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**Datasheet for the decision
of 26 November 2019**

Case Number: T 2248/14 - 3.3.08

Application Number: 10180445.8

Publication Number: 2325304

IPC: C12N9/12

Language of the proceedings: EN

Title of invention:

Modified DNA polymerases for improved incorporation of nucleotide analogues

Patent Proprietor:

Illumina Cambridge Limited

Opponents:

Kilger, Christian
Froud, Clive

Headword:

DNA polymerases/ILLUMINA

Relevant legal provisions:

EPC Art. 123(2)
RPBA Art. 13(1)

Keyword:

Main request - admission (yes); added-subject-matter (yes);

Decisions cited:

Catchword:



Beschwerdekammern

Boards of Appeal

Chambres de recours

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Case Number: T 2248/14 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 26 November 2019

Appellant: Illumina Cambridge Limited
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Decision under appeal: **Decision of the Opposition Division of the
European Patent Office posted on 10 October 2014
revoking European patent No. 2325304 pursuant to
Article 101(3) (b) EPC.**

Composition of the Board:

Chairman B. Stolz
Members: P. Julià
 R. Winkelhofer

Summary of Facts and Submissions

- I. European patent no. 2 325 304 is based on European patent application no. 10 180 445.8 (all references in this decision to the patent application correspond to the published patent application), a divisional patent application of European patent application no. 04 768 438.6, published under the PCT as International patent application WO 2005/024010. The patent was granted with 14 claims.
- II. Two oppositions were filed on the grounds set forth in Articles 100(a), (b) and (c) EPC. The opposition division revoked the patent, as it considered the main request and auxiliary request 1 to contravene Article 123(2) EPC; auxiliary request 1 was also considered to contravene Article 123(3) EPC. All requests had been filed at the oral proceedings before the opposition division.
- III. An appeal was lodged by the patent proprietor (appellant). With the statement setting out its grounds of appeal, the appellant filed a main request and auxiliary requests 1 to 3. The main request was identical to the main request underlying the decision under appeal.
- IV. Opponents 01 and 02 (respondents I and II, respectively) replied to the statement of grounds of appeal. Respondent II submitted new documentary evidence and requested that auxiliary requests 2 and 3 not to be admitted into the appeal proceedings.
- V. As an auxiliary measure, oral proceedings were requested by the appellant and respondent II.

- VI. In a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA 2007), the parties were informed of the board's provisional opinion on the issues of the case.
- VII. None of the parties replied in substance to the board's communication.
- VIII. Oral proceedings were held on 26 November 2019 in the absence of respondent I. At the beginning of the oral proceedings, the appellant withdrew its main request and made auxiliary request 1 its new main request. During the oral proceedings, the appellant withdrew this main request, filed yet again a new main request, and withdrew auxiliary requests 2 and 3.
- IX. Claim 1 of the (final) main request reads as follows:

"1. A 9°N polymerase enzyme wherein the motif A region has one of the following amino acid sequences:

FAI, FAP, VAP AAA, YAS, YAV, SAA, CAA, YAA, QAS, VAG, VAV, FAV or AAT,

wherein the polymerase exhibits an increased rate of incorporation of nucleotides which have been modified at the 3' sugar hydroxyl such that the substituent is larger in size than the naturally occurring 3' hydroxyl group, compared to the 9°N DM control polymerase."

Claims 2 to 4 define preferred embodiments of claim 1. Claims 5 and 6 are directed to a nucleic acid molecule encoding an altered polymerase as defined in any one of claims 1 to 4 and to an expression vector comprising said nucleic acid molecule. Claims 7 and 8 relate to a

method for incorporating modified nucleotides by using a polymerase according to any one of claims 1 to 4.

- X. The submissions of the appellant, insofar as relevant to this decision, may be summarised as follows:

Main request

Consideration/admission into the appeal proceedings

The main request corresponded to the auxiliary request 1 underlying the decision under appeal; this auxiliary request was examined by the opposition division and a decision was taken on it. Its subject-matter was substantially that of the auxiliary request 1 filed with the statement of grounds of appeal and thus, it had been in the appeal proceedings from the beginning. New objections raised against this request at the oral proceedings before the board were late-filed and, even if they were admitted into the appeal proceedings, had no bearing on the admission of this request into the proceedings.

Article 123(2) EPC

Example 2, paragraph [0210] of the patent application, disclosed 9°N polymerases having all amino acid sequences of the motif A region listed in claim 1. These 9°N polymerases exhibited an improved activity compared to the 9°N DM control polymerase, wherein this activity was defined in Example 2 as an enhanced rate of incorporation of nucleotide analogues compared to the parental 9°N DM polymerase - as shown in paragraph [0187] and the heading before paragraph [0200]. Although these 9°N polymerases had a substitution mutation in the motif B region (A485L), it was explicitly stated at the beginning of Example 2 in

paragraph [0186] that an enhanced rate of incorporation of nucleotide analogues compared to the original control polymerase was achieved with polymerase variants carrying changes in the region A alone, i.e. regardless of other possible substitution mutations in the region B. This statement was in line with the whole content of the patent application, in particular with the description of the "[p]referred altered polymerase proteins" of the invention.

Starting in paragraph [0068], which explicitly referred to the "accompanying examples", DNA polymerases with substitution mutations in the motif A region alone were described. Paragraph [0083] disclosed polymerases having most of the amino acid sequences listed in claim 1 and having no other mutations than those in the motif A region. Paragraph [0084] stated that, "[a]s further demonstrated in the experimental section", all these polymerases had a substantially improved incorporation of nucleotide analogues compared to the 9°N DM control polymerase. It was within this context that paragraph [0094] described, as preferred polymerases of the invention, 9°N polymerases having all the amino acid sequences of the motif A region listed in claim 1. Although a substitution mutation at position 485 in region B (A485L) was indicated therein, this mutation was understood to be, in this context, only optional and not compulsory. This was also explicitly stated in paragraph [0106] which referred to substitutions in the motif B region as being only optional.

Although all 9°N polymerases described in Example 2 had substitution mutations in the motif A and B regions, paragraphs [0068] *et seq.* explicitly referred to the 9°N polymerases of the (accompanying) examples and

stated that the mutations in the motif A region alone were relevant, regardless of the other mutation in the motif B region. This was in fact the take-home message of the description and of the whole patent application; the message conveyed, directly and unambiguously, to the skilled person.

Moreover, if the mutated 9°N polymerases exhibited an increased rate of incorporation of nucleotide analogues compared to the 9°N DM control polymerase, they necessarily exhibited also an increased rate when compared to the wild-type 9°N polymerase, because the 9°N DM polymerase exhibited an increased rate over that of the wild-type 9°N polymerase.

- XI. The submissions of respondent II, insofar as relevant to this decision, may be summarised as follows:

Main request

Consideration/admission into the appeal proceedings

The main request corresponded to auxiliary request 1 underlying the decision under appeal. This auxiliary request was filed at the oral proceedings before the opposition proceedings and, since it was late-filed, there had been no opportunity for the opponents to consider all issues and objections arising from its amendments, in particular not those related to Article 84 EPC. The less so, since a decision was taken on Article 123(2) EPC and no other articles of the EPC were considered. Since the main request was filed only at the oral proceedings before the board, the first occasion for the respondent to raise these issues, in particular those related to Article 84 EPC, were at these oral proceedings before the board. Indeed, the subject-matter of the main request raised new issues

under Article 84 EPC and thus, it should not be admitted into the proceedings.

Article 123(2) EPC

There was no basis in the patent application for 9°N polymerase enzymes having the functional and structural features characterising the 9°N polymerase enzymes of claim 1; all the 9°N polymerases having the amino acid sequences in the motif A region listed in claim 1 had an additional mutation in the motif B region (A485L). The 9°N polymerases described in Example 2, paragraph [0210] of the patent application, had all the amino acid sequences in the motif A region listed in claim 1, but they all had an additional mutation in the motif B region (A485L) - as explicitly stated in paragraph [0186]. The statement in paragraph [0186] to polymerase variants that carried changes in region A alone was made in comparison to the 9°N DM control polymerase, which had a substitution mutation in the motif B region (A485L).

The disclosure in paragraph [0068] of the patent application was generic and did not describe any of the amino acid sequences listed in claim 1. Although there was a reference to the "accompanying examples", all the 9°N polymerases described in the examples of the patent application had a substitution mutation in the motif B region (A485L). Several of the amino acid sequences listed in claim 1, but not all of them, were disclosed in paragraph [0083] as "the most preferred embodiments of the invention". All specific amino acid sequences listed in claim 1 were described only in paragraph [0094]; however, they were not disclosed alone but together with (plus) a substitution mutation in the motif B region (A485L). There was no indication

in paragraph [0094] that allowed to interpret the presence of the mutation in the motif B region as being only optional; such interpretation was wrong and, even grammatically, incorrect, since it required to ignore the conventional meaning of the punctuation (positioning of the commas) present in the paragraph. Nor could such interpretation be based on the reference in paragraph [0106] to the substitution mutations in the motif B region as being only optional, because there was no reference in paragraph [0106] to the specific amino acid sequences listed in claim 1 or in paragraph [0094]. The disclosure in paragraph [0106] was generic and not even limited to polymerases of the family B polymerase, let alone to specific members of this family, such as the 9°N polymerase.

- XII. The submissions made in writing by respondent I in relation to Article 123(2) EPC against the auxiliary request 1 filed with appellant's grounds of appeal, are relevant and apply also to the (final) main request. These submissions, which focused on the disclosure in paragraph [0094] of the patent application, were substantially identical to, and based on the same arguments, as those made by respondent II.
- XIII. The appellant (patent proprietor) requests that the decision under appeal be set aside and the patent be maintained on the basis of claims 1 to 8 of the main request submitted at the oral proceedings before the board.
- XIV. Respondent I (opponent 01), in writing, and respondent II (opponent 02) request that the appeal be dismissed.

Reasons for the Decision

Main request

Consideration/admission into the appeal proceedings

1. The main request corresponds to auxiliary request 1 underlying the decision under appeal. Its submission at the oral proceedings before the board represents an amendment of the appellant's case in the sense of Article 13 RPBA 2007.
2. Except for the definition of the control polymerase at the end of claim 1, the main request is identical to the auxiliary request 1 filed with appellant's statement of grounds of appeal. Whilst the definition in claim 1 of the main request reads "... 9°N DM control polymerase" (cf. point IX *supra*), the definition in claim 1 of the auxiliary request 1 filed with appellant's grounds of appeal read "... 9°N double mutant (DM) control polymerase" (underlined by the board).
3. In their replies to the statement of grounds of appeal, none of the respondents addressed the amended definition of the control polymerase in claim 1 of then auxiliary request 1, nor did they object to the admission of this auxiliary request into the appeal proceedings.
4. Moreover, when addressing the subject-matter of then auxiliary request 1, the appellant (in the statement setting out its grounds of appeal) and both respondents (in their reply thereto) referred to the reasons/arguments provided by the opposition division under Article 123(2) EPC against the auxiliary request 1 underlying the decision under appeal. Therefore, the

objection raised under Article 123(2) EPC and the reasons/arguments submitted by the parties in appeal proceedings apply - in a straightforward manner and without further consideration - to both, then auxiliary request 1 as well as to the current main request.

5. The admission of the main request into the appeal proceedings results thus in the board examining the objection raised under Article 123(2) EPC and the reasons/arguments provided by the opposition division in the decision under appeal as well as those given by the parties in the statement of grounds of appeal and in their reply thereto. This is fully in line with the function of an appeal as defined in the established case law, namely to give a judicial decision upon the correctness of a separate earlier decision taken by an examining or opposition division (cf. "Case Law of the Boards of Appeal of the EPO", 9th edition 2019, V.A.1, 1133, and V.A.4.12, 1244).
6. Therefore, the main request is admitted into the appeal proceedings.

Article 123(2) EPC

7. As regards the content of the original disclosure of the patent application, the following points are common ground between the parties:
 - 7.1 Although several specific amino acid sequences in the motif A region are disclosed in paragraph [0083] and in claim 9 of the patent application, not all the specific amino acid sequences listed in claim 1 are disclosed therein, in particular, not the triplets FAP and VAP. The fifteen specific amino acid sequences in the

motif A region listed in claim 1 are disclosed only in paragraphs [0094] and [0210] of the patent application.

- 7.2 As observed by the opposition division in the decision under appeal, the 9°N polymerases with the amino acid sequences in the motif A region disclosed in Example 2, paragraph [0210] of the patent application, contain a substitution mutation in the motif B region (A485L) which is also present in the 9°N DM control polymerase (cf. paragraph [0186] of the patent application).

*The disclosure in the "Description of the invention";
paragraph [0094]*

8. Under the heading "Preferred altered polymerase proteins", paragraphs [0068] to [0085] of the patent application disclose polymerases having one, two or three substitution mutations in the motif A region alone. The presence of other mutations outside the motif A region is not excluded - as explicitly mentioned, although in a generic manner, in paragraphs [0079], [0082] and [0085] for polymerases having one, two or three substitution mutations in the motif A region, respectively. Indeed, these polymerases are those exemplified in the patent application, such as the polymerases described in Example 2, which have substitution mutations in the motif A region and an additional substitution mutation outside the motif A region, namely in the motif B region (A485L). It is in this sense that the references to the "accompanying examples" and to the "experimental section" in these paragraphs must be understood.
9. Immediately thereafter, starting in paragraph [0086], there is a disclosure of polymerases having one, two or three substitution mutations in the motif A region and

additionally comprising one, two or three substitution mutations in the motif B region; these are, in fact, the polymerases described in Example 2 of the patent application. It is in this context that the disclosure of paragraph [0094] is found, namely altered polymerases comprising substitution mutations in each of the motif A and B regions (cf. paragraph [0093] of the patent application).

10. It is thus in this context that the sentence in paragraph [0094], namely "[p]articularly preferred polymerases according to the invention are 9°N polymerases having one of the following motif A region sequences: FAP, VAP, ..., FSS or VAL, most preferably YAV or YAS, **plus** a substitution mutation at position 485 in region B, most preferably A485L" (emphasis by the board), must also be interpreted. In the board's view, the term "plus" immediately after the comma requires - directly and unambiguously - the presence of a substitution mutation in the motif B region in addition to those explicitly disclosed in the motif A region of the altered 9°N polymerases. And, indeed, the presence of this substitution mutation in the motif B region is required for each and every one of the disclosed motif A region sequences of the altered 9°N polymerases, and not only for the "most preferably YAV or YAS", as submitted by the appellant.

11. The board agrees with respondent II as regards the disclosure in paragraph [0106] of the patent application, wherein the substitution mutations in the motif B region are indicated as optional ("the amino acid substitutions in the motif A region, and **optionally** the motif B region", emphasis by the board). The disclosure in this paragraph is however generic and summarises in a general manner all the information

provided in the previous paragraphs, but it does not refer to any of the specific amino acid sequences in the motif A region disclosed, *inter alia*, in paragraphs [0083] and [0094]. Moreover, the above sentence in paragraph [0106] refers not only to substitution mutations in the motif A and B regions in general, but to further changes in the amino acid sequences of the altered polymerases such as "substitutions, deletions, additions, fusion, etc.", all defined only in a generic manner. The subject-matter of claim 1 may be rendered obvious on the basis of the content of the patent application but it does not belong to the technical information explicitly or implicitly disclosed by the patent application (cf. "Case Law", *supra*, II.E.1.3.3, 438).

12. Therefore, the disclosure in paragraph [0094] of the patent application is not a basis for the subject-matter of claim 1.

The disclosure in Example 2; paragraphs [0186] and [0210]

13. As stated above, it is common ground between the parties that all altered 9°N polymerases with the amino acid sequences in the motif A region described in Example 2, paragraph [0210] of the patent application, have a substitution mutation (A485L) in the motif B region. It is however disputed whether the reference in paragraph [0186] to variants carrying changes "in region A **alone**" (emphasis by the board) - directly and unambiguously - informs the skilled person that, regardless of the mutation in the motif B region, the substitution mutations in the motif A region alone are relevant for achieving enhanced rates of incorporation of nucleotide analogues (cf. paragraph [0187]), i.e. the subject-matter of claim 1.

14. The disclosure in paragraph [0186] of the patent application, which concerns altered 9°N polymerases having the specific substitution mutations in the motif A region described in paragraph [0210], informs the skilled reader that the specific properties - structural (motif A and B regions) and kinetic (incorporation rates of nucleotide analogues) - of the altered 9°N polymerases constructed in Example 2 are "compared to the parental 9°N DM". This paragraph informs the skilled person on the control polymerase used in these experimental studies ("compared to the original mutant", "compared to control polymerases", "the parental sequence of 9°N DM"). It is thus in this context that the reference to "changes in region A alone" in paragraph [0186] is read and interpreted by a skilled person, i.e. the (structural) changes present in the altered 9°N polymerases - compared to the 9°N DM control polymerase - are in the "region A alone". The altered 9°N polymerases carry **only** changes in the region A when compared to the 9°N DM control polymerase, since both, altered 9°N polymerases and 9°N DM control polymerase, have the same amino acid sequence in the motif B region, i.e. the same substitution mutation A485L.

15. The disclosure in paragraph [0186] of the patent application is completely silent, and nothing is derivable therefrom, on the relevance of the substitution mutation (A485L) in the motif B region. It does not suggest, imply or lead the skilled person - certainly not in a direct and unambiguous manner - to altered 9°N polymerases without this substitution mutation in the motif B region. Indeed, the relevance of this mutation (A485L) in the motif B region is disclosed in paragraph [0052] of the description, where

it is stated that the amino acid residue at position 485 in the 9°N polymerase "is thought to play a role in changing the activation energy required for the enzymatic reaction". For the purpose of a direct comparison, as indicated in Example 2 (study the effect of amino acid changes in the motif A region on the rate of incorporation of nucleotides analogues), a skilled person would therefore certainly use a reference enzyme with the A485L substitution mutation.

16. Indeed, the take-home message of the patent application is the identification of the functional relevance of the specific amino acid sequence in both, motif A and motif B regions, as summarised in paragraph [0052], namely the role of the specific amino acid residues in the motif A region as "steric gate" keepers controlling the access of the nucleotide analogues, and the role of the specific amino acid residues in the motif B region controlling the "activation energy required for the enzymatic reaction". Thus, the specific amino acid sequences in both motif A and B regions are highly relevant for the specificity and reactivity of the (altered) 9°N polymerase.
17. Therefore, the disclosure in paragraphs [0186] and [0210] of the patent application is also not a basis for the subject-matter of claim 1.

Conclusion

18. It follows from the considerations above that the subject-matter of claim 1 and thus, the main request contravenes Article 123(2) EPC.
19. In the absence of an allowable request, the appeal must be dismissed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:



L. Malécot-Grob

B. Stolz

Decision electronically authenticated