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

Case Number: W 0005/02 - 3.3.8

Application Number: PCT/US 00/20 142

Publication Number: WO 01/07 613

IPC: C12N 15/12

Language of the proceedings: EN

Title of invention:

Method for enhancing RNA or protein production using non-native 5' untranslated sequences in recombinant viral nucleic acids

Applicant:

Large Scale Biology Corporation

Opponent:

-

Headword:

RNA or protein production/LARGE SCALE BIOLOGY CORP.

Relevant legal provisions:

PCT Art. 34(3)(a)
PCT R. 13.1-13.3, 68.2 68.3(c), 68.3(e)

Keyword:

"Lack of unity (no)"

Decisions cited:

W 0006/90, G 0001/89

Catchword:

-



Case Number: W 0005/02 - 3.3.8
International Application No. PCT/US 00/20142

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

Applicant: Large Scale Biology Corporation
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Subject of the Decision: Protest according to Rule 68.3(c) of the Patent Cooperation Treaty made by the applicants against the invitation of the European Patent Office (International Preliminary Examining Authority) to restrict the claims or pay additional fees dated 21 August 2001.

Composition of the Board:

Chairman: L. Galligani
Members: F. Davison-Brunel
B. Günzel

Summary of Facts and Submissions

I. International patent application PCT/US 00/20142 (published as WO-A-01/07613) was filed on 20 July 2000 with 36 claims of which claims 1, 7, 18, 33 and 35 read as follows:

"1. A recombinant viral nucleic acid comprising:

(a) a first sequence which comprises a non-native 5'-untranslated sequence,

and

(b) a second sequence which is downstream of and operatively linked to said first sequence, wherein the amount of RNA or protein produced from said second sequence is increased compared to the amount produced in the absence of said first sequence."

"7. The recombinant viral nucleic acid according to claim 1 wherein said non-native 5'-untranslated sequence is constructed by moving the ATG start codon downstream to a new site, thus creating an artificial leader sequence."

"18. A recombinant viral nucleic acid comprising a non-native sequence inserted in any nucleotide position 5' to the initiation codon of said recombinant viral nucleic acid, wherein the amount of RNA or protein produced from said recombinant viral nucleic acid is increased compared to the amount produced in the absence of said non-native sequence."

"33. A method for enhancing the production of a protein in a host comprising the steps of expressing in said host a recombinant viral nucleic acid comprising:

- (a) a first sequence which comprises a non-native 5'-untranslated sequence,
- and
- (b) a second sequence which is downstream of and operatively linked to said first sequence, wherein said second sequence comprises a coding sequence encoding said protein."

"35. A method for enhancing the production of a protein in a host comprising the steps of expressing in said host a recombinant viral nucleic acid comprising:

- (a) a non-native sequence inserted in any nucleotide position 5' to the initiation codon of said recombinant viral nucleic acid and a coding sequence encoding said protein."

Claims 2 to 6, 8 to 17 directly or indirectly related to further features of the subject-matter of claim 1. Claims 19 to 32 directly or indirectly related to further features of the subject-matter of claim 18. Claims 34 and 36 respectively related to further features of the subject-matter of claims 33 and 35.

II. On 21 August 2001, the European Patent Office (EPO) acting as an International Preliminary Examining Authority (IPEA) invited the applicant to pay within a time limit of one month one additional examination fee pursuant to Article 34(3)(a) and Rule 68.2 PCT because the application was considered not to comply with the requirements of unity of invention (Rule 13.1-13.3 PCT).

The IPEA observed that recombinant viral nucleic acids with non-native 5' untranslated sequences and their use in increasing RNA or protein production were already known from the prior art, for example from Virology 255 (1999) pages 312 to 323.

They defined the problem underlying the application as the provision of further such viral nucleic acids and considered that the claims providing a solution to this problem could be divided into two groups which were defined as follows:

"Claims 1-6, 8-17, 33-36 (partially), 7 completely
A recombinant viral nucleic acid comprising a non-native 5' untranslated sequence which has been constructed by moving the ATG start codon downstream to a new site.

Claims 1-6, 8-17, 33-36 (partially), 18-32 completely:
A recombinant viral nucleic acid comprising a non-native sequence inserted in any nucleotide position 5' to the initiation codon. A vector, an isolated host cell, a method for enhancing the production of a protein in a host cell, a method for enhancing the production of a protein in a host comprising said non-native 5'-untranslated sequence.",

The reasons given for lack of unity between these two groups were as follows:

" Due to the fact that recombinant viral nucleic acids with non-native 5'-untranslatable sequences have been known from the prior art, due to the essential difference in primary structure of the nucleic acids of the different groups of solutions, and due to the fact

that no other technical features can be distinguished which, in the light of the prior art could be regarded as special technical features, there is no single inventive concept underlying the plurality of claimed inventions."

III. On 12 September 2001, the applicant paid under protest one additional examination fee in respect of the additional invention (Rule 68.3(c) PCT). It was argued that:

"...all claims shared a same special technical feature... The special technical feature is the addition of additional nucleotide sequences 5' of the start codon in a recombinant viral nucleic acid construct...

...constructing a recombinant viral nucleic acid comprising a non-native 5'-untranslated sequence by moving the ATG codon downstream of a new site is the (*sic*) encompassed by inserting a non-native sequence in any nucleotide position 5' to the initiation codon."

IV. On 13 November 2001, the IPEA review panel informed the applicant that the findings of lack of unity by the IPEA were justified for the reasons given on 21 August 2001 (Section II, above). In particular, it was pointed out that "In Fig.1 of D1, it is shown that additional nucleotides in the leader sequence are present... In consequence, the feature "addition of additional nucleotide sequences 5' of the start codon" cannot represent the common special technical feature linking the two groups of alledged inventions." The applicant was then invited under Rule 68.3(e) PCT to pay a protest fee within one month.

- V. The protest fee was paid on 10 December 2001, the same arguments being provided in reply to the decision of the review panel as were presented on 12 September 2001 (Section III, above).

Reasons for the Decision

1. The protest in respect of the payment of a further examination fee is admissible.
2. According to the PCT regulations (cf. Rule 13.1 PCT), the international patent application shall relate to one invention only or to a group of inventions so linked as to form a single inventive concept. If the IPEA considers that the claims lack this unity, it is empowered, under Article 17(3)(a) PCT, to invite the applicant to pay additional fees.
3. Lack of unity may be directly evident a priori, i.e. before the examination of the merits of the claims in comparison with the state of the art revealed by the search (cf., for example, decision W 6/90, OJ EPO 1991, 436). Alternatively, having regard to decision G 1/89 of the Enlarged board of Appeal (OJ EPO 1991, 155), the IPEA is also empowered to raise an objection a *posteriori*, i.e. after having taken the prior art revealed by the search into closer consideration. This practice is laid down in the PCT International Search Guidelines Chapter VII-9. (PCT Gazette Special Issue, 8 October 1998, page 26) which are the basis for a uniform practice of all international searching authorities. The Enlarged Board of Appeal indicated that such consideration represents only a provisional opinion on novelty and inventive step which is in no

way binding upon the authority subsequently responsible for the substantive examination (point 8.1 of the Reasons for the decision).

4. The subject-matter of independent claims 1 and 18 (Section I, above) is a recombinant viral nucleic acid comprising a non-native 5'-untranslated sequence followed by a second sequence to be expressed, claim 18 further specifying that the non-native sequence is inserted 5' of the initiation codon of the sequence to be expressed. The constructs are made for the same purpose which is to obtain enhanced transcription and/or translation of the sequence to be expressed. Accordingly, there is no lack of unity a priori between these two claims.

5. There remains to be assessed whether there is lack of unity *a posteriori* i.e. taking into account the state of the art. Prior art document (1): Virology, Vol. 255, pages 312 to 313 was considered by the IPEA to be novelty-destroying for the subject-matter of *inter alia* claim 1. It discloses recombinant tobamovirus vectors which comprise a first untranslated sequence followed by the open reading frame (ORF) of the green fluorescent protein (GFP) from jelly fish (page 313, right-hand column). This first untranslated sequence originates from the native subgenomic mRNA promoter found upstream of the coat protein ORF in the wild-type virus. This promoter is "unusual" in the sense that sequences within the coat protein ORF between nt +25 and +54 relative to the transcriptional start are required for maximum subgenomic RNA production.

6. In a first construct (TB2-GFP, Figure 1) the GFP ORF is inserted approximately in place of the coat protein

ORF. In a second construct (TTOT-GFP), the GFP ORF is inserted downstream of the 42 first nucleotides within the coat protein ORF, the ATG initiator codon of this ORF being mutated to AGA. Otherwise stated, whereas the coat protein promoter is truncated in the first construct, it is present in full in the second one. A better expression is observed with the latter construct than with the earlier.

7. The IPEA seems to have based its finding of lack of unity *a posteriori* on the fact that, in their view, the second construct fell within the scope of claim 1 as "in Figure 1 of D1, it is shown that additional nucleotides in the leader sequence are present."
8. The Board cannot agree with this finding. Indeed the promoter sequence in the second vector is not of non-native origin. On the contrary, it is the native promoter of the tobamovirus coat protein but for the change of the T and G bases of the coat protein ATG initiator codon respectively to G and A. This change does not make the mutated native promoter sequence a non-native sequence in the sense intended in the application (page 4: a DNA fragment typically having less than 90% homology to the native viral nucleic acid). Consequently, the TTOT-GFP recombinant viral nucleic acid construct is not detrimental to the novelty of the subject-matter of claims 1 or 18. For this reason, the unity of claims 1 and 18 is not affected *a posteriori* by the teaching of document (1).
9. Claim 7 is dependent on claim 1 and, thus, its subject-matter serves to characterize further the invention already claimed in said claim 1. As it does not relate to a separate invention, it need not be considered when

assessing unity.

10. The patent application contains two independent claims in addition to independent claims 1 and 18: claims 33 and 35 (see section I, above). These claims are directed to methods of protein production involving the use of recombinant viral nucleic acids respectively defined as in claim 1 or claim 18. Rule 30(1) PCT should be construed as permitting the inclusion of an independent claim for a given product and an independent claim for the use of said product in the same application (see Guidelines for Examination in the European Patent Office, Part C, 7.1). Therefore, as there is no lack of unity between the subject-matter of claims 1 and 18 (point 8 above), the application may contain claims 33 and 35 without that the requirement of unity as a whole be offended.

11. For these reasons, the protest is justified.

Order

For these reasons, it is decided that:

The refund of the additional examination fee and of the protest fee is ordered.

The Registrar:

The Chairman:

A. Wolinski

L. Galligani

