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Datasheet for the decision of 7 November 2018

Case Number: T 2100/12 - 3.3.08

Application Number: 04730974.5

Publication Number: 1620559

IPC: C12N15/63

Language of the proceedings: EN

Title of invention:
MINICIRCLE VECTOR PRODUCTION

Patent Proprietor:
Mayrhofer, Peter

Opponent:
PlasmidFactory GmbH & Co. KG

Headword:
Minicircle vector/MAYRHOFER

Relevant legal provisions:
EPC Art. 54, 56, 83, 123(2)
RPBA Art. 12(4)

Keyword:
Admission of new evidence (no)
Main request - fulfils requirements of the EPC (yes)

Decisions cited:
T 0023/10, T 0969/14

Catchword:

Europäisches Patentamt
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Beschwerdekammern

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Case Number: T 2100/12 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 7 November 2018

Appellant I: (Patent Proprietor)	Mayrhofer, Peter Feistritzgasse 34 1210 Wien (AT)
Representative:	Lux, Berthold Maiwald Patentanwalts- und Rechtsanwaltsgesellschaft mbH Elisenhof Elisenstraße 3 80335 München (DE)
Appellant II: (Opponent)	PlasmidFactory GmbH & Co. KG Meisenstrasse 96 33607 Bielefeld (DE)
Representative:	Grund, Martin Grund Intellectual Property Group Patentanwalt und Solicitor PartG mbB Nikolaistrasse 15 80802 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 30 July 2012 concerning maintenance of the European Patent No. 1620559 in amended form.**

Composition of the Board:

Chairman	B. Stolz
Members:	M. R. Vega Laso
	D. Rogers

Summary of Facts and Submissions

I. European patent No. 1 620 559 with the title "Minicircle vector production" was granted on the European patent application No. 04730974.5, which had been filed as an international application under the Patent Cooperation Treaty and published as WO 2004/099420 (in the following "the application as filed").

II. The patent was opposed on the grounds for opposition of Article 100(a) in conjunction with Articles 54 and 56; 100(b) and 100(c) EPC.

III. In an interlocutory decision posted on 30 July 2012, an opposition division found that, while the subject-matter of the claims according to the main request then on file lacked an inventive step, account being taken of the amendments introduced into claims 1 to 25 according to the 1st auxiliary request and the description adapted thereto filed during the oral proceedings, the patent and the invention to which it relates met the requirements of the EPC. Hence, the patent could be maintained on that basis.

IV. The patent proprietor and the opponent (appellant I and appellant II, respectively) each filed an appeal against the interlocutory decision and submitted a statement setting out the grounds of appeal. Together with his statement of grounds, appellant I filed eight sets of claims as main request and 1st to 7th auxiliary requests. Appellant II submitted new evidence to support its grounds of appeal. Both parties requested oral proceedings as an auxiliary measure.

V. Each party replied to the statement of grounds of the other party. Together with his reply, appellant I submitted nine sets of claims as 6th to 14th auxiliary requests and new evidence.

VI. In addition to its reply, appellant II submitted further observations. Appellant I requested to be given the opportunity to reply thereto, if the board intended to consider the late submissions of appellant II.

VII. The parties were summoned to oral proceedings. In a communication sent in preparation of the oral proceedings, the board expressed its provisional opinion on procedural issues and some substantive issues concerning Articles 123(2), 83, 54 and 56 EPC.

VIII. During the oral proceedings, which were held on 7 November 2018, appellant I filed as his main request a set of claims identical to that of his previous 1st auxiliary request.

IX. Claims 1 and 12 of the main request read as follows:

"1. A plasmid comprising the following functional units:
- a prokaryotic origin of replication,
- a marker sequence,
- two specific recombinase recognition sequences and
- a multiple cloning site,
- a regulatory element for the expression of the recombinase,

characterized in that it comprises a gene coding for a sequence specific recombinase, whereby the units are arranged on the plasmid in such a way that the plasmid is divided into a miniplasmid and a minicircle upon

expression of the sequence specific recombinase, said miniplasmid comprising the prokaryotic origin of replication, the marker sequence, the gene for the sequence specific recombinase and said minicircle comprising the multiple cloning site without the gene coding for the specific recombinase and wherein a miniplasmid identification sequence for the identification, isolation and removal of the miniplasmid is present on the miniplasmid and/or a minicircle identification sequence for the identification and isolation of the minicircle is present on the minicircle, wherein the sequence specific recombinase is ParA resolvase.

12. The plasmid according to any one of claims 1 to 11, **characterized in that** it comprises a bacteriophage origin of replication on the minicircle."

Dependent claims 2 to 11 relate to various embodiments of the plasmid of claim 1. Claims 13 to 20 concern a kit including a plasmid according to any one of claims 3 to 11. Claims 21 to 25 are directed to methods for the production of a therapeutically useful DNA molecule in the form of a minicircle, and claim 26 is directed to a minicircle obtainable by those methods. Claim 27 relates to a pharmaceutical composition comprising the minicircle of claim 26.

X. The following documents are referred to in this decision:

(1): WO 96/26270, published on 29 August 1996;

(5): B.W. Bigger et al., 22 June 2001, The Journal of Biological Chemistry, Vol. 276, No. 25, pages 23018 to 23027;

(13): "Additional experimental data", received on 2 May 2012;

(14): P. Mayrhofer et al., 2008, The Journal of Gene Medicine, Vol. 10, pages 1253 to 1269;

(21): A.-M. Darquet et al., 1997, Gene Therapy, Vol. 4, pages 1341 to 1349; and

(22): P. Kreiss et al., 1998, Vol. 49, pages 560 to 567.

XI. The submissions made by appellant I concerning issues relevant to this decision, were essentially as follows:

Admission of the set of claims of the main request into the proceedings

The main request was submitted as a reply to an *obiter dictum* in the decision under appeal. The objection that, in the absence of a tight control of the expression of the ParA recombinase, the problem of increasing recombination efficiency was not solved, had been raised by the opponent at a late stage of the opposition proceedings. The focus of the discussion on inventive step at the oral proceedings had been on other issues.

Article 123(2) EPC

The objection to the negative feature in claim 1 was rather a clarity objection than an objection under Article 123(2) EPC.

In the passages on page 11, lines 4 to 10, lines 20 to 22 of the application as filed a "*bacteriophage origin of replication*" was disclosed without limiting it to an origin of replication of a non-lysogenic phage.

Article 83 EPC

The claims as granted and the application as filed contained a detailed description in which way the elements of the parental plasmid have to be arranged. Based on plasmid pHCNparA disclosed in, e.g., Figure 5 of the application, the skilled person only had to rearrange one of the sites for sequence specific recombination in order to insert the multiple cloning site, as apparent from Figure 1 of document (13). This required only routine laboratory work. Hence, the requirements of Article 83 EPC were met.

Article 54 EPC

The subject-matter of claim 1 was not directly and unambiguously derivable from document (1). In order to arrive at the claimed method, a person skilled in the art would have to make a selection from various lists and combine different embodiments described in document (1).

Article 56 EPC

Starting from document (1), the objective technical problem to be solved was the provision of a parental plasmid allowing for an increased recombination efficiency during the production of minicircles. The solution proposed in claim 1 was not obvious. Document (1) taught two different approaches for

increasing the recombination efficiency: either the integration of the gene coding for the recombinase into the genome of the host or the use of a combination of recombinases. It did not teach a plasmid including a gene coding for a sequence specific recombinase (the ParA resolvase) located in the non-therapeutic region of the plasmid. None of the documents on file provided any hint towards the solution proposed in claim 1.

XII. The submissions by appellant II, insofar as they are relevant to the present decision, may be summarised as follows:

Admission of the set of claims of the main request into the proceedings

The main request should not be admitted into the proceedings because it could have been presented in opposition proceedings (see decisions T 23/10 of 18 January 2011 and T 969/14 of 5 June 2018). The request addressed an objection of lack of novelty over document (1) which had been raised already in the notice of opposition. Moreover, the feature introduced into claim 1 was taken from the specification.

Article 123(2) EPC

The subject-matter of claim 1 extended beyond the content of the application as filed because the negative feature "*without the gene coding for the specific recombinase*" had no basis in the application. In the passage on page 6, fifth paragraph of the application as filed the absence of the gene coding for the specific recombinase in the minicircle was disclosed only in combination with the absence of any of the prokaryotic regulation units. If the objected

negative feature was redundant - as the opposition division erroneously found -, it should be deleted from the claim.

The amendment introduced into claim 12 to characterize the origin of replication on the minicircle as a "*bacteriophage origin of replication*" offended against Article 123(2) EPC. Reading the passage on page 11, lines 20 to 22 together with the subsequent sentences of the application as filed, the skilled person would realize that the bacteriophages could only be non-lysogenic bacteriophages. Since the feature "*non-lysogenic*" was missing in claim 12, its subject-matter extended beyond the content of the application as filed.

Article 83 EPC

The patent did not include any example of a plasmid in which the gene coding for the ParA recombinase was located in the non-therapeutic miniplasmid region, as required by claim 1. Such plasmid was described only in the post-published document (13) (see Figure 1). It was apparent from this document that, starting from a precursor plasmid disclosed in the application as filed, three different cloning steps were necessary in order to arrive at the claimed plasmid. The skilled person would have to carry out those cloning steps without any guidance from the application. Since this amounted to undue burden, the requirements of Article 83 EPC were not met.

Article 54 EPC

Contrary to the view of the opposition division, a person skilled in the art reading document (1) would

understand that a multiple cloning site was described not only for the specific plasmid pXL2960, but generally for any of the plasmids disclosed in the document. There was no reason why the skilled person would not consider combining a feature taken from an example with the general disclosure of document (1), especially in view of the fact that a multiple cloning site was a well-known feature of plasmids used for cloning. Moreover, the feature "*a regulatory element for the expression of the recombinase*" introduced into claim 1 could be derived from page 12, lines 9 and 10 of document (1). Hence, the claimed plasmid lacked novelty over document (1).

Article 56 EPC

The subject-matter of the claims did not involve an inventive step. The sole difference between the plasmid described on page 12 of document (1) and the plasmid as defined in claim 1 was the nature of the recombinase enzyme, which according to claim 1 was the parA resolvase. However, the patent did not provide any practical example for a plasmid falling under the scope of claim 1, and there was no evidence on file that the use of parA resolvase as recombinase had a particular technical effect. Document (13) did not include any comparative results as regards the recombination efficiency using the plasmid described in document (1) and that of claim 1.

As stated in document (14), a high yield of minicircles could be achieved only if the gene encoding the parA resolvase was expressed under stringent control. However, the regulatory element specified in claim 1 could be any promoter, including a constitutive promoter. In any case, the use of an inducible promoter

for controlling the expression of a recombinase in order to produce minicircle vectors was known from document (5). Hence, combining the teachings of documents (1) and (5) a person skilled in the art would arrive at the plasmid of claim 1 without applying any inventive skills.

XIII. Appellant I requested that the decision under appeal be set aside and the patent maintained upon the basis of the main request filed at the oral proceedings before the board.

XIV. Appellant II requested that the decision under appeal be set aside and the patent be revoked.

Reasons for the Decision

Admission of the set of claims of the main request into the proceedings

1. Claim 1 of the present main request, which is identical to claim 1 the 1st auxiliary request filed by appellant I together with its statement of grounds of appeal, specifies that, in addition to the five functional units recited in claim 1 of the patent as granted (prokaryotic origin of replication, marker sequence, two specific recombinase recognition sequences, multiple cloning site and a gene coding for a sequence specific recombinase), the plasmid comprises a regulatory element for the expression of the recombinase. This feature can be derived from claim 11 of the application as filed and was included in claim 8 as granted, which has been deleted in the present main request.

2. Appellant I asserted that the amendment introduced into claim 1 addressed the issue of whether the claimed technical effect of a more efficient production of minicircles was achieved if the expression of the sequence specific recombinase was not tightly controlled. This issue had been raised by the opponent for the first time in its reply to the communication issued by the opposition division in preparation of the oral proceedings, and was only tangentially discussed during the oral proceedings. However, in the decision under appeal (see section 7 starting on page 13 of the decision) the opposition division expressed - as *obiter dictum* – an opinion on the issue which was adverse to the patent proprietor (the present appellant I).

3. In view of the circumstances of the present case, which differ clearly from those in decisions T 23/10 of 18 January 2011 and T 969/14 of 5 June 2018, the board has no reason to suspect that appellant I intended to withhold the present main request in opposition proceedings, as appellant II alleged. The objection addressed by the present main request was raised by the opponent at a very late stage of the opposition proceedings, and at the oral proceedings before the opposition division the discussion seems to have been focused on the question of whether the claimed subject-matter is obvious in view of the state of the art, a question that in the decision under appeal was answered in the affirmative. Hence, only from the *obiter dictum* in the decision under appeal could appellant I learn that, with regard to the question of whether there is a technical effect linked to the position of the parA recombinase in the plasmid, the absence of a control mechanism for the parA recombinase in the claimed plasmid was considered to be prejudicial to an inventive step. Appellant I duly reacted to the

opposition division's comments in the decision under appeal by filing, together with his statement of grounds of appeal, a set of claims in which claim 1 is directed to a plasmid which includes a regulatory element for the expression of the recombinase, which now constitutes the appellant's main request.

4. The board does not share appellant II's view that the amendment introduced into claim 1 of the main request does not address the *obiter dictum* in the decision under appeal because the plasmid according to the amended claim does not require a stringent control of the expression of the sequence specific recombinase. This issue will be dealt with below in connection with the assessment of inventive step.

5. In view of the above, the board, exercising the discretion conferred by Article 12(4) RPBA, decides to admit the claims according to the main request into the proceedings.

Admission of documents (21) and (22) into the proceedings

6. Appellant I requested the admission of documents (21) and (22) into the proceedings. These documents were submitted as evidence that the recombination efficiency observed for two of the plasmids described in document (1) is well below the recombination efficiency shown in document (13) and (14) for a plasmid according to claim 1 of the 1st auxiliary request underlying the decision under appeal. Appellant II opposed the admission of this new evidence.

7. Document (1) was filed together with the notice of opposition, and documents (13) and (14) were submitted during the opposition proceedings as evidence that the

plasmids according to the invention were efficiently divided into a miniplasmid and a minicircle. In fact, the question whether or not the plasmids according to the invention provide a higher recombination efficiency compared to the plasmids described in document (1), was a controversial issue in the proceedings before the opposition division. Hence, if relevant, documents (21) and (22) could - and should - have been presented already in opposition proceedings. Appellant I did not allege any circumstances that may have prevented it from submitting this evidence in due time. Hence, exercising its discretion under Article 12(4) RPBA the board does not admit documents (21) and (22) into the appeal proceedings.

Article 123(2)(3) EPC

Claim 1

8. Like the opposition division (see section 3.1, second paragraph of the decision under appeal), the board is of the view that the feature "*... said minicircle comprising the multiple cloning site* ***without the gene coding for the specific recombinase***" (emphasis added by the board) in present claim 1 is implicit from the disclosure in claim 1 of the application as filed. Claim 1 as originally filed specifies that, upon expression of the sequence specific recombinase, the plasmid is divided into a miniplasmid and a minicircle, the miniplasmid comprising the prokaryotic origin of replication, the marker sequence and the gene for the sequence specific recombinase, and the minicircle comprising the multiple cloning site. Hence, since the gene for the sequence specific recombinase is on the miniplasmid, it follows that it is not on the minicircle.

9. In the board's view, appellant II's objection does not appear to be an objection based on Article 123(2) EPC, but rather one concerning the clarity and conciseness of claim 1. However, Article 84 EPC is not a ground for opposition. Since the objected feature was already present in claim 1 as granted and has not been subject of any amendment during the opposition or appeal proceedings, compliance with Article 84 EPC cannot be examined (see G 3/14, OJ EPO 2015, A102), and an amendment to the claim by deleting the objected feature – as suggested by appellant II - would offend against Rule 80 EPC.

Claim 12

10. The board shares also the opposition division's view that there is a basis in the application as filed for the generic wording "*bacteriophage origin of replication*" in claim 12 (see section 3.3 of the decision under appeal concerning claim 13 of the main request then on file). In particular, the use of a bacteriophage origin of replication without any further limitation to a specific type of bacteriophages is derivable from the passage bridging pages 10 and 11 and the first full paragraph on page 11.

11. Hence, the board concludes that neither claim 1 nor claim 12 is directed to subject-matter which extends beyond the content of the application as filed. It should be noted that, for arriving at this conclusion, the board considered only those arguments put forward by appellant II in due time, and disregarded those presented for the first time during the oral proceedings.

12. The findings in the decision under appeal concerning Article 123(3) EPC (see sections 3.2 und 3.4 of the decision) were not contested in appeal proceedings.

Article 83 EPC

13. The reasons given in the decision under appeal in connection with the 1st auxiliary request then on file (see paragraph bridging pages 15 and 16 of the decision) apply, *mutatis mutandis*, also to the present main request.

14. Appellant II argued that, in view of the lack of a specific example for a plasmid that includes a sequence coding for the parA resolvase in the application as filed, the skilled person was not able to arrive at a plasmid as claimed without an undue burden. In particular, appellant II pointed to Figure 1 of document (13) as evidence that, starting from plasmid pHCNparA as disclosed in the application as filed, three additional cloning steps were required.

15. These arguments are not convincing. In the board's opinion, the application as filed provides clear guidance as to the position of the gene encoding the sequence specific recombinase on the plasmid: the gene must be located such that, when the plasmid is divided into a miniplasmid and a minicircle, it is present in the miniplasmid. The board shares the opposition division's view that, having this technical information at hand, a person skilled in the art at the relevant date could find out without any difficulties a suitable position on the plasmid. The cloning steps required for inserting the parA resolvase gene into the plasmid did not represent an undue burden or require any skills beyond those of the average skilled person.

16. Neither the findings in the decision under appeal concerning the construction of a functional arabinose promoter-parA expression unit – which apply to claim 9 of the present main request – nor those concerning the bacteriophage origin of replication – which apply to claim 12 – were contested in appeal proceedings.

17. Hence, the requirements of Article 83 EPC are met.

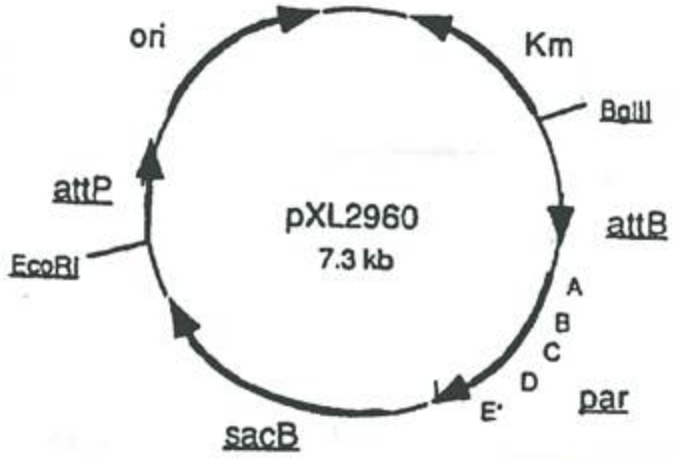
Article 54 EPC

18. In the decision under appeal, the opposition division found that document (1) did not destroy the novelty of the subject-matter of claim 1 of the main request then on file.

19. This finding applies also to the present main request. The board shares the opposition division's view that the feature "*multiple cloning site*", which is explicitly described in connection with plasmid pXL2960, cannot be regarded as implicit for any other plasmid described in document (1). Even if it is true that the presence of a multiple cloning site is a common feature in many plasmids, for the assessment of novelty a clear line must be drawn between what is actually described in document (1) and what the skilled person would consider obvious in the light of the teaching in that document.

20. The board is also not convinced that a person skilled in the art can derive clearly and unambiguously from document (1) a plasmid comprising two specific recombinase recognition sequences and a gene coding for a sequence specific recombinase, in particular the parA resolvase, where upon expression of this recombinase

the plasmid is divided into a miniplasmid which includes, *inter alia*, the ParA gene, and a minicircle. The passage starting from page 9, line 15 does not describe a plasmid including the gene encoding the ParA resolvase. Although the plasmid described in the passage starting on page 10, line 13 indeed includes the ParA gene, the location of the gene is not disclosed. The plasmid pXL2960, which is mentioned as an example of this embodiment, is depicted in Figure 9 of document (1):



21. In this plasmid, the ParA gene and the sacB gene are located between the recombinase recognition sequences attP and attB. As admitted by appellant II, these sequences cannot be recognized by the ParA resolvase, which in this embodiment does not function as the primary recombinase but only as a resolvase. As a matter of fact, the plasmid described in document (1) is divided into a miniplasmid and a minicircle by a different recombinase, namely the lambda phage integrase encoded by the *int* gene integrated into the chromosome. It should be noted that, while the parA gene is included in the **minicircle** resulting from the

recombination of the plasmid pXL2960 described in document (1), claim 1 of the patent requires that the gene for the sequence specific recombinase is comprised in the **miniplasmid**.

22. As regards the passage bridging pages 11 and 12 of document (1), which describes a method of producing a minicircle as described previously in the document, the board observes that there is no reference to the use of ParA resolvase as sequence specific recombinase. If this passage is read in combination with the previous passages of document (1) describing two different embodiments of the plasmid, the same shortcomings in the disclosure of document (1) as outlined in paragraphs 19 to 21 above are apparent.

23. Hence, the finding in the decision under appeal that the subject-matter of claim 1 is novel over document (1) is correct also as regards the amended claim 1 presently on file. The same applies to the subject-matter of claims depending on or referring, directly or indirectly, to claim 1.

24. The findings of the opposition division on the validity of the priority and those concerning the public availability of document (6) (see, respectively, sections 5.1 and 5.2.1, second paragraph of the decision under appeal) have not been contested in appeal proceedings, and the board sees no reason for a different view. Hence, the requirement of novelty (Article 54 EPC) is fulfilled.

Article 56 EPC

25. In appeal proceedings, it is common ground that document (1) represents the closest state of the art.

The content of document (1) has been outlined above in connection with the assessment of novelty. The recombination system described in document (1) is primarily based on the use of a recombinase that recognises the attP and attB recognition sequences. The gene encoding the recombinase is integrated into the genome of the host cell, but can also be included in the plasmid, in particular in the non-therapeutic region (see page 12, lines 1 to 3). For the purpose of increasing the production of minicircles, in a particular embodiment this recombinase is **combined with** the ParA resolvase (see paragraph bridging pages 10 and 11 of document (1)).

26. In contrast, in the plasmids of the present invention a single recombinase, the ParA resolvase encoded by a gene included in the plasmid, is used to both effect recombination and resolve multimeric forms of the plasmid.

27. The objective problem to be solved starting from document (1) is to provide a plasmid for the efficient production of minicircle vectors.

28. According to the invention, minicircle vectors are produced with high yield as a result of the regulated expression of the parA resolvase which efficiently catalyses recombination at the specific recombinase specific sequences within the plasmid defined in claim 1, resulting in the separation into a minicircle useful for gene therapy and a miniplasmid. The plasmid according to claim 1 is replicated in the host cell in the absence of the parA resolvase and, after induction of the expression of the *parA* gene, the ParA resolvase is produced in an amount commensurate with the number of plasmid copies. The parA resolvase catalyses

efficiently both recombination within the plasmid and resolution of multimers and concatemers, thus allowing the generation of minicircles with a yield of (nearly) 100%.

29. In view of the experimental evidence in documents (13) and (14), the board has no doubt that the problem formulated above is solved by the plasmid defined in claim 1.

30. Appellant II disputed that the presence in the plasmid of a regulatory element for the expression of the recombinase would be sufficient to achieve a stringent control of the expression of the recombinase required for a high yield of minicircles, because also a constitutive promotor could be considered to be a "*regulatory element*" as specified in claim 1. The board does not share this view. It is common general knowledge that a constitutive promotor is an unregulated promoter that allows for **continual** transcription of its associated gene. Hence, a constitutive promoter cannot be considered to be a "***regulatory*** *element*" (emphasis added) as required by claim 1. Appellant II's interpretation of the term "*regulatory element*" is also in contradiction with the statements in paragraph [0029] of the patent:

> "*By providing a regulatory element for the expression of the recombinase the expression of the recombinase can be either* ***inhibited or induced.*** *This allows the expression of the recombinase to occur when necessary. With this system the plasmid can be produced in great quantities before the expression of the recombinase is induced so that a maximum efficiency of minicircle production is achieved.*" (emphasis added)

31. Nor does the board share appellant II's view that the teaching of document (1) alone or in combination with in particular document (5) renders obvious a plasmid with the features specified in claim 1. The passage on page 12 of document (1) to which the appellant II referred, describes in very general terms two different methods for producing minicircles by site-specific recombination *in vivo*. The first method uses a host cell containing the gene encoding the recombinase such that its expression can be regulated ("*... une cellule hôte contenant le gène de la recombinase sous une forme permettant son expression régulée*"). The expression cassette for the recombinase can be on a plasmid, a phage or in the non-therapeutic region of the parental plasmid used to generate the minicircle, and can be under the control of an inducible promotor or a promotor system, or be a temperature-regulated system. In a second method, the expression cassette is introduced into the host cell on a plasmid or a phage, but only after the growth phase, i.e. after replication of the parental plasmid. In this case, a regulatory control of the expression of the recombinase is not required.

32. This passage of document (1) does not suggest to the skilled person the use of the parA resolvase both as recombinase and resolvase, with the aim of generating minicircles with high efficiency. While a recombination system based on the combination of the parA resolvase with a further recombinase, namely the integrase of the bacteriophage λ, is disclosed in the first passage on page 11 of document (1), there is no hint whatsoever in this passage or elsewhere in document (1) that the bacteriophage λ integrase could be disposed of without a detrimental effect on the minicircle yield, since the

parA resolvase would function both as recombinase and resolvase. Hence, appellant II's argument that the plasmid of claim 1 is obvious from the content of document (1) alone, is not persuasive.

33. The same is true if the content of document (1) is combined with that of document (5). The latter document describes a bacterial *cre* recombinase expression system for producing minicircle vectors, in which the recombinase is tightly controlled by the arabinose regulon (*araC*). In the passage to which appellant II referred (see page 23018, right-hand column, starting from the fourth full paragraph), it is stated that a controlled expression of the *cre* recombinase avoids premature recombination and "*... allows to create a cre-expressing bacterial strain, which is both stable and easily controllable ...*" (see sixth full paragraph). The following paragraph reads:

> "*To increase minicircle yield we improved the kinetics of the cre/loxP reaction by modification of the loxP sites (17, 18) to induce a shift in reaction equilibrium toward increased production of minicircle. This will also serve to reduce concatamer formation from multiple copies of minicircle DNA*"

34. While a person skilled in the art reading this passage may become aware that reducing multimer formation could help to increase the minicircle yield, the solution proposed by document (5) for this purpose is a modification of the recombinase recognition sequences, rather than the use of the parA resolvase having both recombinase and resolvase activity, as proposed by the present invention. As stated in the decision under appeal (see last paragraph on page 17), the concept of

the recombinase expression system described in document (5), which is based on a recombinase gene inserted into the genome of the host cell - rather than included in the plasmid as required by claim 1, is clearly different from the concept underlying the present invention. Like the opposition division, the board is persuaded that, if the skilled person had considered combining the teachings of documents (1) and (5), he/she would not have arrived at the concept of the invention, i.e. the regulated expression of the gene encoding the parA resolvase present in the plasmid to be recombined, without hindsight knowledge of the present invention.

35. For these reasons, the subject-matter of claim 1 is considered to involve an inventive step within the meaning of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent on the basis of claims 1 to 27 according to the main request filed at the oral proceedings before the board on 7 November 2018 and a description to be adapted.

The Registrar: The Chairman:

L. Malécot-Grob B. Stolz

Decision electronically authenticated