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D E C I S I O N
of 23 July 1999

Case Number: T 0295/96 - 3.3.4

Application Number: 88200376.7

Publication Number: 0284126

IPC: C12N 15/75

Language of the proceedings: EN

Title of invention:
Stable gene amplification in prokaryotic chromosomal DNA

Patentee:
Gist-Brocades N.V.

Opponent:
Novo Nordisk A/S

Headword:
Gene amplification/GIST-BROCADES N.V.

Relevant legal provisions:
EPC Art. 54, 113(1)

Keyword:
"Novelty, no"
"Reimbursement of appeal fee, no"

Decisions cited:
T 0124/87, T 0153/85

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0295/96 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 23 July 1999

Appellant: (Opponent)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 19 January 1996 concerning maintenance of European patent No. 0 284 126 in amended form.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: F. L. Davison-Brunel
C. Holtz

Summary of Facts and Submissions

I. European patent No. 0 284 126 with the title "Stable gene amplification in prokaryotic chromosomal DNA" was granted on the basis of European application No. 88 200 376.7 with 34 claims for the designated Contracting States AT, BE, CH, DE, FR, GB, GR, IT, LI, LU, NL, SE and 26 claims for the Contracting State ES .

Granted claim 1 for all Contracting States but ES read as follows:

"1. A transformed prokaryotic host cell comprising at least two copies of a DNA sequence in its chromosome, said DNA sequence encoding a polypeptide of interest, wherein said copies are separated by endogenous chromosomal DNA which is vital to the host cell."

Independent claim 2 related to the same transformed cell being obtainable by a specified method.

Dependent claims 3 to 13 related to further features of the transformed prokaryotic cell. Claim 14 was addressed to a method for preparing a transformed prokaryotic cell and dependent claims 15 to 30 related to further features of this method. Claims 31 to 33 were addressed to specific Bacillus strains and claim 34 was addressed to the use of a transformed prokaryotic host as defined in claims 1 to 13 for the production of a polypeptide of interest.

The corresponding method claims were filed for the Contracting State ES.

II. A notice of opposition was filed requesting the revocation of the patent in suit under Article 100(a) EPC (lack of novelty and inventive step).

III. The Opposition Division maintained the patent in amended form on the basis of a new main request. Claims 3 to 13, 15 to 34 (claims 2 to 26 for ES) of this request remained as granted. Claims 1, 2 and 14 (claim 1 for ES) differed from the granted claims 1, 2 and 14 (claim 1 for ES) in that the expression "and said copies are stably maintained" was added after the wording "... endogenous chromosomal DNA which is vital to the host cell".

IV. The Appellants (Opponents) filed an appeal, paid the appeal fee and submitted a written statement setting out the grounds of their appeal, together with 13 further documents.

V. The Respondents (Patentees)made no submission in the appeal proceedings.

VI. The following documents on file are mentioned in this decision:

(1) EP-A-0 127 328

(13) Ferrari, E. and J.A. Hoch, Mol.Gen.Genet., Vol. 189, pages 321 to 325, 1983,

(14) Williams, J. and A. Szalay, Gene, Vol. 24, pages 37 to 51, 1983,

(17) Bacillus subtilis and Other Gram-Positive

Bacteria, Chapter 29, 1993, Editor in Chief A. Sonenshein, American Society for Microbiology, Washington D.C.,

(21) Haldenwang, W.G. et al., J. of Bacteriol., Vol. 142, No. 1, pages 90 to 98, 1980.

VII. With regard to novelty, the Appellants submitted in particular that the strain 857/16 disclosed in document (13) had all of the properties of the transformed prokaryotic strain of claim 1.

In the event claim 1 was found novel, the Appellants argued that it lacked inventive step in view of the teaching of document (1) taken alone or in combination with document (14) or in combination with the skilled person's general knowledge.

It was also argued that the appealed decision suffered from two drawbacks. Firstly, the Opposition Division apparently did not understand the Opponents' reason to cite decision T 124/87 (OJ EPO 1989, 491). Secondly, the Opposition Division based their decision on an aspect (the issue of selection invention) that had never been discussed during the proceedings, causing a violation of Article 113(1) EPC.

VIII. The Appellants requested that the decision under appeal be set aside and the patent be revoked in its entirety. Moreover, it was requested that the appeal fee be refunded for reason of procedural violation. As an auxiliary request, oral proceedings were requested.

There are no requests on file from the Respondents.

Reasons for the Decision

1. The appeal is admissible.

Article 54 EPC, novelty of claim 1:

2. Document (13) (page 323, right-hand column) discloses the **E.coli** recombinant vector p63 which comprises a plasmid related to pBR322, pMB9 and the 5 Kb region of the **Bacillus subtilis** chromosome. Document (21) which is cited in document (13) and which is, thus, to be considered as part of the disclosure of said document in accordance with the case law of the Boards of Appeal (see for example T 153/85 OJ EPO 1988, 001), discloses on page 98 that the 5Kb region contains the tms, spoVC and 0.4 Kb genes. The spoVC gene is said to encode a polypeptide involved in spore development whereas the 0.4 Kb gene is of interest for the study of said development (document (21), page 98).

3. The transformation of p63 in the **Bacillus** strain, JH 857 is described on page 324, left hand column first paragraph of document (13). JH 857 carries the pBR322 related plasmid pFH7 inserted in the integration site for SPâ on the chromosome. Some transformants are, thus, obtained wherein the p63 plasmid is inserted in pFH7 by homologous recombination. A PBS1 transducing lysate of one of the transformants is, then, prepared. Some of the transducing PBS1 phage particles are expected to contain the SPâ:pFH7:p63 DNA and indeed the lysate is capable of transducing the 5Kb **B.subtilis** region of p63 into the strain JH 974 (gua-1, metB3,

tms26), as shown by recovery of JH 974 transductants which are wild type for the tms gene (page 324, right hand column, first paragraph). A further study of these transductants leads to the isolation of strain 857/16, the chromosomal structure of which is given in Figure 2. Strain 857/16 carries a duplication of the 5Kb spoVC, 0.4 Kb, tms region: one set of these genes (spoVC, tms26, 0.4 Kb gene) is found at its normal chromosomal location in the vicinity of the gua-1 marker, the second set of these genes (spoVC, tms^+, 0.4 Kb gene) is found in the vicinity of the metB3 marker where the p63 DNA carried by the transducing phage particle has integrated in the SPâ-pFH7 locus.

4. Figure 2 of document (13) shows in particular the chromosomal structure of strain 857/16: in this strain, the two sets of spoVC, tms26, 0.4 Kb genes are separated by endogenous chromosomal DNA of such a length that it must necessarily be vital to the host cell. It is noticed that this conclusion was later confirmed in document (17) which shows that the spoVC, 0.4 Kb gene region is situated at 7° on the map of the **Bacillus subtilis** chromosome whereas the SPâ-pFH7 locus is at position 190°. They are thus located at about the opposite sides of the circular 360°chromosome.

4. With regard to stability, it is stated in document (13) that the two sets of spoVC, 0.4Kb genes remain intact in the strain containing them.

5. Accordingly, document (13) discloses a strain, 857/16, which comprises two copies of a DNA sequence encoding a polypeptide of interest (the spoVC or 0.4 Kb gene) which are separated by endogenous DNA which is vital to

the host cell, said copies being stably maintained. These features are those of the transformed prokaryotic cell of claim 1. Accordingly, the subject-matter of claim 1 is not novel.

Refund of the appeal fee

6. The Appellants argued that the decision made by the Opposition Division was proceduraly deficient for the reasons that the arguments they had presented in relation to the decision of the Boards of Appeal T 124/87 (loc.cit) had been misunderstood, and that the decision to acknowledge novelty of claim 1 had been taken on the ground that the claimed subject-matter was a selection invention, which ground they had had no opportunity to comment upon.

7. In the Board's view, the fact that the Opposition Division may have misunderstood the arguments presented by the Appellants, if accepted, could only be considered an error in judgment which does not amount to a procedural violation.

8. It is only in their written decision that the Opposition Division defined the subject-matter of claim 1 as a "selection invention" over the teachings of the documents cited in relation to novelty. The two features which led them to this finding were that the claimed prokaryotic host cell contained duplicated copies of genes of interest which were stable and which were separated by vital endogenous chromosomal DNA.

9. The Board notices that this latter feature was already identified as a feature to be discussed in the context

of novelty in the communication sent by the Opposition Division in preparation for oral proceedings. Furthermore, the Minutes of these proceedings show that both features were the two main points discussed in relation to novelty. In the Board's judgment, the Appellants, thus, had ample opportunity to present their comments on the substantive matters even if the Opposition Division somewhat belatedly regrouped them under the term "selective invention". Accordingly, Article 113(1) EPC has been observed.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

3. The request that the appeal fee be refunded is refused.

The Registry: The Chairwoman:

U. Bultmann U. Kinkeldey