Europäisches Patentamt
Beschwerdekammern

European Patent Office
Boards of Appeal

Office européen des brevets
Chambres de recours

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 269/87

Anmeldenummer / Filing No / N° de la demande : 82 303 035.8

Veröffentlichungs-Nr. / Publication No / N° de la publication : 68 691

Bezeichnung der Erfindung: A process for the production of a polypeptide
Title of invention:
Titre de l'invention :

Klassifikation / Classification / Classement : C12N 15/00

ENTSCHEIDUNG / DECISION

vom / of / du 24 January 1989

Anmelder / Applicant / Demandeur : Celltech Ltd.

Patentinhaber / Proprietor of the patent /
Titulaire du brevet :

Einsprechender / Opponent / Opposant :

Stichwort / Headword / Référence : Prochymosin/CELLTECH

EPÜ / EPC / CBE Articles 54(3), 84 and 87 and 88 EPC

Schlagwort / Keyword / Mot clé :
"Priority - Missing essential features"
"Novelty destroying document"

Leitsatz / Headnote / Sommaire

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number : T 269/87

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 24 January 1989

Appellant : Celltech Ltd.
244-250 Bath Road
Slough Sl1 4DY
Berkshire
GB

Representative : Votier, Sidney David
CARPMAELS & RANSFORD
43, Bloomsbury Square
London WC1A 2RA
GB

Decision under appeal : Decision of Examining Division 023 of the European Patent Office dated 30 October 1986 refusing European patent application No. 82 303 035.8 pursuant to Article 97(1) EPC

Composition of the Board :

Chairman : P. Lançon
Members : G. Szabo
U. Kinkeldey
E. Persson
R. Schulte

Summary of Facts and Submissions

I. European patent application 82 303 035.8 filed on 11 June 1982 and published on 5 January 1983 with publication number 68 691, claiming priority of the prior applications of 17 June, 11 November and 1 December 1981 (GB 81 18688, 81 33998 and 81 36185) and 10 February 1982 (GB 82 03907), was refused by the decision of the Examining Division of the European Patent Office dated 30 October 1986, notified on 2 February 1987. The decision was based on Claims 1 to 9. The Claims 1 and 9 were worded as follows:

1. A process for the production of chymosin comprising the step of cleaving methionine-prochymosin produced by a host organism transformed with a vector system carrying a gene coding for methionine-prochymosin.

9. Plasmid pCT 70.

II. The first ground for refusal was that the subject-matter of Claims 1 and 2 was not novel under Article 54(3) and (4) EPC over the disclosures of earlier European patent applications EP-57 350 (Collaborative Research) (1) and EP-77 109 (Unilever) (2). It was stated that these claims were only entitled to the priority of the filing date of the European application, since none of the four priority applications discloses methionine-prochymosin, or the required initiation codon ATG for the process. The provision of this was not even unambiguously implied, i.e. derivable from the priority applications. Therefore, the claims were anticipated by document (1) which was at least entitled to the priority date of 1 December 1987, and by document (2), effective from its priority date 14 October 1981.

The second ground for refusal was the unallowability of Claim 9 under Article 84 EPC. The mere designation of "pCT 70" was arbitrary and provided no technical feature for the claim. Whilst the description of the plasmid in the specification might be adequate, there was no correspondence between the designation used and the technical features in the description (cf. Rule 29(1) EPC).

III. An appeal was lodged on 26 March 1987 by telex message and by the payment of the fee. The message was confirmed by letter of 30 March 1987. A Statement of Grounds was filed on 10 June 1987, together with eight auxiliary sets of claims.

During the course of the oral proceedings on 25 October 1988 the earlier auxiliary requests were replaced by requests A to C, referring to corresponding sets of newly submitted claims. Set A has the following wording:

A1. A process for the production of chymosin comprising the step of cleaving methionine-prochymosin produced by a bacterial host organism transformed with a vector system carrying a gene coding for methionine-prochymosin.

A2. A process for the production of chymosin comprising the steps of

(a) inserting a gene coding for methionine-prochymosin into a vector system,

(b) transforming a bacterial host organism with the gene-carrying vector system and,

(c) cleaving methionine-prochymosin produced by the host organism to form chymosin.

IV. In the Statement of Grounds and in the oral proceedings the Appellant submitted substantially the following arguments:

(a) The subject-matter of the broadest Claims 1 and 2 were entitled to the priority date 17 June 1981. Whether or not there was disclosure of the claimed subject-matter in the priority document was to be decided on the basis of the same principles which govern amendments under Article 123(2). However, features implicit in the disclosure, i.e. derivable directly and unambiguously must also be taken into consideration, in addition to what had been expressly mentioned.

(b) The interpretation of the skilled addressee was relevant, and not that of the non-expert.

(c) Since no expression was possible without the initiation codon ATG, which codes for methionine and would thus inevitably provide this additional amino acid as the first member of the polypeptide prochymosin, the attaching of ATG to the sequence coding for prochymosin and the resulting methionine-prochymosin products were inevitable and directly and unambiguously implied through common general knowledge.

(d) The first priority application already described preparing the messenger RNA from the respective calf tissues, preparing DNA-probes for screening the mentioned messenger RNA population, preparing cDNA via reverse transcriptase from the messenger RNA, cloning of the DNA-fragment, expression of the prochymosin protein, isolation of the protein and cleavage of the prochymosin protein to yield chymosin. The direct

expression of the prochymosin necessarily meant to the skilled person that in fact methionine-prochymosin had been obtained and cleaved. The reference to the need for a promotor implies the direct expression of methionine-prochymosin itself and not, for instance, a cleavable combination thereof with another polypeptide.

(e) The balance of evidence suggests that the application should be allowed to proceed to grant. As regards the standard of disclosure required for a priority document, recent decisions in the U.K. suggested that no enabling disclosure was necessary to establish priority rights (cf. In the Matter of Application No. 85 08864, before the Comptroller, and an appeal decision in the Patents Court, 7.10.88, both yet unreported).

(f) As regards Claim 9, this claim was to be read in conjunction with the disclosure. The application of the Guidelines (C-III, 4.2) to the present context would lead to an over complication of the claim, at the best, or undue limitation, at the worst. Claims had already been granted with a mere accession number in a culture collection, constituting no more definition than the code in Claim 9.

V. The Appellant requested that the decision under appeal be set aside and that the patent be granted on the basis of the claims refused by the Examining Division (main request), or auxiliary requests A to C, as submitted during the oral hearing.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 64 EPC and is admissible.

Main request

Clarity and Support (Article 84 EPC)

2. Claim 9 in the main request is an independent claim relating to a specific plasmid, which has been prepared from other plasmids to provide a structure having certain components and restriction sites, distinguishing the same from other plasmids (cf. Figure 5). The precursor pCT 57 (obtained in turn from pCT 54) was modified to contain certain sequences, and lose others which related to pseudo-prochymosin (cf. pages 29-33). If pCT 70 is a unique molecule, it should be defined in terms of its structure whenever possible. If, on the other hand, the designation has variable components which have no influence on its use, the class represented by the designation should be characterised in the claim at least by the indication of the common essential technical features (Rule 29 EPC). Except when absolutely necessary, claims should not rely in respect of technical features on the description (Rule 29(6) EPC). In order to enable the public to ascertain the scope of the protection provided, the claims should be clear in themselves, whenever this is possible, and contain as much structural information as available and necessary in the circumstances. For instance, product-by-process claims, i.e. definition of a material by reference to features other than those of the entity itself, are only permissible in the absence of relevant structural information.

3. The specification, in particular Figure 5, contained detailed structural information which could have been

included in Claim 9 to enable the public to identify and compare plasmids vis-à-vis the claimed subject-matter. The argument that claims to deposited microorganisms had been allowed in the past cannot be decisive in the present case. Whilst such depositions identify novel microorganisms by implication through their availability, they also open the possibility for comparisons for any member of the public. Depositions may therefore provide the only possibility for support and sufficient disclosure for a particular subject-matter.

4. The Appellant chose to refrain from the deposition of his plasmid in a microorganism and relied on the written specification alone for identification and reproducibility. In view of the essentiality and the availability of the relevant features on the basis of the specification, it would have been necessary to include these in the claim. Without such clear limitations to the essentials, the claim is as uncertain in its scope as references like "as described in the description" (cf. T 150/82, "Claim Categories/IFF", OJ EPO, 1984, 309). Claim 9 is clearly contrary to the requirements in Rule 29 EPC and therefore to those of Article 84 EPC, and is unallowable. Consequently, the main request, of which this claim is a part, must be rejected.

Auxiliary request A.

Amendments (Art. 123(2) EPC)

5. The first auxiliary request A, relates to Claims 1(A) and 2(A). These claims are identical with Claims 1 and 2 of the main request, except that the host is limited to a "bacterial host" in Claim A1. The amendment is supported by the general description (cf. page 6, line 11) and the specific example using an E. coli strain. It complies with the requirement of Art. 123(2) EPC.

Priority (Articles 87 and 88)

6. Claims A1 and A2 relate to the cleavage of methionine-prochymosin to chymosin, in which the former is produced by "a vector system carrying a gene coding for methionine-prochymosin" in a host. In view of the citation of copending European applications in respect of novelty, it is necessary to establish the earliest priority date which these claims can rely upon. Since Article 87 EPC requires that the European filing should also be "in respect of the same invention" as earlier disclosed, the subject-matter of these claims must be identifiable in the relevant priority document.

7. In accordance with Article 87 EPC a European patent application is only entitled to priority in respect of the same invention as was disclosed in the previous application. This means that the subject-matter of the claims of the European application must be clearly identifiable in the documents of the previous application as a whole. Identical wording of definitions is not required (cf. T 184/84, "Ferrit crystal/NGK Insulators", 4 April 1986). However, if any essential element of the invention for which a European patent is sought is missing, there is no right to priority.

8. It was the view of the Board in the decision of a copending appeal that in order to give rise to priority the disclosure of all the essential elements, i.e. features of the invention, in the priority document must either be express, or be directly and unambiguously implied by the text as filed. Missing elements which are to be recognised as essential only later on, are thus not part of the disclosure (cf. T 81/87, Preprorennin/COLLABORATIVE RESEARCH, 24 January 1989, to be reported in OJ EPO). Gaps

with regard to basic constituents in this respect cannot be retrospectively filled on the basis of such knowledge.

The question therefore arises in the present case what are the essential elements, i.e. features of the invention claimed in the European patent application, and whether or not these features are disclosed in the respective priority document (cf. Article 88(4) EPC).

9. Although Claim 1 only defines the starting material as having been prepared by using a corresponding gene in a vector incorporated in a bacterial host, there are a number of features which are implied by the definition. For instance, the production must be by expression and the vector system should otherwise be equipped for such purposes. Some further details, which are necessarily implied by Claim A1 are expressed in Claim A2. One important feature, i.e. the gene coding for the methionine-prochymosin, is supported by the description of a specific process in the European application. Since this feature is only identified in the priority document by a reference to such process of preparation, it would have to be examined whether or not the text of the priority filing gives full support to all its essential constituents. No reliable synthetic approach was available to provide a particular DNA for prochymosin, an otherwise known compound, at the date of the priority document. The required gene is, therefore, solely to be defined and disclosed by its particular route of preparation. This is the characteristic of this gene and its expression product, by implication, and therefore of the inventions relying upon it.

10. The actual steps to obtain the required gene and then the appropriate expression plasmid include in the European application the common stages of preparing a messenger RNA population isolated from a specific tissue, preparing DNA-

probes suitable for hybridizing with at least a part of the desired messenger RNA, screening the messenger RNA population by said corresponding DNA-probes, preparing cDNA via reverse transcriptase from the respective messenger RNAs, cloning the cDNA fragments into vectors and selecting those vectors which are candidates to carry the cDNA fragments. After analysing these vectors, for example by restriction enzyme or DNA sequence analysis further necessary steps can be taken to reclone the cDNA fragment into an expression vector, if the cDNA fragment already represents the desired gene or to combine cDNA fragments of different clones if it turns out that none of the selected clones contains the whole gene and thereafter to insert the complete gene in an expression vector equipped with all necessary further genetic elements for an effective expression of the desired polypeptide.

11. It is now clear from the disclosure in the European application, as well as from those of the cited copending applications, that the genetic precursors of chymosin were not directly obtainable but had to be combined by additional steps from available fragments. This may be due to the size of the molecules and inevitable fragmentations. The European application explains that none of the clones first obtained had carried the full prochymosin gene and it was rather necessary to cleave and combine parts of vectors G1 and B18 after the identification of their relevant structural constituents in order to prepare vector 118 which was then complete and ready to be inserted into a suitable expression vector for the final preparation of prochymosin (cf. Figure 3). To this purpose, further modifications were necessary, for instance, the adding of the ATG initiation codon corresponding to the first amino acid methionine of the product. Only after such steps could the method proceed to obtain the prochymosin gene. To recombine certain specifically tailored fragments from

different clones is thus also, by implication, an essential part of the invention, as claimed.

12. It has been admitted that on the date of the first priority document, the idea of preparing prochymosin or chymosin by the recombinant DNA-technique was not reduced to practice by the Appellant. It rather appears that reduction to practice and thus the recognition of specific difficulties depending on the particular constitution of the desired gene was only successfully achieved step by step in the five relevant applications. For example, the characteristic step of having to combine various clones in a certain manner was apparently not yet appreciated or envisaged. On the contrary, the description in the first priority document boldly alleges that a "single strained prochymosin cDNA" (page 4, lines 17-18) would be in hand (cf. also "the resulting full length prochymosin gene", page 4, line 27) without any particular indication that in fact this was not, or might not, be the case. The first priority document in the present case is wholly silent about the above particular essential step and also about some basic features of the invention implicitly contained in Claims A1 and A2.

13. For instance, the particular process steps outlined in point 9 above include selections and choices which are determined by the circumstances decided from the previous steps and cannot thus be directly and unequivocally derived from the disclosure of the priority documents, as such. Whilst the supplementation of the incomplete gene with the ATG initiation codon could be so implied, being a unique and necessary choice, this would not apply to the other kinds of difficulties encountered in the actual process. The same can be said to a diminishing extent to the second, third and fourth priority documents, respectively, which disclose the essential details gradually.

The argument that the skilled person would supplement the disclosure from his common general knowledge to make it work, should any difficulty be encountered, is no excuse when this is a feature of the definition of the invention, and is missing, not envisaged by the inventor and not implied by the description. Adding such feature later on would be to change the character of the invention itself, as disclosed for priority purposes.

For this reason, Claim A1 and A2 cannot rely for priority purposes on any priority filings, dated 17.6.81, 11.11.81, 1.12.81 and 10.2.82.

Novelty (Article 54(3) and (4))

14. In view of the above, Claims A1 and A2 may only rely on the European application date, and might therefore be affected by the disclosure of document (1), including the content of the European application filed on 8 January 1982. This specification not only describes the preparation of the prorennin (a synonym of prochymosin) gene and its provision with ATG (cf. page 32) but also includes the combination of clones to provide a complete clone (cf. page 19 et seq) and, from that, a prochymosin clone (cf. page 30 et seq).

15. The cleavage of the prochymosin protein, however, to chymosin is neither directly expressed nor unequivocally implied in the disclosure of document (1). The chapter on the expression of "methionine-prorennin" is silent on any further steps (cf. pages 30-32). Any implied cleavage, in terms of "activation", relates to other proteins (cf. page 46, lines 1-5 and page 50, penultimate line to page 51, line 4). The reference to the nucleotides responsible for the formation of the inactive "zymogen part

of rennin (chymosin) (page 57, last lines, to page 58, line 4), which "is removed" to generate active rennins, is no disclosure of the specific cleavage step claimed in the present case, but relates to the DNA level. Document (1) is, therefore, ineffectual in destroying the novelty of Claims A1 or A2 under Art. 54(3) EPC, irrespective of its own priority rights.

16. The other relevant citation is document (2), filed after the present European application on 13 October 1982 relying on a priority filing on 14 October 1981. The decision of the first instance considered the disclosures of document (2) as destroying the novelty of the main claim in the present case. It was suggested that (2) was entitled to the priority date of 14 October 1981, since there was reasonable evidence that the microorganisms and plasmids referred to in the European application were "identical to the microorganisms and plasmids referred to in the prior document". The two descriptions were said to be "almost identical".

17. It is to be examined what disclosures in the relevant first priority document of (2) could be construed as making, as a state of the art, the inventions in the present case, available to the skilled person. Irrespective of the question of priority (as explained by a Board of Appeal in case T 206/83, "Herbicides/ICI", OJ EPO 1987, 5), any document cited under Article 54(2) and (3) EPC must contain an enabling disclosure in order to be novelty destroying. And as also explained in the same case, this requirement as to the sufficiency of disclosure is identical to that under Article 83 EPC (cf. page 9, Point 2). In other words: the cited document must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a man skilled in the art.

18. There is no indication in the decision under appeal that the Examining Division considered the question, whether document (2) satisfied that said requirement of enabling disclosure. In this respect it is particularly to be noted, that the deposits of micro-organisms relating to (2) were made only in May and September 1982, i.e. much later than the date of filing of the priority application. It is unclear, whether the Examining Division was aware of this when it considered document (2) as anticipatory and, if so, attached any importance to this fact, or whether it took the view that the priority application for (2) as such was sufficient for that purpose.

19. Document (2) outlines all steps to obtain the desired end products, including preprochymosin. It is a sort of general recipe of the standard approach to isolate and construct precursors or intermediate substances. The preparation of a great number of plasmids containing at least a part of a desired gene are mentioned by individual names and numbers followed by construction schemes. It is doubtful whether the initial plasmids are publicly available in the absence of reference in this respect. No detailed experimental data of the actual procedure of the necessary steps is given.

20. The suggested scheme is full with references to other publications implying that methods suggested elsewhere should be applied, without making exactly clear what adaptations and modifications would be required to render them successful in the circumstances of the given process. This is particularly important in a field where the repetition of the process inevitably involves variations and deviations, and the knowledge of a model based on facts might assist the correction of the course. The suggested strings of plasmids are uncertain as to their exact compositions. Whilst it may not be absolutely

impossible to proceed on the basis of the citation, a novelty destroying document must, according to standard practice, be enabling without undue burden to a person skilled in the art. In such circumstances, inventions might require an actual demonstration of reduction to practice and corresponding detailed instructions to the public in a document, to become available for the purposes of Article 54 EPC as part of the state of the art. The Board does not consider it appropriate to take a final position on this point without having a reasoned opinion of the first instance. It is therefore the view of the Board that the first instance should examine the matter of sufficiency of the citation.

Other matters

21. The case is therefore to be remitted for further substantive examination on the basis of the above claims. Since the claims of auxiliary set C were not subject of refusal and would have been remitted by the Board even when set A had been unacceptable, it is assumed that the former was not abandoned by the Appellant by implication in any sense.

Order

For these reasons, it is decided that:

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

2. The case is remitted to the Examining Division with the order to continue the prosecution of the application on the basis of Claims 1 and 2 of auxiliary set A.

The Registrar: The Chairman:

F.Klein P.Lançon