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D E C I S I O N
of 10 October 2003

Case Number: T 0397/02 - 3.3.8

Application Number: 91903051.0

Publication Number: 0505500

IPC: C12N 15/67

Language of the proceedings: EN

Title of invention:
Endogenous gene expression modification with regulatory element by way of homologous recombination

Patentee:
Applie Research Systems ARS Holding N.V.

Opponents:
Gruppo Lepetit SpA
Cell Genesys, Inc.

Headword:
Endogenous gene expression/APPLIED RESEARCH SYS

Relevant legal provisions:
EPC Art. 83, 123(2), 84

Keyword:
"Late-filed documents - criteria for admission of some into proceedings"
"Sufficiency of disclosure - main and first auxiliary requests - no"
"Added subject-matter - second auxiliary request - yes"
"Clarity - second auxiliary request - no"
"Reimbursement of the appeal fee paid by the Intervener - yes"

Decisions cited:
T 0721/89, T 0984/00, T 0792/00, T 0292/85, T 0455/91, G 0001/94, T 0027/92, T 0780/95, G 0004/03

Catchword:
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Case Number: T 0397/02 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 10 October 2003

Appellant: (Proprietor of the patent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 7 March 2002 revoking European patent No. 0505500 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: F. L. Davison-Brunel
V. Di Cerbo

Summary of Facts and Submissions

I. European patent No. 0 505 500 with the title "Endogenous gene expression modification with regulatory element by way of homologous recombination" was granted with 21 claims on the basis of European patent application No. 91 903 051.0.

II. Two oppositions were filed. The Opposition Division revoked the patent for the reason that the requirements of Article 83 EPC were not fulfilled in relation to the subject-matter of claim 1 of the set of claims then on file which was identical to the set of granted claims save for the change from "eukaryotic" to "mammalian" in claim 16 and the deletion of "optionally" in claim 18.

Claim 1 read as follows:

"1. A method of activating a normally transcriptionally silent gene within the genome of a eukaryotic cell line and expressing the gene product of said gene, comprising:

(a) inserting a DNA construct into said genome by homologous recombination, said DNA construct comprising a DNA regulatory segment capable of stimulating expression of said gene when operatively linked thereto and a DNA targeting segment homologous to a region of said genome within or proximal to said gene, wherein said construct is inserted such that said regulatory segment is operatively linked to said gene of interest;

(b) culturing the cell line under conditions which permit expression of said gene product; and

(c) collecting said gene product."

Claim 2 was directed to the same method for modifying the expression characteristics of a gene. Dependent claims 3 to 15 were directed to further features of the methods of claims 1 and 2. Claim 16 related to the genome of a mammalian cell line having given features, claims 17 and 18 related to differentiated eukaryotic cell lines capable of expressing a gene product encoded by a normally silent gene. Dependent claims 19 to 21 were directed to further features of the cell lines of claims 17 or 18.

III. The Appellants (Patentees) filed an appeal, paid the appeal fee and submitted a statement of grounds of appeal on 15 July 2002. The only request for consideration by the Board was that refused by the Opposition Division.

IV. Accelerated proceedings were requested by the Appellants on 7 February 2003 in view of infringement proceedings instituted by them on 21 January 2003 in the Netherlands against Transkaryotic Therapies Inc. et al.

V. Oral proceedings were summoned for 9 and 10 October 2003.

VI. On 17 April 2003, the assumed infringer (Intervener) filed a notice of intervention, paid an opposition fee and an appeal fee. The statement setting out the

Intervener's grounds of opposition followed on 23 April 2003. A new ground of opposition was raised under Article 100(c) EPC.

VII. Respondents I (Opponents 1) filed an answer to the grounds of appeal.

VIII. On 17 July 2003, the Board sent a communication under Article 11(1) of the Rules of Procedure of the Boards of Appeal, setting out the main issues to be considered as well as its preliminary, non binding opinion. A time limit of two weeks before the oral proceedings was set for making any written submissions.

IX. Submissions followed from the Intervener, Respondents I and the Appellants. With their last submissions on 25 September 2003, the Appellants submitted 19 new documents (numbered (96) to (114)) and 7 auxiliary requests in addition to the main request (claims refused by the Opposition Division). Respondents I objected to the admission of the new documents in the proceedings.

X. At the oral proceedings, the Appellants replaced the seven auxiliary requests by two new auxiliary requests:

Claim 1 of auxiliary request A read as follows:

"1. A method of activating a normally transcriptionally silent gene within the genome of a eukaryotic cell line and expressing the gene product of said gene, comprising:

a. inserting a DNA construct into said genome by homologous recombination, said DNA construct comprising

i. a DNA regulatory segment capable of stimulating expression of said gene when operatively linked thereto;

ii. a DNA targeting segment homologous to a region of said genome within or proximal to said gene;

iii. a positive selectable marker gene having an associated promoter;

wherein

the placement of the positive selectable marker gene and its promoter is such that the promoter will stimulate expression of its associated gene without simultaneously disrupting in any way the expression of said gene of interest or any other gene of the construct; and

said construct is inserted such that said regulatory segment is operatively linked to said gene of interest without introducing a starting codon;

b. culturing the cell line under conditions which permit expression of said gene product; and

c. collecting said gene product."

Claim 1 of Auxiliary request B was directed to a method of enhancing the expression characteristics of a gene that is not totally transcriptionally silent within the genome of a eukaryotic cell line and expressing the product of said gene, comprising the

same steps (a) to (c) as those of the method of claim 1 of Auxiliary request A.

XI. The following documents are mentioned in the present decision.

(42): Declaration of Dr. M. Heartlein dated 30 November 1999,

(46): Chelly, J. et al., Proc.Natl.Acad.Sci., Vol. 86, pages 2617 to 2621, April 1989,

(58): Kaufman, R.J., Bioprocess Technol. No. 10, pages 15 to 69, 1990,

(61): WO 93/09222 published on 13 May 1993,

(63): Declaration of Prof. W. Brammar dated 26 November 2001,

(96): Comparison of the construct of Example 21 of document (61) and Figure 1 of the patent in suit,

(97): Declaration of Prof. D. Martin dated 24 September 2003,

(98): Declaration of Dr. A. Stern dated 25 September 2003.

(105): Declaration of Dr. D. Stillman dated 25 September 2003.

XII. The Appellants' arguments in writing and during oral proceedings insofar as they were relevant to the present decision may be summarized as follows:

Main request; sufficiency of disclosure in relation to the subject-matter of claim 1:

The general part of the description, pages 5 to 9 gave sufficient instructions for the skilled person to be able to reproduce the invention: how to achieve homologous recombination was described in detail and culturing the cells and collecting the gene product was a matter of routine experimentation. In document (97), paragraph 3, it was stated that once the method was thought of, it was simple to put it into practice. Respondents I themselves had used it to obtain the protein they wanted to produce (document (61)). The same approach as that claimed was also used in document (98). The Appellants had provided a new way to achieve expression which could be fully implemented starting from the generally applicable teaching.

For this reason, the relevance of any example was minimal. Although the case law required that at least one way of carrying out the invention was shown, it also concluded that in some instances, an example was not necessary (T 721/89 of 8 November 1991, T 984/00 of 18 June 2002). The findings in T 792/00 of 2 July 2002 that sufficiency of disclosure could not be acknowledged if the Patentee had failed to give a single reproducible example when the invention went against prevailing technical opinion did not apply since there existed no technical prejudice in the case at issue.

Admittedly, the example provided did not go as far as showing protein production, yet this was not the intended goal. On the contrary, activation of transcription was demonstrated which was the real hurdle to overcome for expression to occur. It did not matter if the transcription originated from a promoter (RSV1) upstream from the promoter (RSV2) where the transcription of the silent gene would be expected to initiate. It was common general knowledge at the filing date of the patent (document (58)) that transcription from an upstream promoter may occlude transcription from a downstream promoter.

Document (42) showed that random recombination in the chromosome of essentially the same construct as exemplified also resulted in transcription starting exclusively from the promoter the furthest away from the silent gene. Thus, using homologous recombination to couple said gene to a functional promoter was not a reason why the claimed method would not work.

On the basis of his/her own common general knowledge, the skilled person would know how to modify the construct described in the example so that transcription would start where required, as attested in documents (63) and (97). And besides, instructions were given in the general part of the specification for example, as to the possibility of reverting the direction of transcription of the selectable marker to prevent its transcription from interfering with that of the silent gene and as to the necessity of making sure that the first AUG on the silent gene mRNA be that of the silent gene.

Auxiliary request A: sufficiency of disclosure in relation to the subject-matter of claim 1:

The method as now claimed in claim 1 would necessarily lead to the synthesis of a transcript and this transcript would be translated into a protein. The example provided the skilled person with such encouragement as was needed to modify the construct in accordance to the wording of the claim in order to obtain the product of the silent gene per se. The requirements of Article 83 EPC were fulfilled.

Auxiliary request B; claim 1, added subject-matter, clarity:

The feature in claim 1: "the placement of the positive selectable marker gene and its promoter is such that the promoter will stimulate expression of its associated gene without simultaneously disrupting in any way the expression of said gene of interest or any other gene of the construct" found a basis in the passage bridging pages 22 and 23 of the application as filed. The skilled person would understand this passage as an implicit disclosure that the transcription of only the selectable marker must be such that it does not interfere with that of the gene of interest because the patent specification taught that all other genes, and therefore their transcripts, were dispensable. The feature complied with the requirements of Article 123(2) EPC.

On page 23 of the application as filed, it was taught that a gene was to be considered silent if no mRNA

could be detected by Northern Blot. It was, thus, clear that the feature "a gene that is not totally transcriptionally silent" meant a gene which was transcribed at a low level as could be detected by this method. The requirements of Article 84 EPC were fulfilled.

XIII. The arguments in writing and during oral proceedings by the Respondents and the Intervener, insofar as they are relevant to the present decision, may be summarized as follows:

Main request; sufficiency of disclosure in relation to the subject-matter of claim 1:

Sufficiency of disclosure in relation to an invention which was claimed to open an entirely new field required that an example would be given of how to carry out this invention: here, that the transcription and translation of the silent gene be demonstrated.

The sole example described in the patent specification did not even provide credible evidence that the transcription of the TSHβ gene occurred, let alone that the direct transcript of said gene had been obtained. In fact, further experimentation had shown that the transcript originated from the RSV1 promoter well upstream of the silent gene and that the resulting mRNA was a hybrid molecule comprising sequences from the neo, RSV2 and silent gene regions, which bore no resemblance to a gene product. The skilled person reading this example would have serious doubts that the claimed method could be put into practice unless the construct was entirely re-designed and this would have

to be done in the absence of any assurance that the measures taken would be adequate.

It was not so that re-designing the construct could be achieved without undue burden on the basis of common general knowledge. The hypothesis of promoter exclusion invoked by the Appellants to explain lack of transcription from RSV2 would not necessarily have been thought of as the right one since one would expect some transcription to take place under such circumstances. Other problems, much more difficult to cure could be the reasons why transcription did not initiate from RVS2, such as DNA secondary structures. The many ATGs which had been inserted upstream of the TSHβ gene start codon during the event of homologous recombination would also have to be eliminated. All this amounted to undue burden.

Auxiliary request A: sufficiency of disclosure in relation to the subject-matter of claim 1:

As already mentioned in relation to the main request, in a case relating to a technical breakthrough, it was incumbent to the patent proprietor to show that the invention could be put into practice. One way to do this was to give a proper working example.

The fact that claim 1 contained some limitations purportedly addressing some of the difficulties one may encounter while trying to obtain gene expression did not change the fact that no evidence was provided that gene expression would be achieved by carrying out the claimed invention within the limitations. The example as it stood was no more of use to illustrate the method

of claim 1 of this request than it had been to illustrate the method of claim 1 of the main request.

Auxiliary request B: claim 1, added subject-matter; clarity:

The passage bridging pages 22 and 23 of the application as filed contained a statement to the avail that the transcription of neither of the genes present in the construct should be disrupting the transcription of the gene of interest or of the other genes of the construct. This statement could not be a basis for the feature of claim 1 that only the transcription of the selective marker gene should not disrupt that of the gene of interest or of the other genes of the construct. The requirements of Article 123(2) EPC were not fulfilled.

The expression "a gene that is not totally transcriptionally silent" was not clear because the notion of "being not totally transcriptionally" silent depended on the method of measurement.

XIV. The Appellants requested that the decision under appeal be set aside and that the case be remitted to the first instance for the assessment of the requirements under Article 123(2) and 56 EPC in respect of the main request; in the alternative, that the case be remitted to the first instance for further prosecution on the basis of the auxiliary requests A) or B) filed at the oral proceedings.

The Respondents requested that the appeal be dismissed.

The Intervener requested that the appeal be dismissed and that the appeal fee be reimbursed.

Reasons for the decision

Admissibility of the intervention:

1. No objections were raised by the Appellants to the admissibility of the intervention of the assumed infringer. The intervention was filed at the appeal stage within three months of the date on which infringement proceedings were instituted by the patent Proprietor against the Intervener. The notice of intervention was duly filed in a written statement and raised a new ground of opposition under Article 100(c) EPC. According to the decision G 1/94 (OJ EPO 1994, 787), intervention of the assumed infringer under Article 105 EPC is admissible during pending appeal proceedings and may be based on any ground of opposition under Article 100 EPC, including fresh grounds. The Intervener paid both the opposition and appeal fees. Thus, the intervention is admissible.

Admissibility of 19 new documents in the proceedings:

2. On 25 September 2003, ie. exactly within the time limit set up in the Board's communication dated 17 July 2003 for the filing of new submissions, the Appellants filed 19 new documents and/or declarations. In the Board's judgement, new submissions filed at a late stage of the proceedings following a Board's communication may not be of any kind. They must of course be relevant (Article 114 EPC) but also they are normally understood

to be made in form of a presentation of arguments or counterarguments in support of a given issue as raised by the Board. They might serve, for example, in assessing a given prior art document on file. Occasionally, this may require the filing of a further document (eg. a textbook) or, more rarely , a declaration of an expert. Submissions which change the framework of the appeal (eg. by raising new aspects) or the filing of new experimental evidence are not normally admitted at this stage. The Board, having in mind that one of its major tasks within inter partes proceedings is to safeguard the principle of equal rights of the parties, which requires that all parties to the proceedings be treated fairly and in particular be given the same opportunities to defend their case, considers it appropriate to exercise its discretion under Article 114(2) EPC in the light of the above criteria.

3. In line with this reasoning, the Board decided in the present case to admit into the proceedings document (96) (this being merely a comparison of figures already on file), document (97)) and the documents referred to therein (documents (106) to (114)), this being a declaration summarising known facts, document (98), it being considered useful expert evidence and document (105) as it contained explanations on documents already on file. All remaining documents were not admitted as they were either superfluous or irrelevant or they contained new experimental evidence never discussed before.

Main request:

Article 83 EPC; sufficiency of disclosure in relation to the subject-matter of claim 1.

The meaning of claim 1

4. Claim 1 relates to a method for activating a silent gene and expressing its product. During the proceedings, it was debated whether the term "gene product" was intended to mean an mRNA transcript of the silent gene or the protein encoded by that gene. As shown below, this issue is not critical to the present decision. Yet, for sake of being complete, it is mentioned here that the Board considers the method of claim 1 to be a method of protein production because firstly, one of the objects of the invention is defined as providing a method for expressing proteins (page 3, lines 57 and 58), secondly, advice is given in the specification on how to ensure correct translation (page 9, lines 6 to 10) and, finally, the claim refers to "collecting the gene product" which expression should be given its generally accepted meaning of "collecting the protein".

The informational content of the patent specification

5. After describing in general terms the objects of the invention, the steps of the method of claim 1 and the features of the DNA construct to be inserted in the chromosome (pages 3 to 5), the patent specification explains the mechanisms involved in homologous recombination (page 6). Then, a detailed review of the essential or optional features of the DNA construct is carried out (pages 7 to 9). On page 9, lines 7 to 9 and

lines 24 to 26, respectively, it is emphasized that the integration of the DNA construct upstream of the silent gene should not introduce any ATG upstream of the start codon of said gene; the ability of the skilled person to ensure that the transcription of the various genes of the construct should not interfere with each other, including with that of the gene of interest is underlined.

6. An example is then given of the insertion of the DNA construct upstream of the rat TSHβ gene. The construct comprises in succession the RSV1 promoter, the neo gene, the RSV2 promoter. Total mRNA is collected from cells having integrated the construct upstream of the TSHβ gene (page 14). It is shown by PCR amplification of the corresponding cDNA that some of the RNA molecules contain TSHβ sequences (page 15). These molecules are not characterized. Neither is the production of the TSHβ protein shown.

7. It is not disputed that, if one would accept that the example showed the production of mRNA molecules containing TSHβ sequences, then this mRNA was not the direct transcript of TSHβ gene which would initiate at the RSV2 promoter and be 2.9 kb in length, but a 4.5 Kb mRNA initiated at the RSV1 promoter. This, of course, implies that the mRNA molecule comprises three distinct parts: the neo mRNA, the nonsensical transcript of the RSV2 promoter and, finally the TSHβ mRNA. Consequently, it is not per se a gene product and furthermore, as it is a hybrid molecule, it cannot be expected to be translated into the final gene product resulting from the expression of the TSHβ gene: the TSHβ protein. In any event, an aberrant protein would be produced even

under the assumption that the TSHβ gene would be transcribed from the RSV2 promoter and translated since the insertion of the DNA construct upstream of the TSHβ gene introduces a number of ATG codons 5' to the start codon of the TSHβ reading frame. Otherwise stated, the example does not show the insertion of a DNA construct in the chromosome in such a way that the regulatory element it contains is operatively linked to the gene of interest, said operative link resulting in the expression of the silent gene product which could be collected. The example is, thus, not suited to show that the claimed subject-matter is enabled.

The case law regarding the relevance of providing a working example of the claimed subject-matter.

8. Sufficiency of disclosure may be acknowledged if at least one way is clearly indicated enabling the skilled person to carry out the invention. (T 292/85, OJ EPO 1989, 275). This, however, does not imply that the "at least one way" has to be in the form of an example. In case T 984/00 (supra), sufficiency of disclosure was acknowledged without a single example of the whole invention being put into practice. The then claimed subject-matter was a cell of a dicotyledonous plant which contained stably integrated into its genome a foreign DNA substantially free of T-DNA genes that control neoplastic growth, and which was transcribed from a promoter different from its natural promoter. The prior art described cells of dicotyledonous plants containing a foreign DNA which was transcribed in the same manner but was accompanied by T-DNA genes controlling neoplastic growth. In this case, where the invention was to achieve a technical effect

(transcription) which had already been documented in the art in similar albeit somewhat less favourable conditions (in the presence of "neoplastic" genes), the Board concluded in the light of the earlier results that there was no reason to doubt that the claimed construct would be transcribed ie. that the claimed cell would be reproducible. A working example was, thus, not necessary for sufficiency of disclosure.

9. The Appellants also cited T 721/89 (supra) as a case where the Board did not see the necessity of an example being present for sufficiency of disclosure to be fulfilled. This decision deals with an invention in the field of mechanics (pre-selected multi-ratio power transmission). Its teachings need not be discussed in detail here as their relevance to the present case is prima facie more difficult to establish than that of T 984/00 (supra) which is the field of genetic engineering.

10. In case T 792/00 (supra), a chimeric protein was claimed which contained a segment of an outer surface protein of a filamentous phage together with a binding domain heterologous to said phage, said binding domain being able to bind a predetermined target and being other than the antigen combining site of an antibody. The only example given in the patent specification was explicitly described as a hypothetical experimental protocol. Additional evidence provided in the course of the proceedings showed that the claimed subject-matter could be reproduced but by following a slightly different protocol. At the priority date, there was a prevailing technical opinion that the claimed subject-matter was not achievable. The Board concluded: "If for

an invention which goes against prevailing technical opinion, the patentee has failed to give even a single reproducible example, sufficiency of disclosure cannot be acknowledged."(cf. point 2 of the Headnote which refers to points 3 to 5 of the reasons)

11. The case law, thus, teaches that although the absence of a workable example is per se not fatal, whether or not the example has legal significance for sufficiency of disclosure depends on the specific circumstances of the case.

Specific consideration of sufficiency

12. As explained in the patent specification pages 2 and 3, up until the priority date, gene expression was achieved by making use of recombinant DNA carrying at the same time the gene to be expressed and the regulatory sequences necessary for its expression. The construct was transformed in host cells where it had a certain probability to insert in the chromosome (random recombination) and to be expressed. The claimed method of gene expression is based on a totally different principle whereby only the regulating sequences are carried by the recombinant DNA, which DNA is inserted in the chromosome upstream of the gene to be expressed in such a specific manner (homologous recombination) that it triggers expression. The invention, therefore, does not consist in adapting an already known method to make it simpler or more efficient (as in case T 984/00, supra). It is conceptually different from the approach taught in the prior art.

Accordingly, as the claimed combination of the known cellular mechanisms of homologous recombination and heterologous transcription was never put to work before, the generic teaching of the patent in suit, which is intrinsically theoretical in nature, cannot per se be a suitable basis for enablement, as it constitutes the mere outline of a line of research.

13. The Appellants argued that by following said teaching, the skilled person would necessarily get to the claimed invention. They pointed to documents (61) and (98) as expert evidence thereto. The Board, however, does not share this view. Document (61) is a post-published document disclosing the transfection of vertebrate cells by homologous recombination. Example 21 describes the targeting and activation of the human EPO locus in an immortalized human fibroblast cell line according to the same general principle as disclosed in the patent in suit. However, the targeting regions B and A are of a length of 6Kb and 2.8Kb, respectively, (page 108, lines 10 to 14). These features do not fall within the generic teaching of the patent in suit which advises that: "The optimum results are achieved when the total region of homology, including both targeting regions, is large, for example one to three kilobases" (page 7, lines 52 and 53, emphasis added by the Board). It is readily apparent that the use of the DNA construct of document (61) with its larger regions of homology is much more favourable to homologous recombination than that of the "generic" DNA construct taught in the patent in suit.

14. Document (98) is a declaration by an expert that the technology taught in the patent in suit was

successfully transferred to the laboratory where she worked. She describes the expression of the silent EPO chromosomal gene by using a DNA construct which essentially carries the same elements as the generic construct in the patent in suit. She, however, also discloses that modifications were introduced in order to optimize the production of EPO protein such as the insertion of polyA signals between each of the transcription units of the DNA construct and the introduction of an optimized leader sequence for the EPO gene. As these differences have a definite impact of gene expression whether it be at the RNA or protein level, this work is not relevant to prove that gene expression can be achieved without them. No direct or indirect teaching can be derived from the patent specification in respect to these features.

15. The Appellants also argued that the skilled person reading the example which showed that transcription had occurred and subsequently finding out that the mRNA obtained was not the direct transcript of the TSHβ gene would immediately foresee the modifications to be carried out to obtain this direct transcript on the basis of such common general knowledge as in documents (42), (58), (63) and (97) or on the basis of the instructions given on page 9 of the patent in suit (see point 5, supra).

16. The Board does not consider this argument to be relevant for the following reasons: on the basis of common general knowledge, the skilled person may be expected to carry out modifications of a routine kind to a tool such as the DNA construct of example 1 in order to make it suitable for carrying out an already

well-tried method. Yet, it is beyond his/her skills to carry out such modifications with the mere hope that they would enable a method for which there is no suggestion in the art that it should work. Indeed, this course of action would imply that the skilled person may be prepared to enter an unpredictable area of research and this, in accordance with the case law, is not within his/her capacities (eg. T 455/91, OJ EPO 1995, 684).

17. In view of these findings, the validity of the Appellants' argument that it was within the ability of the skilled person to perform the modifications assumed to be relevant need not be investigated.

18. Thus, it is concluded that if for an invention which is conceptually different from earlier approaches in the prior art, the Patentee fails to give even a single reproducible example, sufficiency of disclosure cannot be acknowledged. It would amount to undue burden for the skilled person to establish how to put the invention into practice on the basis of a sole generic teaching in the patent.

19. The main request is refused for failing to fulfill the requirements of Article 83 EPC.

Auxiliary request A

Article 83 EPC: sufficiency of disclosure in relation to the subject-matter of claim 1:

20. Claim 1 differs from claim 1 of the main request in that two passages of the generic disclosure in the

patent specification are now inserted in the claim to specify which measures should be taken in order to avoid potential pitfalls when putting the invention into practice. These amendments do not change the reasoning in point 12 above which led the Board to conclude that the generic disclosure without a working example was not sufficient to ensure that the requirements of Article 83 EPC are fulfilled because the invention was conceptually different from the teachings of the prior art.

21. Neither document (61) nor document (98) can be considered as examples of successfully carrying out the claimed invention on the basis of the generic teaching in the patent in suit. As already mentioned in point 13 above, the teachings of document (61) do not fall within said generic disclosure. As for document (98), it contains measures to ensure that transcription will proceed in an orderly manner which are stricter than those in point iii (first par.) of the method of claim 1 since none of the transcripts (including, of course, that of the selective marker) is allowed "to run over" into any of the nearby genes. And the construct also differs in the regulatory elements preceding the silent gene (EPO optimized leader sequence).

22. For these reasons, the same conclusion is reached as with regard to the main request ie. that auxiliary request A fails to fulfill the requirements of Article 83 EPC.

Auxiliary request B

Articles 123(2) and 84 EPC

23. The Appellants argued that the expression:

> "the placement of the positive selectable marker gene and its promoter is such that the promoter will stimulate expression of its associated gene without simultaneouly disrupting in any way the expression of said gene of interest or any other gene of the construct"

in claim 1 finds an implicit basis in the statement in the passage bridging pages 22 and 23 of the application as filed:

> "Those of ordinary skill in this art can determine any appropriate placement of the genes C, D and E and their promoters C', D' and E' such that the promoters will stimulate expression of their associated genes without simultaneously disrupting in any way the expression of the gene of interest or any of the other genes of the construct."

because in the rest of the specification, the genes other than the selectable marker gene are said to be dispensable.

24. The Board understands claim 1 as being directed to a method making use of a DNA construct comprising more than the selective marker gene since the claim refers to "disrupting the expression of the gene of interest or any of the other genes" (emphasis added by the Board). The application as filed teaches that in such a construct, the transcription of not only the selectable marker gene but also that of the other genes should

not be in any way disruptive (passage bridging pages 22 and 23). This information is different from that found in the claim. As the application as filed does not teach that in case where more genes than the selectable gene are present on the DNA construct, only the transcription of the selectable marker gene should not be disruptive, claim 1 contains added subject-matter and does not fulfill the requirements of Article 123(2) EPC.

25. Furthermore, claim 1 is directed to a method for enhancing the expression characteristics of a gene that is not totally transcriptionally silent. On page 9, lines 30 to 33, it is taught that the screening for silent genes may preferably be by means of Northern Blot analysis, which technique allows to determine whether or not mRNA has been produced. This seems to imply that mRNA molecules corresponding to a gene that is not totally transcriptionally silent will be found by that technique but at a low level. However, the use of the term "preferably by Northern Blot analysis" conveys the information that other techniques may also be used. In document (46) (page 2619), it is mentioned that any gene may be transcribed at a very low level in any cell type and that the transcripts may be detected by PCR. Accordingly, the meaning of the term "gene that is not totally transcriptionally silent" depends on the method used to detect transcription and, thus, this expression per se is unclear unless said technique is mentioned. The requirements of Article 84 EPC are not fulfilled.

26. Auxiliary request B is, therefore, not allowable as it contains added subject-matter over the teachings of the

application as filed (Article 123(2) EPC) and lacks clarity (Article 84 EPC).

Reimbursement of the appeal fee

27. The Intervener paid both the opposition and appeal fees and requested the reimbursement of the appeal fee. For an intervener to pay an opposition fee is a requirement under Article 105 EPC. As regards the payment of an appeal fee when a party only intervenes at the appeal stage, the case law contains different views (cf. Case Law of the Boards of Appeal, 4th Edition, 2001, Section VII, D, item 5.4.2), these being mainly centered on the issue of whether the Intervener wants to seek appellant's status in his own right in the sense that he can continue the appeal proceedings if the original appellant withdraws his appeal. Such a question is now pending before the Enlarged Board of Appeal under the number G 4/03.

28. No such issue arises in the case in suit, taking into account that here the intervention was aimed at obtaining the dismissal of the appeal similarly to the position of the Respondents. Thus, in line with several earlier decisions (cf. eg. T 27/92 of 25 July 1994 and T 780/95 of 11 March 1998), the Board orders the reimbursement of the appeal fee to the Intervener, as it also considers that the effectiveness of a notice of intervention filed during appeal proceedings depends on the payment of one fee only, namely the opposition fee.

Order:

For these reasons, it is decided that:

1. The appeal is dismissed.

2. The reimbursement of the appeal fee to the intervener is ordered.

The Registrar

A. Wolinski

BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS ★ BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE ★ CHAMBRES DE RECOURS DE L'OFFICE EUROPÉEN DES BREVETS
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The Chairman

L. Galligani