Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 3 July 2014

Case Number: T 1822/10 - 3.3.08

Application Number: 04077211.3

Publication Number: 1482036

IPC: C12N15/10, C12Q1/68

Language of the proceedings: EN

Title of invention:
A method for increasing the concentration of a nucleic acid molecule

Patent Proprietor:
Medical Research Council

Opponent:
Applied Biosystems, Inc.

Headword:
Nucleic acid concentration/MEDICAL

Relevant legal provisions:
EPC Art. 100(c)

Keyword:
Admission of the main request (no)
First and second auxiliary requests - added matter (yes)

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern
Boards of Appeal
Chambres de recours

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 1822/10 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 3 July 2014

Appellant: (Patent Proprietor)	Medical Research Council 20 Park Crescent London W1B 1AL (GB)
Representative:	Ireland, Jacqueline Frances Mintz Levin Cohn Ferris Glovsky and Popeo LLP Alder Castle 10 Noble Street London EC2V 7JX (GB)
Respondent: (Opponent)	APPLIED BIOSYSTEMS, INC. 850 Lincoln Centre Drive Foster City California 94404 (US)
Representative:	Roques, Sarah Elizabeth J A Kemp 14 South Square Gray's Inn London WC1R 5JJ (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 14 June 2010 revoking European patent No. 1482036 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	M. Wieser
Members:	T. J. H. Mennessier
	C. Heath

Summary of Facts and Submissions

I. The patent proprietor (appellant) lodged an appeal against the decision of the opposition division dated 14 June 2010, whereby European patent No. 1 482 036, granted on European patent application No. 04077211.3, was revoked. The application was a divisional application from European patent application No. 98930958.8, published as international application WO 99/02671. Basis for the revocation was the main request corresponding to the claims as granted, the first and second auxiliary requests filed at the oral proceedings held on 17 March 2010 and the third to fifth auxiliary requests, filed with letter of 17 December 200.

II. The main and the first auxiliary requests were refused for reasons of non-compliance with the requirements of Article 100(c) EPC. The second auxiliary request was not admitted into the opposition proceedings under the provisions of Rule 116 EPC. With regard to the third to fifth auxiliary requests, the decision under appeal states on page 6, that these "*...requests were maintained by the Applicant but were not considered at the oral Proceedings as they retain the same deficiencies of the Main request and AR1*".

III. The patent had been opposed by one party (the respondent) on the grounds as set forth in Article 100(a) (for reasons of lack of novelty and of inventive step), 100(b) and 100(c) EPC.

IV. The appellant filed its statement setting out the grounds of appeal; it maintained the main request (the claims as granted) and submitted seven auxiliary requests. The second and seventh auxiliary requests were new in the procedure.

V. The respondent replied with a letter dated 1 March 2011.

VI. On 9 December 2013, the board issued a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) expressing its preliminary and non-binding views.

VII. On 2 May 2014, the appellant filed a main and two auxiliary requests *"to replace the pending Requests currently held on file."*. The main request and the second auxiliary request corresponded to the second and the seventh auxiliary requests, respectively, filed with the statement of grounds. The first auxiliary request was new in the procedure.

VIII. Claim 1 of these requests read:

Main request:

"1. A method for increasing the concentration of a nucleic acid molecule, said method comprising:
(a) forming aqueous microcapsules in a water-in-oil emulsion, wherein said microcapsules comprise an aqueous internal phase suspended as discrete droplets in a hydrophobic external phase and wherein a plurality of the microcapsules include a nucleic acid molecule and an aqueous solution comprising components necessary for nucleic acid amplification in the aqueous internal phase;
(b) amplifying the nucleic acid molecule in the microcapsules to form further amplified copies of said nucleic acid molecule; and
(c) sorting for said nucleic acid molecule using a tag linked to said nucleic acid, which is a biotin tag that

is introduced by PCR amplification with a 5'biotinylation primer."

First auxiliary request:

"1. A method for increasing the concentration of a nucleic acid molecule, said method comprising:
(a) forming aqueous microcapsules in a water-in-oil emulsion, wherein said microcapsules comprise an aqueous internal phase suspended as discrete droplets in a hydrophobic external phase and wherein a plurality of the microcapsules include a nucleic acid molecule and an aqueous solution comprising components necessary for nucleic acid amplification in the aqueous internal phase;
(b) amplifying the nucleic acid molecule in the microcapsules to form further amplified copies of said nucleic acid molecule; and
(c) enriching for said nucleic acid molecule using a tag linked to said nucleic acid, which is a biotin tag that is introduced by PCR amplification with a 5' biotinylation primer."

Second auxiliary request:

"1. A method for increasing the concentration of a nucleic acid molecule, said method comprising:
(a) forming aqueous microcapsules in a water-in-oil emulsion, wherein said microcapsules comprise an aqueous internal phase suspended as discrete droplets in a hydrophobic external phase and wherein a plurality of the microcapsules include a nucleic acid molecule and an aqueous solution comprising components necessary for nucleic acid amplification in the aqueous internal phase;

(b) amplifying the nucleic acid molecule in the microcapsules to form further amplified copies of said nucleic acid molecule; and
(c) enriching for said nucleic acid by producing the product of the nucleic acid and using a tag linked to said nucleic acid."

IX. Oral proceedings took place on 3 July 2014.

X. The following document is referred to in the present decision:

(D6) T. Oberholzer et al., Chemistry & Biology, Vol. 2, No. 10, 1995, pages 677 to 682

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

Admissibility of the requests

The main request did not contain complex amendments. It corresponded to the second auxiliary request filed with the statement of grounds which was filed in direct reply to the objection that there was no disclosure in WO 99/02671 (corresponding to the parent application as filed) of enriching a nucleic acid by generally using any tag linked to the nucleic acid. The term "sorting" in step c) was used consistently in the description. As derivable from the definitions given on page 21, lines 10 to 20 of the parent application as filed, it had a narrower meaning that the term "enriching".

The first auxiliary request differed from the main request only in that the term "sorting" was replaced by

the term "enriching" as used in claim 1 as granted. It was filed to overcome any objection raised against the use of the term "sorting". Basis for this amendment could be found on page 19, lines 21 to 28 of the parent application as filed.

The second auxiliary request corresponded to the seventh auxiliary request filed with the statement of grounds.

Article 100(c) EPC

First auxiliary request

The passage spanning from page 16, line 24 to page 17 line 12 of the parent application as filed provided support for steps a) and b) of the method of claim 1. Step c) had a basis on page 20, lines 4 to 6 and 8 to 13 which disclosed the use of a biotin tag that was introduced by PCR amplification with a 5'-biotinylation primer to perform the enrichment of the nucleic acid molecule.

Step b) of claim 1 was an expression step. The term "expression" had to be understood in its broadest sense. Expression was not limited to the process of "transcription and translation" but encompassed the process of replication of a nucleic acid (see page 7, lines 9 to 13 and page 17, lines 4 to 8). The use of the term "Even" in this latter citation, indicated that techniques which did not involve a "transcription/ translation" also fell under this term. Further basis could be found on page 24, lines 12 to 17 and page 34, lines 10 to 14 of the parent application as filed. It was clear from document D6 (see the Abstract on page 677) that replication had to be an amplification, as it

resulted in the amplification of the nucleic acid molecule, i.e. in the production of multiple copies of that molecule. The tag was covalently linked to these copies. This binding activity (see page 9, lines 26 to 27) allowed the enrichment according to step c). Thus it was evident that the only requirement for the achievement of an enrichment was the selection of gene products, which, in the case of step c) of claim 1 were the copies of the nucleic acid molecule produced by amplification.

Second auxiliary request

Basis for the clarifying amendment "by producing the product of the nucleic acid" was found throughout the parent application as filed, for instance on page 4, lines 9 to 10 of the parent application as filed. This term had to be understood to define the conversion of a nucleic acid into its gene product (page 4, lines 26 to 27).

In step c) of the method of claim 1 the gene product was a nucleic acid which had a binding activity as acknowledged on page 27, lines 17 to 18.

The subject-matter of claim 1, step c) amounted to a reasonable generalisation of the enrichment described in the parent application as filed.

XII. The submissions made by the respondent, insofar as they are relevant to the present decision, may be summarized as follows:

Admissibility of the requests

The replacement of the term "enriching" by "sorting" resulted in an extension of the protection conferred by the patent, contrary to the requirements of Article 123(3) EPC.

The first auxiliary request was filed in the course of the appeal proceedings. The amendments contained did not *prima facie* overcome the objections raised under Article 100(c) EPC in the decision under appeal.

The introduction of the feature "by producing the product of the nucleic acid" in claim 1 of the second auxiliary request could have already been made in the opposition proceedings. Moreover, also this amendment did not *prima facie* overcome the objections raised under Article 100(c) EPC in the decision under appeal.

Article 100(c) EPC

First auxiliary request

Replication was not the same as amplification. Document D6 was not a textbook and did not qualify amplification as an example of replication. According to the disclosure in the parent application as filed (see page 4, line 26 to 27 and many other places such as page 4, lines 12 to 15, page 5, lines 11 to 14, page 13, lines 12 to 13 and 15, page 16, lines 15 to 16) expression of a gene product from the nucleic acid molecule involving transcription, possibly followed by translation, was an essential feature of the disclosed method for enriching a nucleic acid. The feature described on page 20, lines 4 to 6 had been taken out of its context by the appellant and had to be read together with the preceding paragraphs. In fact biotin was not used as a tag but only as a linker to bind a ligand or substrate

to the nucleic acid molecule. Finally, there was no indication in the parent application as filed that the gene product of the nucleic acid molecule could be copies thereof.

Second auxiliary request

There was no general reference in the parent application as filed to "producing the product of the nucleic acid". The only disclosure to be found referred to the expression of a genetic element to produce its respective gene product. Tags were generally described only in the context of more specific embodiments, such as the use of ligands or substrates for the gene product. There was therefore no basis in the parent application as filed for the generalisation made in claim 1.

XIII. The appellant requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request or of one of the two auxiliary requests, all filed with the letter of 2 May 2014.

XIV. The respondent requested that the appeal be dismissed.

Reasons for the Decision

Admissibility of the requests

1. The main request and the second auxiliary request correspond to the second and the seventh auxiliary requests, respectively, filed together with the statement of grounds. The first auxiliary request was filed on 2 May 2014, i.e. after the appellant had filed its statement of grounds of appeal.

Main request

2. Claim 1 of the main request differs from claim 1 as granted in that, *inter alia*, the term "enriching" has been replaced in step c) by the term "sorting".

3. "Sorting" is a process aiming at separating a given component from a mixture of a number of components to isolate said given component. This is reflected by paragraph [0075] of the patent specification. "Enriching", in the context of a method according to claim 1, is a process aiming at increasing the concentration of the sole nucleic acid contained in a microcapsule. These two terms define two different processes with unrelated aims. They cannot interchangeably be used in a patent claim without changing the scope of protection conferred by the claim.

4. Therefore, as claim 1 *prima facie* contravenes the requirements of Article 123(3) EPC, the board decides not to admit the main request into the proceedings.

First auxiliary request

5. Claim 1 of the first auxiliary request derives from the second auxiliary request filed with the statement of grounds from which it differs only in that in step c) the term "sorting" has been replaced by the term "enriching". Thereby, it differs from claim 1 as granted only in that the nature of the tag has been specified by adding a feature taken from the description (see paragraph [0070] of the patent specification). This amendment appears to be a direct reply to the argument that there was no disclosure in

the parent application as filed of enriching a nucleic acid by generally using any tag linked to said nucleic acid (see page 3, first full paragraph of the decision under appeal). Therefore, using the discretion conferred to it by Article 13(1) RPBA, the board decides to admit the first auxiliary request into the proceedings.

Second auxiliary request

6. Claim 1 of the second auxiliary request differs from claim 1 as granted only in that it has been specified in step c) that the enrichment was achieved by producing the product of the nucleic acid and using a tag linked to said nucleic acid. This amendment appears to be a direct reply to the opposition division's view that there was no disclosure of direct enrichment of the nucleic acid with the help of a tag without an expression step (see page 5, top paragraph of the decision under appeal). Therefore, the board decides to admit the second auxiliary request into the proceedings.

Article 100(c) EPC

First auxiliary request

7. The passage from page 16, line 24 to page 17, line 12 of the parent application as filed, in combination with page 14, line 27 to page 15, line 5 provides support for steps a) and b) of the method according to claim 1.

8. Page 20, line 4 to 6 describes that a ligand or a substrate may be linked to the nucleic acid molecule through biotinylation by amplification with a 5'-biotinylation primer such that the biotin and the

nucleic acid are covalently linked. This feature is missing in step c) of the method according to claim 1 which does not mention a ligand or substrate.

9. On page 20, lines 9 to 13 it is specified that the biotinylated nucleic acid may be coupled to a polystyrene bead that is coated with avidin or streptavidin which bead can be derivatised with a substrate or ligand.

10. When read in connection with the preceding description it is clear that these two passages on page 20, referred to above and relied on by the appellant, do not describe an enrichment of the nucleic acid. Contrary to the appellant's assertion, biotin is not used as a tag itself but as a linker to connect the nucleic acid with a ligand or substrate. According to page 19, lines 21 to 24 "*the polypeptide or other molecular group or construct is a ligand or a substrate which directly or indirectly binds to or reacts with the gene product in order to tag the genetic element. This allows the sorting of the genetic element* ***on the basis of the activity of the gene product.***" (emphasis added by the board). A similar disclosure, referring to a method relying on exactly the same mechanism is found directly after the two passages relied on by the appellant (see page 20, lines 15 to 26).

11. Therefore, the passage on page 20, lines 4 to 6 does not provide any support for step c) of claim 1, which refers to an enrichment of a nucleic acid molecule using a biotin tag linked to said nucleic acid.

12. The board decides that claim 1 contains amendments introducing subject-matter that extends beyond the content of the application as filed. Therefore, the

first auxiliary request does not meet the requirements of Article 100(c) EPC.

Second auxiliary request

13. Claim 1 differs from claim 1 of the first auxiliary request in that the enrichment of step c) is achieved by producing the product of the nucleic and by using a tag linked to the nucleic acid.

14. The appellant argues that basis for the amendment of step c) can be found throughout the parent application as filed and that this amendment confirms that the enrichment for amplified nucleic acids does not need to occur directly, but subsequently to other steps.

15. However, a review of the description of the parent application as filed shows that the production of the gene product is always associated with gene expression (see page 4, lines 7 to 8, page 7, lines 16 to 20, page 8, lines 28 to 29, page 27, lines 1 to 2, and page 36, lines 20 to 22).

16. Regarding the use of a tag linked to the nucleic acid, the comments made in points (8) to (12) above apply also to this request. For this purpose a substrate or ligand, which may be attached to the nucleic acid by a variety of means (for instance through biotinylation) and which directly or indirectly binds to or reacts with the gene product is used to tag the nucleic acid and to thereby allow its enrichment.

17. Step c) of claim 1 neither mentions any gene expression resulting in the production of the gene product nor any gene activity or any ligand or substrate being linked to the acid nucleic molecule.

18. Step c) thus features a non-permissible generalisation from the specific disclosure in the parent application as filed.

19. The board decides that claim 1 contains amendments which introduce subject-matter extending beyond the content of the parent application as filed. Therefore, the second auxiliary request does not meet the requirements of Article 100(c) EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski M. Wieser

Decision electronically authenticated