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Datasheet for the decision of 24 April 2007

Case Number: T 1491/05 - 3.3.08

Application Number: 99910039.9

Publication Number: 1071762

IPC: C12N 15/11

Language of the proceedings: EN

Title of invention:
Control of gene expression

Applicant:
Commonwealth Scientific and Industrial Research Organisation

Opponent:
-

Headword:
Gene expression/CSIRO

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

Keyword:
"Main request and auxiliary requests I to IV: added matter (yes)"
"Auxiliary request V: lack of clarity (yes)"

Decisions cited:
-

Catchword:
-

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Case Number: T 1491/05 **-** 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 24 April 2007

Appellant: Commonwealth Scientific and Industrial Research Organisation
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 11 July 2005 refusing European application No. 99910039.9 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: T. J. H. Mennessier
C. Rennie-Smith

Summary of Facts and Submissions

I. The applicant (appellant) lodged an appeal against the decision of the examining division dated 11 July 2005, whereby the European patent application No. 99 910 039.9 with publication number 1 071 762 was refused. The application, entitled "*Control of gene expression*", originated from an International application published as WO 99/49029 (which will be referred to in the "Reasons" as the application as filed).

II. Basis for the refusal were the three requests then on file, namely the main and the first auxiliary request filed on 13 May 2005, and the second auxiliary request filed on 14 June 2005: the main request was refused for lack of novelty, the first auxiliary request for lack of inventive step, and the second auxiliary request for lack of sufficient disclosure and lack of inventive step.

III. On 11 November 2005, the appellant filed a statement setting out the grounds of appeal and indicating that the claim requests to be considered were the three requests on which the decision under appeal was based.

IV. The examining division did not rectify its decision and referred the appeal to the Board of Appeal (Article 109 EPC).

V. Observations by a third party were filed under Article 115 EPC on 12 January 2007 enclosing four additional documents.

VI. On 15 January 2007, the Board issued a communication containing a provisional and non-binding opinion on some pending issues.

VII. In reply to that communication, the appellant sent its comments on 24 March 2007 and filed a new main request and four auxiliary requests numbered I to IV to replace all the requests on file.

VIII. The appellant filed on 12 April 2007 a corrected version of the main and the four auxiliary requests I to IV of 24 March 2007.

IX. At the oral proceedings which took place on 24 April 2007, the appellant maintained all its requests on file and filed a new auxiliary request I, its previous auxiliary requests I to IV being renumbered as auxiliary requests II to V.

X. Claim 1 of the respective requests on file reads as follows:

(a) **Main request**:

"1. A method of repressing, delaying or otherwise reducing the expression of a target gene in a eukaryotic cell, said method comprising:
(i) selecting a foreign nucleic acid molecule which comprises multiple copies of a nucleotide sequence (a) which is substantially identical to the nucleotide sequence of said target gene or a region thereof; wherein said region is a structural region corresponding to coding regions of the gene, optionally further comprising untranslated sequences,

said nucleotide sequence (a) is greater than 20 to 100 nucleotides in length,
and wherein the multiple copies are presented as an interrupted palindrome sequence,
(ii) producing a synthetic gene comprising said foreign nucleic acid molecule operably under the control of a single promoter sequence,
iii) introducing said synthetic gene into said cell, and
iv) expressing said synthetic gene in said cell,
wherein said method is not a method for treatment of the human or animal body by surgery or therapy, or a diagnostic method practised on the human or animal body."

(b) **Auxiliary request I:**

"1. A method of repressing, delaying or otherwise reducing the expression of a target gene in a eukaryotic cell, said method comprising:
(i) selecting a foreign nucleic acid molecule which comprises multiple copies of a nucleotide sequence (a) which is substantially identical to the nucleotide sequence of a region of said target gene;
wherein said gene is a structural region corresponding to coding regions,
said nucleotide sequence (a) is greater than 20 nucleotides in length,
and wherein the multiple copies are presented as an interrupted palindrome sequence,
(ii) producing a synthetic gene comprising said foreign nucleic acid molecule operably under the control of a single promoter sequence,
iii) introducing a synthetic gene into said cell, and

iv) expressing said synthetic gene in said cell,
whereby reduced or eliminated expression of the target gene may be attributed to reduced or delayed translation of the mRNA transcription product of the target gene, as a consequence of sequence-specific degradation of the mRNA transcript of the target gene by an endogenous host cell system,
wherein said eukaryotic cell is in cell or tissue culture."

(emphasis added by the Board)

(c) **Auxiliary request II**:

"1. A method of repressing, delaying or otherwise reducing the expression of a target gene in a eukaryotic cell, said method comprising:
(i) selecting a foreign nucleic acid molecule which comprises multiple copies of a nucleotide sequence (a) which is substantially identical to the nucleotide sequence of said target gene or a region thereof;
wherein said region is a structural region corresponding to coding regions of the gene, optionally further comprising untranslated sequences,
said nucleotide sequence (a) is greater than 20 to 100 nucleotides in length,
and wherein the multiple copies are presented as an interrupted palindrome sequence,
(ii) producing a synthetic gene comprising said foreign nucleic acid molecule operably under the control of a single promoter sequence,
iii) introducing said synthetic gene into said cell, and
iv) expressing said synthetic gene in said cell,

wherein said eukaryotic cell is in cell or tissue culture."

(d) **Auxiliary request III**:

"1. A method of repressing, delaying or otherwise reducing the expression of a target gene in a eukaryotic cell, said method comprising:
(i) selecting a foreign nucleic acid molecule which comprises multiple copies of a nucleotide sequence (a) which is substantially identical to the nucleotide sequence of said target gene or a region thereof;
wherein said region is a structural region corresponding to coding regions of the gene, optionally further comprising untranslated sequences,
said nucleotide sequence (a) is greater than 20 to 100 nucleotides in length,
and wherein the multiple copies are presented as an interrupted palindrome sequence,
(ii) producing a synthetic gene comprising said foreign nucleic acid molecule operably under the control of a single promoter sequence,
iii) introducing said synthetic gene into said cell, and
iv) expressing said synthetic gene in said cell,
whereby reduced or eliminated expression of the target gene may be attributed to reduced or delayed translation of the mRNA transcription product of the target gene, as a consequence of sequence-specific degradation of the mRNA transcript of the target gene by an endogenous host cell system,
wherein said eukaryotic cell is in cell or tissue culture."

(emphasis added by the Board)

(e) Claim 1 of **auxiliary request IV** reads exactly as claim 1 of auxiliary request II.

(f) **Auxiliary request V**:

"1. A synthetic gene which is capable of repressing, delaying or otherwise reducing the expression of a target gene in a eukaryotic cell,
wherein said synthetic gene comprises a foreign nucleic acid molecule comprising multiple copies of a nucleotide sequence (a) which is substantially identical to the nucleotide sequence of said target gene or a region thereof,
wherein said region is a structural region corresponding to coding regions of the gene, optionally further comprising untranslated sequences,
said nucleotide sequence (a) is greater **than 20 to 100 nucleotides in length**,
and wherein the multiple copies are presented as an interrupted palindrome sequence,
and the foreign nucleic acid is operably under the control of a single promoter sequence."

(emphasis added by the Board)

XI. The submissions made by the appellant, insofar as they are relevant to the decision, may be summarised as follows:

Article 123(2) EPC

Main request, and auxiliary requests II and IV

The proviso implying that the transcription of the mRNA product should not be exclusively repressed or reduced which characterised the method claims as filed was not to be regarded as an essential feature for all the embodiments of the method of the invention as outlined in the description. In particular, the introductory paragraph of the summary of the invention on page 6 did not refer to such a proviso. Similarly, in the paragraph bridging pages 25 and 26, it was explained that in order to obtain expression of the nucleic acid molecule in the cell, tissue or organ the only requirement was to produce a synthetic gene comprising a nucleotide sequence in operable connection with a promoter sequence which was capable of regulating expression therein.

Therefore, the absence of the proviso in method claims of these requests was not objectionable under Article 123(2) EPC.

Auxiliary requests I and III

Claim 1 contained in step iv) a statement ("*whereby [..] system*") which was equivalent to the aforementioned proviso. In both cases it was emphasized that the reduction of the expression of the target gene was only the consequence of a modification at the level of translation, not transcription.

Article 84 EPC (Auxiliary request V)

The expression "*greater than 20 to 100 nucleotides in length*" was clear and should be interpreted as meaning greater than 20 nucleotides.

XII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request of 12 April 2007 or auxiliary request I filed during the oral proceedings or auxiliary requests II to V filed on 12 April 2007.

Reasons for the Decision

Main request and auxiliary requests II and IV

1. There is a number of different objections to be raised against claim 1 of these requests, some of them also being raised to request V (e.g. the clarity objection to the feature "greater than 20 to 100", see points 10 to 12 infra). However, the focus of the discussion at oral proceedings in respect of these requests was the issue of the missing proviso and its consequences under Article 123(2) EPC.

2. The application as originally filed describes various embodiments of a method of modulating the expression of a target gene in an animal cell, tissue or organ which all are consistently subject to **a proviso**. This proviso, although being spelled out in two different ways and having an uncertain meaning, has a limiting effect on the method as disclosed. It reads: "subject to the proviso that the transcription of said mRNA product is

not exclusively repressed or reduced" (cf page 6, lines 29 to 30; page 15, lines 9 to 11; page 24, lines 1 to 3; page 26, lines 18 to 19; original claims 1 and 24), or "subject to the proviso that a reduction in transcription is not the sole mechanism by which this occurs and said reduction in transcription is at least accompanied by reduced translation of the steady-state mRNA pool" (cf passage bridging pages 17 and 18).

3. The proviso has been omitted from claim 1 of the requests at issue and no other feature counterbalances that omission. The appellant is of the view that the proviso is not mandatory because it does not generally apply to all embodiments of the method as demonstrated by the first paragraph summarising the invention on page 6, lines 12 to 20 and by the paragraph bridging pages 25 and 26 which do not contain any such proviso.

4. The appellant's view cannot be shared by the board for the following reasons :

4.1 While it is true that the first introductory paragraph of the "Summary of the invention" on page 6 does not refer to the proviso, it is a fact that this proviso is contained in the following paragraph which, when stating that the present invention provides a method of modulating the expression of a target gene in an animal cell, tissue or organ, makes that very method explicitly subject to the proviso, which is subsequently emphasized throughout the description. Thus, the said proviso is presented as an integral part of the invention.

4.2 As regards the passage bridging pages 25 and 26, this can only be read in connection with the following passage on page 26 which with the operative word "accordingly" refers to a method of modulating the expression of a target gene in a cell, tissue or organ characterised *inter alia* by the proviso.

5. Thus, in the Board's judgement, the proviso, regardless of the clarity of its meaning, is an essential technical feature of the method as originally disclosed and its omission from the claim, in absence of any counterbalancing feature(s), introduces subject-matter which extends beyond the content of the application as filed. Thus, the requirement of Article 123(2) EPC is not complied with. Therefore, if only for this reason, the main request as well as auxiliary requests II and IV must be refused.

Auxiliary requests I and III

6. In claim 1 of auxiliary requests I and III the appellant has introduced in step iv) the feature *"whereby reduced or eliminated expression of the target gene may be attributed to reduced or delayed translation of the mRNA transcription product of the target gene, as a consequence of sequence-specific degradation of the mRNA transcript of the target gene by an endogenous host cell system*" in an attempt to overcome the objection under Article 123(2) EPC which is the ground for the refusal of the main request as well as auxiliary requests II and IV (cf points 1 to 5 supra). In the appellant's view, this feature, which finds formal support on page 17, lines 9 to 14 of the application as filed, is equivalent to the proviso as

it links the modulated expression of the target gene to a modification at the level of translation, rather than transcription.

7. Apart from the fact that the added feature is in the form of a possibility (cf the expression "may be attributed") and thus has a problem of clarity, the Board does not see an equivalence between the two features. This is because the present feature attributes the modulating effect on translation to **a degradation of the mRNA transcript of the target gene,** nothing being mentioned about transcription, while the proviso refers to the fact that the transcription of that mRNA transcript is not exclusively repressed or reduced. The latter is seen as implying that translation is **at least to a certain extent** but not totally repressed and reduced. This is confirmed also by the different wording of the proviso in the passage bridging pages 17 and 18: "a reduction in transcription is not the sole mechanism by which this occurs and said reduction in transcription is at least accompanied by reduced translation of the steady-state mRNA pool". The appellant's interpretation that the proviso covers situations where the transcription is neither repressed not reduced is not tenable.

8. Thus, the problem remains of the omission of the proviso which characterised the method as originally disclosed and which finds no counterbalance in the added feature (which in any case raises a clarity problem under Article 84 EPC).

9. For these reasons, auxiliary requests I and III must be refused under Article 123(2) EPC.

Auxiliary request V

10. Claim 1 of auxiliary request V is directed to a synthetic gene which comprises a nucleotide sequence (a) being **greater than 20 to 100 nucleotides in length**.

11. The Board considers that this definition is not equivalent to the clear definitions which would be provided by any of the expressions "greater than 20 nucleotides" or "greater than 100 nucleotides" and necessarily implies something else which remains totally obscure.

12. Thus, claim 1 does not comply with the clarity requirement of Article 84 EPC. Therefore, auxiliary request V must also be refused.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski L. Galligani