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Datasheet for the decision of 13 July 2021

Case Number: T 1624/18 - 3.3.08

Application Number: 09782258.9

Publication Number: 2321413

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Language of the proceedings: EN

Title of invention:
DNA MINI-CIRCLES AND USES THEREOF

Applicant:
Global Life Sciences Solutions Operations UK Ltd

Headword:
DNA mini-circles Rolling Circle Amplification/GLOBAL LIFE SCIENCES SOLUTIONS OPERATIONS

Relevant legal provisions:
EPC Art. 56
RPBA 2020 Art. 17, 25(2)
RPBA Art. 12(4)

Keyword:
Admission of new documentary evidence (no);
Main request - inventive step (no);
Admission of first auxiliary request (no);

Decisions cited:
G 0010/93, T 2184/10

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 1624/18 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 13 July 2021

Appellant: (Applicant)	Global Life Sciences Solutions Operations UK Ltd 19 Jessops Riverside 800 Brightside Lane Sheffield S9 2RX (GB)
Representative:	Lee, Nicholas John Kilburn & Strode LLP Lacon London 84 Theobalds Road London WC1X 8NL (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 18 January 2018 refusing European patent application No. 09782258.9 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	B. Stolz
Members:	P. Julià
	E. Mille

Summary of Facts and Submissions

I. European patent application no. 09 782 258.9 (published as EP 2 321 413), originally filed under the PCT and published as WO 2010/026099, was refused by an examining division of the EPO. Basis for the refusal was a (sole) request filed on 27 November 2017 containing claims 1 to 6. The request was considered not to fulfil the requirements of Article 56 EPC.

II. The applicant (appellant) lodged an appeal and, with the statement setting out the grounds of appeal, filed a main request, a first auxiliary request, and new documentary evidence (documents (7) to (9)).

III. The board summoned the appellant to oral proceedings. In a communication pursuant to Article 17 of the Rules of Procedure of the Boards of Appeal (RPBA 2020), the appellant was informed of the board's provisional opinion on the issues of the case.

IV. With a letter dated 2 July 2021, the appellant, without making any substantive submissions, informed the board of its intention not to attend the oral proceedings.

V. Oral proceedings were held on 13 July 2021 in the absence of the appellant.

VI. The following documents are cited in this decision:

(1): WO 2006/003721 (publication date: 12 January 2006);

(2): WO 2004/013350 (publication date: 12 February 2004);

(7): C.M. Radding, J. Biol. Chem., 1991, Vol. 266, No. 9, pages 5355 to 5358;

(8): H.M. Chatwin and D.K. Summers, Microbiology, 2001, Vol. 147, pages 3071 to 3081;

(9): M. Camps, Recent Pat DNA Gene Seq., 2010, Vol. 4, No. 1, pages 58 to 73.

VII. Claim 1 of the request refused by the examining division read as follows:

"1. A method for generating a circular nucleic acid in vitro, comprising:

providing a nucleic acid template, wherein the nucleic acid template is a circular nucleic acid and comprises a recombination site;

amplifying the circular nucleic acid template by rolling circle amplification to form a concatamer, wherein the concatamer comprises tandem repeat units of the circlar nucleic acid template sequence, comprising a plurality of recombination sites; and

incubating the concatamer with a recombination protein to generate circular nucleic acids, wherein the recombination protein is chosen from a Cre recombinase, a bacteriophage lambda integrase, a yeast Flp recombinase, or a bacterial XerCD recombinase."

Dependent claims 2 to 6 were directed to different embodiments of the method of claim 1.

VIII. The examining division identified document (2) as the closest prior art. The technical difference between the disclosure of this document and the claimed method was considered to be the implementation of a suggestion made in document (2). The objective technical problem was formulated as the provision of a method for the *in vitro* production of circular nucleic acids, wherein the concatemeric nucleic acids amplified by Rolling Circle Amplification (RCA) were resolved. This technical problem was solved by the claimed *in vitro* method. In view of the disclosure of document (2), the examining division concluded that claims 1, 2 and 5 did not fulfil the requirements of Article 56 EPC. With further reference to document (1), the examining division considered claims 3, 4 and 6 not to fulfil the requirements of Article 56 EPC.

IX. The **main request** filed in appeal proceedings is identical to the request underlying the decision under appeal (*supra*). Claim 1 according to the **first auxiliary request** filed in appeal proceedings reads as claim 1 of the main request except for the fact that the recombination site and the recombination protein are defined as being a loxP site and a Cre recombinase, respectively (the subject-matter of claims 3 and 4 of the main request).

X. The arguments of the appellant, insofar as relevant to the present decision, may be summarised as follows:

Main request; Article 56 EPC

There were several technical features distinguishing the claimed *in vitro* method from the method disclosed in the closest prior art document (2). These features had not been properly taken into consideration by the

examining division. In particular, the claimed *in vitro* method had the following mandatory and advantageous features that were not present in the method disclosed in document (2):

i) the conversion of concatamers to monomers (in document (2) being only optional);

ii) the use of site specific recombination (which provided a recombination different from homologous recombination; the RecA used in the method disclosed in document (2) was not a recombinase but a single stranded binding protein promoting homologous recombination);

iii) the post-amplification addition of the recombinase, i.e. after the (RCA) amplification step, with disclosure of the required incubation times (post-amplification was mentioned in document (2) only as an option, but there was no teaching of site-specific recombination or any guidance on required incubation times);

iv) the production of monomer circles as end-products of the claimed *in vitro* method, not a mixture (monomers, dimers, trimers, etc.) of circular products and/or larger circles (multimers) as would be produced by the method disclosed in document (2);

v) the provision of a method for generating nucleic acid mini-circles for vaccination.

In the light of these differences, the objective technical problem was not to provide an *in vitro* method of the method suggested in document (2) - as stated by the examining division, but to provide a method for

producing nucleic acid mini-circles suitable for vaccination. The claimed *in vitro* method solved this technical problem and the skilled person following the teachings of document (2) would not have arrived at the claimed *in vitro* method in an obvious manner.

First auxiliary request; Article 56 EPC

The objective technical problem was the provision of a reliable and robust method for production of mini-circles of uniform size, i.e. monomers, for vaccination. Advantageously and contrary to the circular nucleic acids produced by the method described in document (2) (page 9, lines 12 to 15), the circular nucleic acids generated by the claimed *in vitro* method did not need to be supercoiled for having a high transformation efficiency.

XI. The appellant (applicant) requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request or, in the alternative, of the first auxiliary request.

Reasons for the Decision

1. The present decision is based on the same grounds, arguments and evidence on which the board's provisional opinion was based. It was neither questioned by the appellant, nor did other aspects come up that would require its reconsideration.

Admission of new evidence

2. According to the case law, the function of an appeal is to give a judicial decision upon the correctness of a separate earlier decision taken by an examining or

opposition division. Appeal proceedings are not an opportunity to re-run or re-open proceedings before any of these divisions (cf. "Case Law of the Boards of Appeal of the EPO", 9th edition 2019, V.A.1, 1133).

3. Documents (7) to (9) were filed by the appellant with the statement setting out the grounds of appeal. According to Article 12(3) RPBA 2020, these documents would normally be, as a rule, part of the appeal proceedings. However, Article 25(2) RPBA 2020, in conjunction with Article 12(4) RPBA 2007, leaves it at the discretion of the Boards of Appeal to hold inadmissible, i.e. to exclude, *inter alia*, evidence filed for the first time with the statement of grounds of appeal which could have been submitted in the proceedings leading to the decision under appeal.

4. The admission of documents (7) to (9) into the appeal proceedings is thus at the board's discretion (Article 25(2) RPBA 2020; Article 12(4) RPBA 2007; see also "Case Law", *supra*, V.A.4, 1206, in particular, V.A.4.10, 1223, and V.A.4.11, 1227).

4.1 Whilst documents (7) and (8) were published before the filling date of the patent application, document (9) is a post-published document. All three documents are publications in scientific journals. Document (7) is a review of the functional mechanisms of the RecA protein, and documents (8) and (9) are concerned with the ColE1 Pcer promoter and the ColE1-like plasmid replication, respectively. These elements are all cited in document (2) for exemplifying the teachings of this document. The appellant referred to documents (7) to (9) for supporting the arguments on Article 56 EPC.

4.2 No reason was given by the appellant, neither in the statement of grounds of appeal nor in its reply to the board's communication pursuant to Article 17 RPBA 2020, why these documents could not have been filed at earlier stages of the proceedings.

4.3 In the communication, the board did not rely upon any of documents (7) to (9) when assessing the problem and solution approaches formulated by the examining division and the appellant and arriving at its provisional negative opinion on Article 56 EPC.

5. Thus, the board, in the exercise of its discretion, decided not to admit any of documents (7) to (9) into the appeal proceedings.

Main request

6. The main request is identical to the request refused by the examining division, i.e. the request underlying the decision under appeal, and thus, it already forms part of the appeal proceedings.

7. The examining division considered this request not to fulfil the requirements of Article 56 EPC; no other objections were raised against the subject-matter of this request.

8. In the communication pursuant to Article 17 RPBA 2020, the board referred to decision G 10/93 (OJ EPO, 1995, 172), wherein the Enlarged Board of Appeal stated that, where the examining division had refused an application, the board has the power to examine whether the application or the invention to which it relates meets the requirements of the EPC. This also holds good for requirements that the examining division had not

considered in the examination proceedings or had regarded as fulfilled (cf. "Case Law", *supra*, V.A.3.3, 1195). In the present case, the board, with further reference to the case law, raised several objections under Article 84 EPC alone and/or in combination with Article 83 EPC against the subject-matter of claim 1.

9. In particular, the board referred to the case law establishing that a claim must be clear and comprehensible from a technical point of view, that is to say it must explicitly indicate or specify all essential features needed to define the invention or, in other words, which are necessary for solving the technical problem with which the patent application is concerned (cf. "Case Law", *supra*, II.A.3.2, 292). Likewise, reference was also made to the case law establishing that, for the purpose of assessing novelty and inventive step, it is not allowed to read into a claim restrictive features which are not suggested by the explicit wording of the claim (cf. "Case Law", *supra*, I.C.4.8, 122, and II.A.6.3.4, 312).

10. In the light of this case law, the board examined several features characterising the claimed *in vitro* method such as, *inter alia*, the third step of said method which requires the recombination protein or recombinase to "generate circular nucleic acids" without further characterising or defining these circular nucleic acids. As a result of this examination, the appellant was informed that, in the board's view, the main request did not fulfil the requirements of Article 84 EPC alone and/or in combination with Article 83 EPC. As stated above, the appellant has neither replied to the board's communication nor provided any arguments to rebut the board's provisional opinion.

11. In view of the fact that the examining division refused the patent application solely on the basis of lack of an inventive step and that the board, in its communication pursuant to Article 17 RPBA 2020, assessed also whether the main request fulfilled the requirements of Article 56 EPC, the board refrains from examining in further detail the objections raised under Article 84 EPC.

Article 56 EPC

12. As regards the technical features which, according to the appellant, distinguish the claimed *in vitro* method from the method disclosed in the closest prior art, document (2), the board observes that not all of them are mentioned in claim 1 and thus, in line with the established case law mentioned above, they are not taken into account when formulating the objective technical problem to be solved (cf. "Case Law", *supra*, I.C.4.8, 122).

12.1 Claim 1 requires the claimed method to generate "circular nucleic acids", it is completely silent as regards the nature and properties of these circular nucleic acids and thus, includes monomers as well as mixtures (monomers, dimers, trimers, etc.) of circular nucleic acids, and larger (multimers) circular nucleic acids. There is no requirement in claim 1 other than the steps explicitly mentioned, there is no requirement as regards the conditions under which these steps are carried out (concentrations, incubation times, temperatures, etc.), let alone those conditions that may provide only monomers and exclude, as argued by the appellant, multimers and mixtures of circular nucleic acids. In this context, the board, in its communication

pursuant to Article 17 RPBA 2020, drew the appellant's attention to the established case law that requires to apply the same standard when assessing the disclosure of a prior art document, in this case document (2), and that of the patent application (cf. *inter alia*, decision T 2184/10 of 20 May 2014, point 14.3 of the Reasons, and decisions cited therein).

12.2 Claim 1 requires the provision of a circular nucleic acid template comprising a recombination site. There is no requirement and/or limitation as regards the method by which said template is obtained or produced, or its original source. Likewise, as stated above, there are no requirements and/or limitations as regards the use of the generated circular nucleic acids; certainly not a requirement to be suitable and/or appropriate for use in vaccination. Moreover, claim 1 by using the term "comprising" in the preamble does not exclude the presence of further steps either before, concomitantly, or after those explicitly mentioned in the claim (cf. "Case Law", *supra*, II.A.6.2, 308).

12.3 Claim 1 refers to "a recombination site" in general and not to a particular recombination site of a specific recombinase (the subject-matter of claim 2). In its broadest interpretation, this term may be understood as a site where recombination takes place, nothing more, nothing less. As far as the circular nucleic acid template comprises a sequence which allows and results in recombination, regardless of the properties of said sequence and the efficiency of such recombination, this sequence falls within the broadest interpretation of the term "a recombination site" (cf. "Case Law", *supra*, I.C.4.8, 122; and II.A.3.3, 295). RecA recombinase and homologous recombination are not excluded from the scope of claim 1 by reference to "a recombination site"

in general, but only by requiring the recombinant protein to be selected from one of the four specific recombinases explicitly mentioned in claim 1, namely "a Cre recombinase, a bacteriophage lambda integrase, a yeast Flp recombinase, or a bacterial XerCD recombinase".

13. As regards the disclosure of the closest prior art document (2), the board considers the following points to be relevant:

13.1 Document (2) discloses a method comprising steps (a) and (b) which are described as "(a) providing a DNA or cDNA library ..., wherein the library is comprised in a circular vector and is produced *in vitro* ...", and "(b) amplifying the library by rolling circle amplification, thereby forming concatamers ..." (cf. page 2, lines 16 to 19; page 5, lines 21 to 24; and claim 1). The rolling circle amplification is carried out *in vitro* (cf. page 2, lines 7 and 8; page 24, lines 25 and 26), and the conversion of the concatamers to monomers is described as being "advantageous" and as one preferred embodiment of the invention (cf. page 8, lines 28 and 29; and claims 15 to 19). Likewise, the provision of circularised monomers is also disclosed as being "preferred" (cf. page 9, lines 14 to 15; and claims 16 to 18). Thus, steps (a) and (b) provide a circular nucleic acid template which is amplified by *in vitro* rolling circle amplification to form a concatamer (wherein the concatamer necessarily comprises tandem repeat units of the circular nucleic acid template sequence), and wherein the concatamers are (advantageously, preferably) converted to circularised monomers. Indeed, this disclosure is exemplified by amplifying a cDNA library (in a circular vector) using an *in vitro* rolling circle amplification, obtaining

linear monomers, and circularising them (cf. page 23, line 5 to page 24, line 29).

13.2 Although the conversion of the concatamer to monomers is exemplified by using a restriction enzyme cleavage site and digestion by a restriction enzyme (cf. claims 8 and 16), reference is also explicitly made in document (2) to two other possible alternative methods, one of them being the introduction of a "recombination recognition site, such as the Flp recombinase recognition site, for subsequent looping out of monomers using the Flp enzyme" (cf. page 8, lines 33 to 35; page 9, lines 2 and 8 to 10). The fact that only one of the three conversion methods explicitly described in document (2) is exemplified, does not deprive the other two non-exemplified conversion methods of any relevance or credibility. The less so, in particular, for the use of a recombination site and a recombinase, because in the Example of document (2), just after describing the embodiment that relies upon the use of a restriction enzyme cleavage site and a restriction enzyme, reference is also explicitly made to the use of a recombinase, namely the RecA recombinase (cf. page 25, lines 6 to 14).

13.3 Although RecA, unlike the recombinases mentioned in claim 1, is not a site-specific recombinase but a single-stranded nucleic acid binding protein which promotes homologous recombination,RecA necessarily requires the presence of homologous sequences for a recombination event to take place. In this sense, this homologous sequence is a recombination site, regardless of whether it is a site-specific or a non-specific recombination site. The circular nucleic acid template must comprise (at least) one of these homologous sequences which is amplified by RCA and present along

the concatamer. Upon incubation with the RecA recombinase, monomers are generated through the (looping out) mechanism described in document (2). Both the RecA properties and the recombination mechanism were well-known to the skilled person, who certainly also knew from both, the prior art and the disclosure of document (2), that the presence of homologous sequences (recombination site) within the circular nucleic acid template is essential for carrying out the method described in document (2). In any case, the disclosure of document (2) is not limited to the specific RecA recombinase, but refers to "recombination recognition sites" and "recombinases" in general. In addition, reference is made - directly and unambiguously - to the use of Flp recombinase and its site-specific recombinant recognition site, one of the recombinases mentioned in claim 1 of the main request, for resolving concatamers obtained by RCA (page 8, lines 28 to 35).

13.4 In the paragraph describing the use of the RecA recombinase on page 25 of document (2), it is also stated that "[t]he recombinase step may be performed at either simultaneously with the rolling circle amplification, [or] after the amplification ..." (cf. page 25, lines 12 and 13). Although both alternatives are mentioned, the recombinase step exemplified in document (2) is performed after amplification by *in vitro* rolling circle amplification. Claim 15 of document (2) refers also to the conversion of "the amplified library concatamers" to monomers and thus once amplified, or after amplification, by *in vitro* rolling circle amplification. Therefore, the simultaneous performance of both steps, namely RCA and recombinase, is not considered to be a preferred embodiment of the method disclosed in document (2).

Moreover, in the board's view, a skilled person would not have contemplated the simultaneous performance of both steps in view of the drawbacks and disadvantages referred to by the appellant in the statement setting out the grounds of appeal, which, in the board's view, were, if not well-known to the skilled person, then certainly obvious to him/her.

14. In the light of the above considerations and the disclosure of document (2), in particular the references to recombination recognition sites/ recombinases in general and to the specific Flp recombinase, as well as of the technical differences between the disclosure of this document and the subject-matter of claim 1, the board considers that the objective technical problem to be solved cannot be defined as formulated by the appellant, namely the provision of a method for generating or producing nucleic acid mini-circles suitable for vaccination. The formulation put forward by the examining division is considered more appropriate (cf. point VIII *supra*). No inventive skills were needed to put the proposal on page 8 of document (2), to resolve the concatamers by introducing a FLP recognition site into the vector, into practice. Moreover, in view of the disclosure and teachings of document (2) and the common general knowledge, a skilled person had a reasonable expectation of success, the more so since there is no requirement in claim 1 as regards the efficiency of recombination, yield of generated circular nucleic acids, etc. (cf. "Case Law", *supra*, I.D.7.1, 200). Thus, no inventive skill or undue burden was required for a skilled person to arrive at the claimed method.

15. Therefore, there is no reason for the board to deviate from the findings of the examining division. The main

request does not fulfil the requirements of Article 56 EPC.

Admission of the first auxiliary request into the proceedings

16. According to Article 12(3) RPBA 2020, the auxiliary request would normally be, as a rule, part of the appeal proceedings. However, Article 25(2) RPBA 2020, in conjunction with Article 12(4) RPBA 2007, leaves it at the discretion of the Boards of Appeal to hold inadmissible, i.e. to exclude, *inter alia*, requests filed for the first time with the statement of grounds of appeal which could have been submitted in the proceedings leading to the decision under appeal.

17. The first auxiliary request results from a limitation of the main request by, *inter alia*, introducing subject-matter of a dependent claim into claim 1. In particular, the recombination site and recombination protein are defined in claim 1 of this first auxiliary request as being a loxP site (the subject-matter of claim 3 of the main request) and a Cre recombinase, respectively. Claim 2 of the first auxiliary request further defines the Cre recombinase as being from bacteriophage P1 (the subject-matter of claim 4 of the main request).

18. The board considers that, in view of the type and nature of the amendments introduced into the first auxiliary request as well as the large number of opportunities given to the appellant in the first instance proceedings for filing new claim requests, in particular at the oral proceedings before the examining division - even though this opportunity was waived by the appellant by not attending these proceedings, the

first auxiliary request could, and should, have been filed at an earlier stage of the proceedings.

19. Moreover, in the communication pursuant to Article 17 RPBA 2020, the appellant was also informed that the amendments introduced into the first auxiliary request were considered by the board not to overcome the objection raised under Article 56 EPC against the main request. The board examined the technical features characterising the claimed *in vitro* method and the advantages or effects alleged by the appellant to result from these features (reliable and robust production of mini-circles of uniform size which have a high transformation efficiency without being supercoiled) over the method disclosed in the closest prior art document (2). With reference to the established case law on comparative tests and bonus effects (cf. "Case Law", *supra*, I.D.10.9, 271, and I.D.10.8, 270, respectively), the board concluded that the first auxiliary request does not fulfil the requirements of Article 56 EPC. The appellant has neither replied to the board's communication nor provided any arguments to rebut the board's provisional opinion.

20. In view of all these considerations, the board, in the exercise of its discretion, decided not to admit the first auxiliary request into the appeal proceedings.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

L. Malécot-Grob B. Stolz

Decision electronically authenticated