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Bezeichnung der Erfindung: Recombinant DNA means and method
Title of invention:
Titre de l'invention :

Klassifikation / Classification / Classement : C12N 15/00

ENTSCHEIDUNG / DECISION

vom / of / du 24 January 1989

Anmelder / Applicant / Demandeur : Collaborative Research Inc.,

Patentinhaber / Proprietor of the patent /
Titulaire du brevet :

Einsprechender / Opponent / Opposant :

Stichwort / Headword / Référence : Preprorennin/COLLABORATIVE

EPÜ / EPC / CBE Articles 54(3), 83, 84, 87 and 88 EPC

Schlagwort / Keyword / Mot clé : "Priority - missing essential features"

Leitsatz / Headnote / Sommaire

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 previous application as a whole. Identical wording is not required.

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. points 5 to 13 of the reasons).

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Case Number : T 81/87 - 3.3.2

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

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Decision under appeal : Decision of Examining Division 023 of the European Patent Office dated 13 October 1986 refusing European patent application No. 82 100 124.5 pursuant to Article 97(1) EPC

Composition of the Board :

Chairman : P. Lançon
Members : G. Szabo
P. Gori
E. Persson
P. Rotter

Summary of Facts and Submissions

I. European patent application 82 100 124.5 filed on 8 January 1982 and published on 11 August 1982 with publication number 57 350, claiming priority of the prior applications of 16 January and 1 December 1981 (US-225 717 and 325 481), was refused by the decision of the Examining Division of the European Patent Office dated 13 October 1986. The decision was based on Claims 1 to 27 of the main request and Claims 1 to 15 of the auxiliary request. The Claims 1 to 3 and 22 of the former were worded as follows:

1. A transformable living cell selected from the group consisting of fungi, yeast, bacteria and mammalian cells containing genetic material derived from recombinant DNA material and capable of expressing bovine rennin.

2. A transformable living cell selected from the group consisting of fungi, yeast, bacteria and mammalian cells containing genetic material derived from recombinant DNA material and capable of expressing bovine pre-prorennin.

3. A transformable living cell selected from the group consisting of fungi, yeast, bacteria and mammalian cells containing genetic material derived from recombinant DNA material and capable of expressing bovine prorennin.

22. Recombinant DNA material coding for a polypeptide signal sequence and having the following nucleotide and polypeptide sequence coding the said polypeptide

ATG AGG TGT CTC GTG GTG CTA CTT GCT GTC TTC GCT CTC TCC CAG GGC
MET ARG CYS LEU VAL VAL LEU LEU ALA VAL PHE ALA LEU SER GLN GLY.

II. One of the grounds for refusal was that the subject-matter of Claims 1 to 3 of the main request, as far as bacteria were concerned, was not novel in view of the disclosure of EP-A-77 109 (Unilever) (document (1)) under Article 54(3) EPC. The application-in-suit was not entitled to rely on the first priority filing on 16 January 1981 because the disclosure was incomplete and insufficient. None of the phages described at that time contained the complete preprorennin nucleotide sequence. Since the citation (1) properly relied on its priority date (14 October 1981), which was earlier than the second priority date of the Applicant (1 December 1981) and disclosed the expression of preprorennin, prorennin and rennin, the claims referred to were anticipated.

Another ground for refusal was that Claims 1 to 3 were not supported by the description which exemplified only the use of cells of Escherichia and Saccharomyces species. Since there was not enough information as to how expression might be achieved with different hosts, the description was insufficient under Article 83 EPC and the claims were unsupported in the sense of Article 84 EPC. In addition, Claims 22 and 23 of the main request were also unallowable under Article 84 EPC in view of internal inconsistencies (cf. Paragraph 4.2 of the decision).

The auxiliary requests were rejected on similar grounds.

III. An appeal was lodged on 12 December 1986 with the payment of the fee. A Statement of Grounds was filed on 10 February 1987 and further explanations were submitted on 24 April 1987. A Communication from the Board cited EP-A-68 691 (Celltech) (document (2)) as another copending application. In reply the Appellant filed additional submissions and evidence in the form of four Affidavits. Prior to that

Unilever filed observations under Article 115(1) EPC which were communicated to the Appellant. An oral hearing was held on 12 October 1988. The Appellant submitted a new set of Claims 1 to 24 to replace earlier claims, as the main set, and two auxiliary sets.

IV. In his submissions and at the oral hearing the Appellant argued substantially as follows:

(a) The Examining Division had wrongly assumed that the cited copending application (1) was supported by the depositions of microorganisms containing relevant plasmids at the time of its priority filing. In fact, deposition was only carried out much later, in May and September 1982. Priority of 14 October 1982 could therefore not be recognised for the citation (1), and it was the application in suit which anticipated the same.

(b) As to the question of whether or not the Appellant's first priority document duly disclosed the claimed invention, it was submitted that all essential features had been identified in that document. In fact, the disclosure was the first in the field suggesting a route through preprorennin to the other precursors. Preprorennin had been properly identified as having additional sixteen amino acids when compared with the structure of the known prorennin, and the corresponding DNA sequence had been suggested to contain 48 additional nucleotides (cf. page 5).

(c) The description of the process for obtaining the necessary phages containing the preprorennin sequence was adequate and enabled the skilled person to reproduce the invention. The expert affiants had testified that they would have had no difficulty to

obtain preprorennin and its derivatives according to the disclosure of the first priority document. If the phages contained only parts of the full sequence, it would have been only a matter of general knowledge to sequence the fragments, determine the common restriction sites and recombine the parts to obtain the desired complete gene. This was actually done later on but the skilled person would have been fully aware of how to cope with such situations.

V. The Appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the following sets of claims all submitted during the oral proceedings:

Claims 1 to 24 of the main request, or alternatively
Claims 1 to 16 of the first auxiliary request, or
Claims 1 to 16 of the second auxiliary request.

Reasons for the Decision

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

Amendments (Art. 123(2) EPC)

2. Claim 18 of the present main request relates to the additional nucleotide sequence which characterises the preprorennin gene as compared with the prorennin gene, and corresponds to former Claim 22 rejected in the decision of the first instance. The claim is supported by the description since the nucleotide sequence is derivable when Claims 15 and 16 are compared, and avoids the ambiguity of the earlier presentation. It is therefore acceptable from the formal point of view.

3. Claims 1 and 2 are based on former Claims 2 and 3, except that the lists of transformable living cells does not now include mammalian cells. The rest of the Claims 3 to 21 are identical with claims earlier on file and are adequately supported by the documents as originally filed (cf. decision of the Examining Division, page 17). All these claims are allowable under Art. 123(2) EPC. As regards new Claims 22 to 24, these refer to the activation of bovine prorennin or preprorennin, presumably for milk clotting. The meaning of this phrase does not appear to be clear but the matter could be dealt with in further prosecution in view of the final conclusions of the Board.

Sufficiency, clarity and support (Articles 83 and 84 EPC)

4. As regards the use of cells of various origin according to Claims 1 and 2, the disclosure repeatedly emphasises that these are such as to enable expressions of proteins. It was known at the time of filing that in addition to bacterial cells, various fungi, e.g. yeast cells, were suitable for the purpose. The specification itself refers to various preferred Escherichia and Saccharomyces strains in this respect. Thus, the terms in the claims are not without formal support, since it would be unfair to restrict the claims to the exemplified strains in the disclosure excluding those which may be used in the future. From the disclosure, it is implied for the skilled person that only those cellular organisms are relevant for use which have the capability to provide expressions of the desired proteins (cf. T 292/85, "Polypeptide expression/GENENTECH I", 27.1.1988, pages 10-13, Point 3.1, to be reported).

Thus, the disclosure in the European application is not insufficient or unsupported in these respects under Articles 83 and 84 EPC.

Priority (Articles 87 and 88 EPC)

5. Claims 1 and 2 of the main set relate to a transformable living cell containing genetic material which is inter alia "capable of expressing bovine pre-prorennin" or "prorennin" respectively. In view of the citation of other copending European applications in respect of novelty, it is necessary to establish the earliest priority date which these claims can rely upon.

6. 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 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.

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 documents (cf. Article 88(4) EPC).

7. Although Claim 1 only defines the starting genetic material as being derived from recombinant DNA material of the stated capability of expressing preprorennin for instance in a bacterial host, there are a number of features which are implied by the definition. For instance, the genetic material must otherwise be equipped for such purposes. The starting material itself, being a novel plasmid 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 prorennin, an otherwise known compound, let alone for preprorennin of unknown composition at the date of the priority document. The required genes are, therefore, solely to be defined and disclosed by their particular route of preparation. This is then characteristic of these DNA precursors, by implication, and therefore of the inventions relying upon them.

8. The actual steps to obtain the required preprorennin gene and then the appropriate plasmid include 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.

9. It is, however, clear from the disclosure in the European application, as well as from those of the cited copending applications, that the genetic precursors of rennin 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 obtained carried the full preprorennin gene. Rather recombinant phage 293-207 carried an insert bearing the sequence from nucleotide 1 to at least nucleotide 1360 except for nucleotides 848-961 which are deleted, while phage 293-118/37 only carried an insert bearing the sequence from nucleotide 229 to 1460. It was necessary to cleave and combine parts of phages 293-207 and 293-118/37 after the identification of their relevant structural constituents in order to prepare the gene which was complete and suitable to allow expression of preprorennin. Only after such steps could the method proceed to obtain for instance the prorennin gene.

To recombine certain specifically tailored, fragments from different clones is thus also, by implication, an essential part of the invention, as claimed.

10. It has been admitted that on the date of the first priority document, the idea of preparing prorennin or rennin by the recombinant DNA-technique was not reduced to practice by the Appellant. 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 293-207 already contains the "entire preprorennin sequence" (page 17, lines 16 and 17) (cf. also suggestions on page 17, lines 21-22) without any particular indication that in fact this was not, or might not, be the case. In addition, some essential steps further downstream

in the process, including the recloning steps and the selection of the suitable vector system, i.e. the successful path within the choice of numerous possibilities, were also missing from the disclosure defining the process and thereby the product obtainable in such manner. The first priority document was actually silent about such essential steps and thereby some basic features.

11. Whilst the presentation of the process up to the isolation of phages 293-208 and 293-118/37 was complete, the further disclosure based on what may be called a general outline of the standard approach failed to reveal some unsuspected characteristics which were peculiar to the route to the preprorennin gene.

When starting to reduce such a standard approach to practice in this specific field of recombinant DNA technique, the skilled person may be confronted with a lot of difficulties depending on whether there are for example precursor forms of the desired gene or suitable base sequences for application of restriction enzymes to cut the DNA at appropriate sites etc. Thus each gene which is scheduled to be prepared by recombinant DNA techniques presents unique problems which, in the whole cumbersome procedure, can only be solved step by step, each solution step being dependent on the recognition of circumstances derived from the analysis of the results of the foregoing step. 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 the

evidence filed by the Appellant to support priority misses the point concerning lack of basic disclosure.

12. Although no identical wording is required as stated in Point 6. above, the Board takes the view that in order to give rise to priority the disclosure of 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. Gaps with regard to basic constituents in this respect cannot be retrospectively filled by relying on knowledge acquired in this manner. It could become a misuse of the priority system if some parties in a competitive situation were allowed to jump ahead of others on the basis of mere expectations omitting the critical feature of the invention altogether. Such criticality was particularly apparent for features necessary to prepare the prorennin gene, which are not in the state of the art, and cannot be provided in any other way but the invention itself.

13. In conclusion the first priority document does not disclose all the critical features of the claimed invention as required. These only appear in the second priority document and in the European application.

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

14. In view of the above conclusion Claims 1 and 2 may only rely on the second priority date and might therefore be affected by the disclosure of document (1) filed on 13 October 1982, relying on a priority filing on 14 October 1981.

It was suggested that (1) was entitled to the priority date of 14 October 1981 since there was reasonable evidence that 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".

15. It is to be examined what disclosures in the relevant first priority document of (1) could be construed as making the inventions in the present case available to the skilled person (Art. 54(2) EPC). 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. 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.

16. There is no indication in the decision under appeal that the Examining Division considered the question, whether document (1) satisfied that said requirement of enabling disclosure. In this respect it is particularly to be noted, that the deposits of micro-organisms relating to (1) 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 (1) as anticipatory and, if so, attached any importance to this fact, or whether it took the view that the priority application for (1) as such was sufficient for that purpose.

17. Document (1) outlines all steps to obtain the desired end products, including preprochymosin, which is a synonym for preprorennin. It is a sort of general recipe of the standard approach to isolate and construct precursors or intermediate substances. The preparations 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 references in this respect. No detailed experimental data of the actual procedure of the necessary steps is given.

18. 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 theoretically 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.

19. The observations filed on behalf of the Applicants in respect of application (1) do not dispel the problems concerning the content of the same as a citation under Article 54 EPC. However, 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.

20. As far as further document (2) (EP-68 691 Celltech) is concerned, this copending application was filed on 11 June 1982, after the European application in the present case. The relevant priority filings for document (2) were dated 17 June, 11 November and 1 December 1981. However, the question whether or not this application could rely on these dates was also an issue in the copending appeal case T 269/87, decided on 24 January 1989 by the Board 3.3.2. According to the decision these priority documents failed to disclose some essential features of the same subject-matter, which is relevant to the claims in the present appeal, and fail to give support to establish priority rights. The Board in the present case concurs with the view and dismisses therefore document (2) from consideration.

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 prosecution of the application on the basis of the claims presented in all requests at the oral hearing.

The Registrar: The Chairman:

F.Klein P.Lançon

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