptidase Y enzyme and found clear support on page 31 of the originally filed specification.

Auxiliary Request B

The respective claims of this request literally recited calcitonin-glycine which was expressively described as one example for an additional amino acid at the C-terminus of

human calcitonin in the specification as originally filed, and thus allowable.

VI. The Appellants requested that the decision under appeal be set aside and that a patent be granted on the basis of the set of claims filed with the letter dated 18 May 1988 (main request);

alternatively set A filed with the Statement of Grounds (first auxiliary request);

or set B filed with the Statement of Grounds (second auxiliary request).

Reasons for the Decision

1. The appeal is admissible.

2. The only question at issue in these appeal proceedings is the allowability of amendments in the claims with regard to Article 123(2) EPC.

2.1 According to the wording of Article 123(2) EPC a European patent application "may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed."

2.2 Following the wording of this article, it is apparent that on the special merits of each case the "subject-matter" representing the amendments has to be compared to the "content of the application as filed" i.e. its objective technical disclosure has to be examined with the eyes of the skilled person. Such an examination of the facts would ensure the right of the public not to be confronted with an extent of protection resulting from the granted patent,

which could not have been established by a skilled person having studied the whole content of the technical disclosure of the originally filed patent application.

2.3 The present case relates to the judgment of an amendment representing a generalisation of a feature mentioned expressly in the application as originally filed.

As correctly emphasised by the Appellants during the proceedings, the application is directed to the preparation of a precursor molecule of human calcitonin, processable after its expression in a host organism to authentic human calcitonin. The general term "processable" is described in more detail in as far as the precursor molecule contains, in addition to the amino acids representing the authentic human calcitonin, a couple of amino acids "in front" of the authentic polypeptide and a couple of amino acids "at the end" of and thus exceeding the last amino acid of the human calcitonin polypeptide. These amino acids have to be cleaved away, i.e. "processed", to achieve the authentic protein. In addition, in the particular case of human calcitonin a further processing step is necessary to arrive at the authentic protein. This is the amidation of the amino acid at the C-terminus of the protein, which in this case is a proline. The explicit disclosure as to this processing step can be found on page 16 where it is stated that "The glycine residue (+1), an important consideration in the construction of the expression vectors described below, is in vivo required during processing events for the amidation of the adjacent carboxyl terminal amino acids"; further it is stated that "Thus in human calcitonin glycine + 1 is required for the amidation of the carboxyl - terminal proline residue (32), a feature required for biological activity".

The description continues on page 17 referring to the production of "either human calcitonin or human calcitonin with an additional glycine residue at the carboxy-terminal end". On page 24, headed by "Calcitonin and Calcitonin-gly Fusions with trp E" it is stated that "the initial step involves the modification of the calcitonin sequence so that the ultimate amino acid in the fusion protein is either the proline corresponding to the authentic terminal amino acid in calcitonin or so that a further glycine is translated. The purpose of this construction relates to the final processing envisaged in calcitonin production and is fully described below." Finally, on page 31, one can find the following paragraph:

"The peptide liberated by this procedure differs from authentic calcitonin only in that in authentic calcitonin the C-terminal amino acid is a prolinamide rather than a proline (or proline-glycine) amino acid. Conversion of the liberated peptide into authentic calcitonin is possible through the use of C-terminal modification activity of yeast carboxypeptidase Y"

followed by the citation of references (I) and (II).

2.4 The application as originally filed does not contain any further information about apparent variations or equivalents and, therefore, the explicit disclosure relates to the glycine as the additional amino acid at the carboxy-terminal end of human calcitonin for the purpose of an amidation either of proline or glycine by means of carboxypeptidase Y, and nothing more.

Main Request

2.5 Since the amendment used in the claims in question relates to "an amino acid" which is a general term covering i.a.

glycine, it has now to be examined whether this general term adds subject-matter to the specific mentioning of the amino acid glycine, i.e. whether the specific mentioning of the amino acid glycine represents an embodiment exemplifying a more general, implicit disclosure of the invention or subject-matter being essential in a manner that it is not unequivocal to replace it by the general term.

2.6 To answer this question, it is important to note that the description of the method of amidation refers to two prior art references (I and II), which according to the Appellant's statements, have to be seen as part of the disclosure of the present patent application. Reference was made to a decision of a Board of Appeal (T 6/84, see above paragraph V). There it was decided that structural features of the means for performing a chemical process which were not mentioned in the application documents themselves but in a document to which they refer may be incorporated into a patent claim if they unequivocally form part of the invention for which protection was sought.

2.7 The Appellants admit that the teaching of the included prior art references are not directly of assistance to the reader of the specification of the present patent application wishing to conduct a C-terminal modification on a calcitonin-analog. They do not directly teach adding an amide to an amino acid sequence or modifying a C-terminal extension to produce a C-terminal amide. The skilled person needs to study the references (I) and (II) closely in order to ascertain how to use these teachings to make authentic human calcitonin.

2.8 However, the Board cannot agree to the conclusions drawn by the Appellants from this fact, namely that it was

precisely because the mentioned references did not spell out what to do, the skilled person would have inevitably derived, directly and unambiguously, the subject-matter now claimed. Instead, the unequivocal information derivable from references (I) and (II), in the Board's opinion, was the use of carboxypeptidase Y to catalyze peptide bond formation whereby an amidase activity is observed. No unequivocal disclosure is given about any particular amidation.

2.9 In combination with the specific description of the present patent application thus these references teach how to use carboxypeptidase Y to amidate the amino acid proline at the carboxy-terminal end of calcitonin. According to the present application this can be done by amidation of the amino acid proline, which is the carboxy-terminal end -amino acid of the authentic calcitonin or of glycine being added at the carboxy-terminal end of authentic human calcitonin. Thus, even if it were agreed that references (I) and (II) are to be incorporated into the disclosure of the present application as far as they unequivocally form part of the invention for which protection is sought, it is not allowed to extend the disclosure of these prior art references beyond what can be said to be unequivocally disclosed therein, when read in conjunction with the disclosure of the present application.

2.10 Further, the mentioned use of carboxypeptidase Y for the necessary amidation of the carboxy-terminal end amino acid proline in authentic human calcitonin apparently is not dependent on a further added amino acid. The addition of glycine, therefore, is based on the knowledge that this is the amino acid adjacent to the proline in naturally occurring calcitonin before any processing steps in vivo are carried out. If an in vitro processing is desired as

in the present case, relating to a recombinant DNA technique production of calcitonin, the skilled person's first choice of a certain means would be the one of which it is already known that it works. Only in particular cases where it might be known that alternatives to naturally occurring means are equally, or for any reasons even better suited, the skilled person would possibly deviate from the workable way given in nature. The Appellants did not submit that at the priority date of the present application an information of that kind was available. It is thus the explicit and implicit teaching of the present application that if there should be any amino acid extending the carboxy-terminal end of the authentic human calcitonin for an in vitro processing by carboxypeptidase Y it has to be glycine.

2.11 Under these circumstances the Board finds that, if a skilled reader is confronted with the claim mentioning "an additional amino acid at the C-terminus of the amino acid sequence of human calcitonin" and the description mentioning solely glycine as the additional amino acid, being the adjacent amino acid in the natural precursor form of human calcitonin and the above-defined unequivocal disclosure of references (I) and (II), he would conclude that glycine is, if any, the amino acid necessary for the enzymically processing of the precursor to arrive at the necessary amidation of the proline. "If any", because it is not even necessary to add any amino acid, the carboxypeptidase Y being also efficient to amidise the proline itself.

2.12 The generalisation of the explicit disclosure of the addition of one specific amino acid to any amino acid thus has only "formal" support in as much as the amino acid is "glycine". In view of the technical subject-matter disclosed in the application as originally filed, this

generalisation is not allowed because of the reasons given above.

2.13 The Appellants referred to two decisions, mentioned above under paragraph V, which deal with the allowability of a generalisation of a specific means under Article 123(2) EPC.

Both decisions state that it is the change of content, i.e. the amended content minus the original content, that has to be examined - an examination also applicable to amendment by generalisation (T 194/84, see above); further that a general applicability of a specific teaching has to be evident to the person skilled in the art (T 159/86, see above). As the examination above has shown the amended content minus the original content represents new subject-matter and the use of a general term instead of a specific feature was not evident to the skilled person in the present case. These decisions thus do not support the Appellant's case.

Further, the Board fully agrees with the general remarks as to the function of Article 123(2) EPC given in a recent decision by a Board of Appeal (T 118/89 "Bauelement" pages 2.3 to 2.5, of 19 September 1990, not published in OJ EPO), in particular to the general statements about the the so-called "novelty-test" for the judgment of the requirements of Article 123(2) EPC the Board has nothing to add in the circumstances of the present case.

The main request is thus not allowable.

First Auxiliary Request

2.14 The wording of the claims in questions of this auxiliary request no longer relates to the addition

of "an amino acid" but rather refers to the use of the C-terminal modification activity of the yeast enzyme carboxypeptidase Y to produce human calcitonin correctly amidated at the C-terminus. This is explicitly disclosed in the application as originally filed as cited above under paragraph 2.3.

The set of claims according to the first auxiliary request (set A) is thus allowable with regard to Article 123(2) EPC.

2.15 Since the claims of the first auxiliary request are allowable there is no need to discuss the claims of the second auxiliary request.

Order

For these reasons, it is decided that:

1. The decision of the Examining Division is set aside.

2. The case is remitted to the Examining Division for further prosecution on the basis of Claims 1 to 13 of set A (first auxiliary request).

The Registrar: The Chairman:

P. Martorana P. Lançon