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Bezeichnung der Erfindung: Structural genes encoding the various allelic and maturation forms of preprothaumatin, recombinant cloning vehicles comprising said structural genes and expression thereof in transformed microbial host cells
Title of invention:
Titre de l'invention :

Klassifikation / Classification / Classement : C/2N 15/00

ENTSCHEIDUNG / DECISION

vom / of / du 27 January 1988

Anmelder / Applicant / Demandeur : Unilever N.V. et al

Patentinhaber / Proprietor of the patent /
Titulaire du brevet :

Einsprechender / Opponent / Opposant :

Stichwort / Headword / Référence : Preprothaumatin/UNILEVER

EPÜ / EPC / CBE Articles 83 and 84, Rule 28 EPC

Kennwort / Keyword / Mot clé : "Sufficiency - biological macromolecules - identical repeatability of examples"

Leitsatz / Headnote / Sommaire

There is no requirement under Article 83 EPC to the effect that a specifically described example of a process must be exactly repeatable. Variations in the constitution of an agent (here: genetic precursor) used in a process are immaterial to the sufficiency of the disclosure provided the claimed process reliably leads to the desired product (§6).

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Case Number : T 281/86 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2.
of 27 January 1988

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Decision under appeal : Decision of Examining Division 023 of the European Patent Office dated 11 February 1986 refusing European patent application No. 81 201 355.5 pursuant to Article 97(1) EPC.

Composition of the Board :

Chairman : P. Lançon
Members : G. Szabo
F. Benussi
G. Paterson
P. Rotter

Summary of Facts and Submissions

I. European patent application 81 201 355.5, filed on 11 December 1981 and published on 23 June 1982 with publication number 54 331, claiming priority of the prior application on 12 December 1980, was refused by the decision of the Examining Division 023 of the European Patent Office dated 11 February 1986. Claims 1, 2, 4, 6 8 and 10-12 are worded as follows:

"1. A DNA sequence selected from the group consisting of

(i) DNA sequences encoding

(a) non-processed preprothaumatin according to the formula of Figure 2 (preprothaumatin gene), or

(b) partly processed preprothaumatin according to the formulae of Figure 3 (prothaumatin gene) and Figure 4 (prethaumatin gene), and

(ii) the various allelic forms of the preprothaumatin gene given in Figure 5, and

(iii) the mutated various allelic genes encoding preprothaumatin with one or more mutations at positions 47, 507 and 513 as given in Figure 6.

2. Recombinant plasmids comprising

(i) a DNA sequence as claimed in Claim 1, and

(ii) an inducible or constitutive regulon which regulates the expression of said DNA sequences.

4. Recombinant plasmids according to Claim 3, selected from the group consisting of pUR 521, pUR 522 and pUR 523.

6. Recombinant plasmids according to Claim 5, selected from the group consisting of pUR 531, pUR 532 and pUR 533.

8. Recombinant plasmids according to Claim 7, selected from the group consisting of pUR 541, pUR 542 and pUR 543.

10. A bacterial culture comprising E. coli cells containing any one of the recombinant plasmids as claimed in Claims 2-8 with or without the AATT sequence originating from the linker as described in Claim 9 situated between the regulon and the structural gene of the recombinant plasmid.

11. A process for producing preprothaumatin, prethaumatin, prothaumatin or a processed form thereof by incorporating the recombinant plasmids as claimed in any one of Claims 2-8 in a microbial cloning vehicle, transforming microbial host cells with said vehicle, cultivating the transformed cells and isolating the protein produced by said cells.

12. A process for producing preprothaumatin, prethaumatin, prothaumatin or a processed form thereof by incorporating the recombinant plasmids as claimed in any one of the Claims 2-8 in a microbial cloning vehicle, transforming E. coli host cells with said vehicle, cultivating the transformed cells and

isolating the protein produced by said cells".

II. The ground for the refusal was that:

(a) the process described in the specific example (page 8, line 9 to page 10, line 18) was not exactly repeatable since the resulting plasmid pUR 100 could not be identified among the other genotypes obtained by the procedure in question, since the complete DNA sequence of pUR 100 had not been disclosed; and

(b) the further procedures starting from pUR 100 disclosed at page 10, line 20 to page 16, line 34, leading inter alia to the plasmids of Claims 4, 6 and 8, were also not repeatable and therefore insufficient under Article 83 EPC.

According to the decision (cf. pages 6 and 7), however, it remained undecided whether or not

(i) Claims 4 and 6, as far as they relate to plasmidic compounds pUR 522, 523 and 531 would be allowable under Rule 28 EPC if the deposition numbers were included in the claims;

(ii) bacteriophage RF M13-mp2 (cf. original page 11, line 30) was, as a starting material, available at the filing date and whether there was any guarantee that it remained permanently available to the public;

(iii) the description of the regulon in functional terms in Claim 2 was allowable under Articles 83 and 84 EPC in view of the non-availability of some yet to be specified versions; and

(iv) the non-repeatability of the above defined process under (a) was in conflict with process Claims 11 and 12, and product Claim 10.

III. The Appellant filed a Notice of Appeal against the decision on 21 April 1986 with the payment of the fee, and submitted a Statement of Grounds on 21 June 1986 together with new sets of auxiliary claims.

The Appellant submitted substantially the following arguments in support of the appeal:

(a) The process leading to plasmid pUR 100 was fully disclosed in the specification. Whilst this process was not exactly repeatable since small variations could be expected, the skilled person would have nevertheless found that the plasmid so obtained also contained the nucleotide sequence shown in Figure 2 or one which related to an allelic form of the preprothaumatin gene. Such sequences would also be equipped with additional dC- and dG-tails of varying length. All these forms of the plasmid should be equally suitable for obtaining preprothaumatin and the other thaumatin precursors thereafter.

(b) The route to further modified plasmids such as pUR 101 etc. was fully disclosed with reference to the Figures. Any differences in sequences could be countered by using appropriate restriction enzymes corresponding to different restriction sites. Thus, such differences in structure would not prevent the skilled person to carry out the claimed invention.

IV. As to the issues left undecided by the Examining Division, the Appellant argued with reference to the points (i) to (iv) raised (cf. under II) as follows:

(i) As a safety measure E.coli strains containing various plasmids described in the specification were deposited under Rule 28 EPC at the American Type Culture Collection. In the absence of any intervening publication the filing date of the European application was relevant.

(ii) Regarding the availability of some microorganisms which were suitable for the purpose, it was in this case irrelevant that specifically the RF M13-mp2 strain had actually been used to develop the plasmids in question. A number of other strains were also available which could be equally used for the purpose.

(iii) As to the availability of various other regulons not described in the application, the Appellant was entitled to a broad protection which could only be attained if a functional definition was permissible. In the field of catalysts and polymers, patents were granted although some of such components had not been completely disclosed in view of trade secrets, in spite of the fact that there was also a risk that commercially available products would disappear from the market.

(iv) Since the preparation of various thaumatin-like proteins was reproducible, there was no reason to object to Claims 10 to 12, in view of explanations under III(a) and (b).

V. The Appellant requests that the decision be set aside and the application be allowed on the basis of set III of claims which was the basis of the decision under appeal or of the auxiliary requests (set I or II).

Reasons for the Decision

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

2. No formal objections can be raised against the present wording of the claims which is adequately supported by the disclosure.

3. Claim 1 of set III relates to DNA sequences (genes) which encode for prepro-, the pre-, or the pro-thaumatin, as well as to some allelic forms of the first gene or certain mutations thereof. All these genes are exactly defined in the claim by reference to Figures 2, 3, 4, 5 and 6, respectively. The definitions are closed ("consisting of"), leaving no room for unspecified additional structural features. It can be seen from Figure 5 that the preprothaumatin gene (sequence 32-736) is the longest one, embracing the structures coding for the shorter pre-, and prothaumatin variants (sequences 32-718 and 98-736). The locations and character of allelic variations and mutated forms are exactly specified in Figures 5 and 6. Claim 2, on the other hand, relates to plasmids comprising the above sequences, as well as an operative regulon.

Sufficiency

4. It is clear from the description that all these nucleotide sequences and corresponding plasmids are to be prepared from plasmid pUR 100 "containing an almost complete copy of thaumatin mRNA" (page 10, lines 17-18). This nevertheless means that this plasmid includes the complete prepro-thaumatin DNA sequence, since after splitting with Pst I it yields an even longer 32-795 chunk (cf. Figure 10 and page 10, line 25 et seq). The process leading to this primary genetic precursor may show natural variations depending on the starting material and on the variance of

the plasmid population. For instance, additional dC- and dG-tails of various lengths are involved. There are, nevertheless, tests described to determine the exact nature of the inserts (cf. page 9, line 30 to page 10, line 18). Since the insert must include a code for preprothaumatin according to Figure 2, any plasmid containing this essential structural part can be identified. It can be ascertained in this manner whether or not the plasmid at this stage corresponds to what is described as pUR 100, the primary genetic precursor of the process according to the patent application. The plasmid pUR 100 itself is not claimed.

Identical repeatability

5. Whilst it is accepted that it is unlikely that the plasmid obtained on the basis of following the specific disclosure would be identical with pUR 100 originally prepared, there is no doubt that such products should be equally suitable for further processing and ought to lead just as well to the three thaumatin precursors and the suggested variant proteins through expression.

It is always the case in chemistry that the outcome of experiments show some fluctuations in yield, quality etc. This is irrelevant for sufficiency unless the invention requires certain characteristics in this respect. It should therefore be even less relevant if only the conditions and the means used to carry out a process show inevitable variations as long as the ultimate result is the same. The variants within the designation pUR 100 are means of such character.

6. It is therefore the view of the Board that there is no requirement under Article 83 EPC to the effect that a specifically described example of a process must be exactly repeatable. Variations in the constitution of an agent used

in a process are immaterial to the sufficiency of the disclosure provided the claimed process reliably leads to the desired product. As long as the description of the process is sufficiently clear and complete, i.e. the claimed process can be put into practice without undue burden by the skilled person taking common general knowledge also into consideration, there is no deficiency in this respect.

7. In the absence of evidence to the contrary, the Board accepts that all the finite number of DNA sequences specified in Claim 1 of set III could be obtained by following the instructions of the application, irrespective of the inevitable structural variations of the primary pUR 100 or its close analogues which are formed by the process. It appears from the explanations from the Appellant (Statement of Grounds, page 4, line 19, et seq.) that any differences in the sequence can be handled by the skilled person appropriately, e.g. by using different restriction enzymes etc. The sufficiency of disclosure with regard to an intermediate plasmid in this field of genetic materials primarily depends on a utilisable possession of basic DNA structures and other components which are needed to lead to other plasmids and finally to the expression of a desired polypeptide at the end of a complex process. As long as such potential is verifiable and there are no elements or components in the plasmid which would contradict this, the description is not insufficient on this basis.

8. Since the primary genetic precursor for the processes described at page 10, line 20 to page 16, line 34, under Claim 9 (Set III) leading to further plasmids (including those of Claims 4, 6 and 8) and to proteins under Claims 11 and 12 is available, in the Board's view the skilled person is in a position to carry out the claimed inventions in these respects as well.

According to the cited passages a 32-795 sequence is obtained from pUR 100. This is actually further split to provide fragment A (32-108) which is then united again with a fragment B (109-791) obtained by a different splitting process from pUR 100 (cf. Figures 10 and 11, and corresponding description, leading to pUR 101). The resulting plasmid containing a 32-791 sequence should then be optionally further processed to contain only the prethaumatin (32-718) or the prothaumatin (98-791) sequence (Figures 13 and 14), or further treated to prepare mutants (Figures 15 and 16). In any case the so provided plasmids also yield the appropriate sequences which can be incorporated in the suitable vectors pUR 201, 301 or 401, to provide three new plasmids for each thaumatin precursor (Figures 17, 18 and 19) or other mutated forms (Figures 19 and 20). These plasmids have the ability to express the required polypeptides (page 17, lines 10 to 37), in appropriate hosts, to yield detectable amounts of the desired end-product. Thus no insufficiency under Article 83 EPC arises on account of the preparation or the further use of plasmid pUR 100, with regard to the claims of set III, and the same applies to the other sets with the exception of Claim 1 of set I (cf. paragraph 11).

Undecided issues

9. The Examining Division also raised some further issues concerning sufficiency of description and claims, i.e. matter related to Articles 83 and 84 EPC, without full reasoning and without making any decision (cf. II.(i) to (iv) and corresponding submissions IV.(i) to (iv)). It is understandable that the Examining Divisions were reluctant to carry out substantive examinations on various issues as long as there was prima facie a fatal flaw involved in the application, but even in such cases, at least all issues coming under the same ground of objections, as for instance interrelated matters of insufficiency, should be dealt with

so that the risk of repeated appeals can be avoided. It would have been more proper if the Examining Division had made reasoned further objections, instead of merely raising suspicions, which are, in any case, potentially unfairly prejudicing the Applicant's position.

10. In view of the above and in order to avoid a loss of instance for the Appellant, the Board prefers to exercise its right to remit the case to the first instance in respect of the outstanding matters on insufficiency. Nevertheless, it is apparent that some of these issues are similar or identical to those which have been decided by the present Board in case T 292/85, ("Polypeptide expression/GENENTECH I", 27 January 1988, to be reported in OJ). Thus, the first instance is in a position to resolve some of the further problems accordingly. There are, in any case, other basic issues outstanding for the substantive examination.

11. The Board, in the circumstances, finds it also inappropriate to investigate of its own accord other issues which were first introduced at the appeal stage. Nevertheless, it must be observed that Claim 1 of set I of the auxiliary request is much broader than that of set III and relates to a number of unidentified allelic or mutant variants of thaumatin precursors. Whether or not the functional limitation to "thaumatin-like" properties is sufficiently meaningful, and whether or not the embodiments of the invention can be carried out by the skilled person on the basis of the description involves questions which go beyond the principles relevant to the sufficiency of disclosure relating to the Claim 1 of the original set III. Similarly, Claims 11 and 12 of set III refer to the use of "microbial" cloning vehicles which go beyond the use of bacteria specifically dealt with in the above decision referred to (T 292/85). No specific objections in this

respect have so far been mentioned by the first instance.

12. Questions may also be raised with regard to the disclosure on page 8, lines 16-23, where it is not immediately clear how the required mRNA could be identified without undue burden by the skilled person. Furthermore, there is no literature reference suggested in relation to the method outlined in paragraph 8d, on page 12, line 33 to page 13, line 8 and Figure 15, which could be accepted as representing common general knowledge about such methodology on the date of the application. Finally, it is also unclear how the presence of the various polypeptide products could unambiguously be identified on the basis of page 17, lines 28-37, unless full sequencing was already common knowledge at the relevant time.

13. So far as the points raised in paragraphs 11 and 12 are concerned, the Board wishes to make it clear that it makes no findings in these respects, and is merely mentioning them by way of observation. The first instance is entirely free to come to its own conclusions on these points during prosecution.

Order

For these reasons, it is decided that:

1. The decision of the first instance is set aside.

2. The case is remitted to the Examining Division for further prosecution.

The Registrar: The Chairman:

F. Klein P. Lançon

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