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Datasheet for the decision of 11 March 2009

Case Number: T 0462/07 - 3.3.04

Application Number: 89103252.6

Publication Number: 0330221

IPC: C12Q 1/68

Language of the proceedings: EN

Title of invention:
End labeled nucleotide probe

Patentee:
Enzo Biochem, Inc.

Opponent:
Akzo Nobel N.V.

Headword:
End Labeled Nucleotide probes/ENZO

Relevant legal provisions (EPC 1973):
EPC Art. 123(2), 83, 54, 56

Keyword:
"Main request - added subject-matter (no) - sufficiency of disclosure (yes) - novelty (no)"
"Auxiliary request I - added subject-matter (no) - novelty (yes)- inventive step (no)"
"Auxiliary request II- added subject-matter (no) - novelty (yes)- inventive step (no)"

Decisions cited:
T 0342/02

Catchword:
-

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Case Number: T 0462/07 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 11 March 2009

Appellant: (Patent Proprietor)
Enzo Biochem, Inc.
325 Hudson Street
10014 New York, N.Y. (US)

Representative:
Barth, Renate, Dr
Vossius & Partner
P.O. Box 860767
D-81634 München (DE)

Respondent: (Opponent)
Akzo Nobel N.V.
Velperweg 76
NL-6824 BM Arnhem (NL)

Representative:
Prins, Hendrik Willem
Arnold & Siedsma
Sweelinckplein 1
NL-2517 GK Den Haag (NL)

Decision under appeal:
Decision of the Examining Division of the European Patent Office posted 3 January 2007 revoking European patent No. 0330221 pursuant to Article 102(1) EPC 1973.

Composition of the Board:

Chairman: R. Gramaglia
Members: B. Claes
D. Rogers

Summary of Facts and Submissions

I. European patent No. 0 330 221 (application No. 89 103 252.6) claiming priority from US 160607 filed on 26.02.1988 was filed on 24.02.1989. The patent relates to end labeled nucleotide probes and was granted on the basis of 18 claims.

II. Notice of opposition against the present patent had been filed by the opponent on the grounds of Articles 100(a), 100(b) and 100(c) EPC.

III. The opposition division revoked the patent because the main request (claims as granted) and the three auxiliary requests then on file did not comply with the requirements of Article 123(2) EPC.

IV. A first appeal against the decision of the opposition division was lodged by the patent proprietor (appellant).

V. The present board in a different composition decided that the claims of the main request filed during the oral proceedings on 9 June 2005 met the requirements of Article 123(2)(3) EPC (cf. decision T 0342/02, paragraphs 9 and 15 of the reasons). The case was then remitted to the opposition division for further prosecution.

VI. This second appeal lies from the decision of the opposition division issued on 3 January 2007 to revoke the patent anew. The reasons for the rejection were lack of novelty and lack of clarity of the claims then on file.

VII. With a statement of grounds of appeal dated 14 May 2007, the appellant submitted a Main Request and Auxiliary Requests I and II. The claims of the Main Request were identical to those of the main request filed during the first appeal oral proceedings on 9 June 2005 before the previous board, which claims were found by that board to meet the requirements of Article 123(2)(3) EPC (see paragraph V supra).

Claims 1 and 2 of the Main Request read as follows:

"1. An oligo- or polynucleotide which
(a) has at least one non-radioactive detection moiety directly attached to each of the 5′ and 3′ end nucleotides thereof, or
(b) has at least one non-radioactive detection moiety being biotin as biotin-11-dUMP attached to each of the 5′ and 3′ end nucleotides thereof."

"2. The oligo- or polynucleotide of claim 1 wherein in (a) said non-radioactive detection moiety comprises biotin or a biotin analogue."

Claim 1 of Auxiliary Requests I read as follows:

"1. An oligo- or polynucleotide probe which
(a) has at least one non-radioactive detection moiety directly attached to each of the 5′ and 3′ end nucleotides thereof, or
(b) has at least one non-radioactive detection moiety being biotin as biotin-11-dUMP attached to each of the 5′ and 3′ end nucleotides thereof."

Claim 1 of Auxiliary Requests II read as follows:

"1. An oligo- or polynucleotide which
(a) has at least one non-radioactive detection moiety directly attached to each of the 5' and 3' end nucleotides thereof, wherein said non-radioactive detection moiety comprises biotin or a biotin analogue, or
(b) has at least one non-radioactive detection moiety being biotin as biotin-11-dUMP attached to each of the 5' and 3' end nucleotides thereof."

VIII. The board sent a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal indicating its preliminary non-binding opinion on all the pending issues. The parties' attention was drawn, inter alia, to the board's intention to deal during the oral proceedings with the issue of inventive step, given that the priority on which the patent relied dated back to 1988.

IX. Oral proceedings were held on 11 March 2009 in the absence of both the appellant and the respondent, who had previously announced that they would not attend.

X. The following documents are cited in the present decision:

A EP-A-0 251 283;

D2 EP-A-0 232 967;

D4 EP-A-0 117 777;

D5 Tournon J., Nucleic Acids Research, Vol. 2, No. 8, pages 1261-1273 (1975);

D9 EP-A-0 225 807.

XI. The submissions in writing by the appellant (patentee), insofar as they are relevant to the present decision, can be summarized as follows:

Main Request
Novelty

– A carbamate (-NH-(C=O)-O-) or an ethylenediamine ($-NHCH_2CH_2NH-$) group did not fall under the definition of the term "non-radioactive detection moiety". Moreover, "direct" attachment to an oligo- or polynucleotide meant attachment without a linker. Therefore, the modified oligo- or polynucleotides described in documents D2 and D5 did not affect the novelty of the claims.

Inventive step

– Although there was sufficient knowledge in the prior art as to how to prepare them, there was no motivation for the skilled person to synthesise polynucleotide probes bearing a non-radioactive label directly attached at both their 3'- and 5'-ends. No prior art reference indeed disclosed or suggested direct attachment of the non-radioactive label at both the 3’ and 5’ end, or suggested that such way of labeling would provide a probe endowed with a high degree of sensitivity, while being

devoid of problems of hybrid instability and diminished hybridization.

Auxiliary Request I
Article 123(2)(3) EPC

– Compared to claims 1 and 8 of the Main Request, the term "probe" had been incorporated into these claims. This term was based on page 4, first and second full paragraph of the description as originally filed.

Novelty

– The arguments provided in support of the Main Request also extended to the claims of this request.

Inventive step

– The arguments provided in support of the Main Request also extended to the claims of this request.

Auxiliary Request II
Article 123(2)(3) EPC

– The claims of this request differed from those of the Main Request in that the non-radioactive detection moiety in clause (a) of claim 1 has been further defined to comprise biotin or a biotin analogue. This feature was based on claim 2 of the Main Request.

Novelty (Article 54 EPC)

– The arguments provided in support of the Main Request also extended to the claims of this request.

Inventive step (Article 56 EPC)

– The arguments provided in support of the Main Request also extended to the claims of this request.

XII. The submissions in writing by the respondent (opponent), insofar as they are relevant to the present decision, can be summarized as follows:

Main Request
Sufficiency of disclosure (Article 83 EPC)

– The patent lacked technical information as to how to proceed for directly attaching a non-radioactive detection moiety to the 5’-end and/or to the 3’-end of the oligo- or polynucleotide according to claim 1, part (a) or for indirectly attaching biotin-11-dUMP to both the 5’-end and the 3’-end of the oligo- or polynucleotide according to claim 1, part (b).

Novelty (Article 54 EPC)

– Any chemical structure directly or indirectly coupled to the 5’-end and/or the 3’-end of the oligo- or polynucleotide could be considered as a "non-radioactive detection moiety" according to

claim 1 (a), since it could be detected by any physical or chemical detection method. Therefore, documents D2 and D9 disclosing such chemical structure-bearing polynucleotides were novelty-destroying for the claims.

– Compound V illustrated in Figure 1 of document D5 was a dinucleotide doubly labeled by a naphthalene group and by a pyrene group. This compound was thus novelty-destroying for the claims.

Inventive step (Article 56 EPC)

– The patent in suit did not describe oligonucleotide probes labelled at both ends with non-radioactive moieties. Therefore, the experiments showing the superior properties of these oligonucleotide probes labelled at both ends were missing from the patent.

– Therefore, there was no indication whatsoever that the problem the appellant argued to be solved (the provision of more sensitive probes) was actually solved (by direct attachment of labels to both ends of the oligonucleotides).

– The problems arising with internally labeling oligonucleotide probes was known in the art and it was no surprise that an oligonucleotide with labels close to the ends performed better than an oligonucleotide with internal labels.

Auxiliary Request I
Sufficiency of disclosure (Article 83 EPC)

– The arguments provided in support of the Main Request also extended to the claims of this request.

Novelty (Article 54 EPC)

– The term "probe" in claims 1 and 8 did not bring about any further limitation vis-à-vis the disclosure of documents D2, D5 and D9.

Inventive step (Article 56 EPC)

– The arguments provided in support of the Main Request also extended to the claims of this request.

Auxiliary Request II
Sufficiency of disclosure (Article 83 EPC)

– The arguments provided in support of the Main Request also extended to the claims of this request.

Novelty (Article 54 EPC)

– Document D9 disclosed the use of biotin labels on page 10, line 33.

Inventive step (Article 56 EPC)

– The arguments provided in support of the Main Request also extended to the claims of this request.

XIII. The appellant (patentee) requested in writing that the decision under appeal be set aside and that the patent be maintained on the basis of the Main Request, or alternatively, on the basis of one of the Auxiliary Requests I and II, all filed with letter dated 14 May 2007.

The respondent (opponent) requested in writing that the appeal be dismissed.

Reasons for the Decision

All claim requests
Sufficiency of disclosure (Article 83 EPC)

1. Both the parties consider that a non-radioactive detection moiety is "directly attached" to an oligonucleotide if no linker is present between these molecules. The board also agrees with this position. The respondent argued that the patent lacked technical information as to how to proceed for directly attaching a non-radioactive detection moiety to the 5'-end and/or to the 3'-end of the oligo- or polynucleotide according to claim 1, part (a) of all requests, or for indirectly (i.e., via a linker) attaching biotin-11-dUMP to both the 5'-end to the 3'-end of the oligo- or

polynucleotide according to claim 1, part (b) of all requests.

2. As regards **directly** attaching a non-radioactive detection moiety to the 5’-end and/or to the 3’-end of the oligo- or polynucleotide according to claim 1, part (a) of all requests, the patent in suit only provides information (see page 2, lines 17-38 and page 6, line 20 to page 6, line 7 and Example 1 to 3) as to how to ("indirectly") attach biotin to the 3’-end and/or 5'-end of polynucleotide via a linker, without addressing polynucleotides having "directly attached" labels. However, in the board's view, the skilled person was in a position to prepare oligo- and polynucleotides having "directly attached" labels. This is because document D5 taught the direct reaction of the activated fluorophores, namely naphthalene isocyanate and anthracene isocyanate with the 5'-OH and 3'-OH of the protected nucleosides (see Fig. 1 on page 1262). It was further stated that this synthesis method was applicable to longer chains (see page 1262, under "Chemical Synthesis"). Moreover, the skilled person was able to select further activated fluorophores from those listed in Table 1 ("Labelling Compound") of document D2. Further, document D2 taught on page 9, lines 35-41 that nucleotides having a "directly" attached label (e.g., 3'-dimethylaminonaphthoyl-ATP and -CTP) could be enzymatically incorporated at the 3'-terminus of a polynucleotide by means of terminal deoxynucleotidyl transferase (TdT). Finally, as regards the reagents for directly labeling with biotin, biotin-N-succinimide (see document A, page 6, lines 18-19) was available. The skilled person applying the DNA labeling chemistry

described above was thus in a position to arrive at the oligo- and polynucleotides having "directly attached" labels covered by claim 1 (a) of all requests.

3. As for the possibility for the skilled person to prepare polynucleotides having biotin-11-dUMP to both its 5'- and 3'-ends (see claim 1, part (b) of all requests) in the light of the information provided by the patent, in the board's opinion, the skilled person could enzymatically (TdT) label e.g., compound 9 at its 3'-end (see Table 1 on page 7 of the patent) with biotin-11-dUTP. Moreover, it can be derived from page 7, lines 37-38 of the patent that it was possible to synthesise by phosphoramidite chemistry an oligonucleotide having a biotin-11-dUTP at its 3'-end by using the modified trifluoroacetylpropenyl nucleotide attached to the solid support. Starting from this solid-phased trifluoroacetylpropenyl nucleotide and proceeding as done for compound 9, the skilled person would arrive at oligonucleotides having labels attached through a linker to both the 5'- and 3'-ends of polynucleotides.

In view of the foregoing and in the absence of evidence to the contrary, the board considers that the claims fulfil the requirements of Article 83 EPC.

Main request
Article 123(2)(3) EPC

4. The present board in a different composition decided that the claims of the main request filed during the first appeal oral proceedings on 9 June 2005, and hence the claims of the present Main Request, which are

identical, met the requirements of Article 123(2)(3) EPC (cf. decision T 0342/02, paragraphs 9 and 15 of the reasons). The present board sees no reason to deviate from this finding.

Novelty

5. Compound V in Fig. 1 on page 1262 of document D5, comprising two nucleotides, falls under the definition of the term "oligonucleotide" (see document D9, page 7, line 3). Two activated fluorophores, namely naphthalene isocyanate and anthracene isocyanate are caused to directly react with the 5'-OH and 3'-OH ends, respectively, of this oligonucleotide. Compound V thus bears both a naphtalene isocyanate and an anthracene isocyanate group directly attached at its 5'-OH and 3'-OH extremities, respectively. Therefore this document is novelty destroying for claim 1 of the main request.

6. The appellant argues that compound V has been labeled indirectly, via a linker (the carbamate group -NH-C(=O)-O-) and that hence it does not fall under claim 1 reciting "directly attached".

The board disagrees with the appellant's view above that the -NH-C(=O)-O- (carbamate) moiety in the labeled molecules of Fig. 1 is a linker. It is simply the derivatized original isocyanate (R^1-N=C=O + HO-R^2 --> R^1-NH-C(=O)-O-R^2). In fact, nothing else (no linker) than the activated fluorophore and the protected nucleoside has been added. Therefore, these non-radioactive detection moieties are directly attached to each of the 5’- and 3’- end nucleotides", as required by present claim 1.

7. In conclusion, claim 1 of the main request does not fulfil the requirements of Article 54 EPC and this request must thus be refused.

Auxiliary Request I
Article 123(2)(3) EPC

8. The claims of this request differ from those of the Main Request, found by the previous board to satisfy the requirements of Article 123(2)(3) EPC (see paragraph V supra), in that claim 1 and 8 of Auxiliary Request I comprise the term "probe". This amendment is based on page 2, lines 51 and 52 of the description as originally filed. Claims 1 and 8 of this request thus satisfy the requirements of Article 123(2) EPC. Given the restrictive nature of the term "probe", the requirements of Article 123(3) EPC are also fulfilled.

Novelty

9. The claims of Auxiliary Request I relate to labelled oligo- and polynucleotide **probes**.

Documents D2 and D9

10. The respondent maintained that documents D2 and D9 disclosing polynucleotides probes bearing linking groups such as -NH-CH_2-CH_2-NH_2 at their 5'-OH and 3'-OH ends were novelty-destroying for the claims. The respondent reasoned that any chemical structure directly or indirectly coupled to the 5’-end and/or the 3’-end of the oligo- or polynucleotide could be considered as a "non-radioactive detection moiety",

since it could be detected by any physical or chemical detection method.

11. The first question to be addressed is thus whether or not the expression "non-radioactive detection moiety" includes linkers in addition to labels. Only following this preliminary analysis can a decision be taken on the novelty-destroying nature (or not) of documents D2 and D9.

12. It is true that a linker can also be derivatized and detected as if it were a label. Paragraph (iii.) on page 5 of the patent indeed illustrates the addition of N-biotinyl-6-aminocaproic acid N-hydroxysuccinimide ester to oligonucleotides having allylamino sidearms (the "linkers"). However, this reaction is slow (see the term "overnight" at line 34; see also "18 h" on page 19, line 51 of document D9). For kinetic reasons, these reactions should be expected to be even slower and less complete if the oligonucleotide probes are immobilized on a filter via a complementary strand, to which they hybridize. Therefore, on the evidence before the board, linkers do not perform as well as labels in terms of reaction time and completeness. The board must conclude that the skilled person would consider that a linker does not fall under the commonly accepted definition of the term "non-radioactive detection moiety" referred to in the claims. Hence, documents D2 and D9 disclosing polynucleotides bearing linking groups such as $-NH-CH_2-CH_2-NH_2$ at their 5'-OH and 3'-OH ends are not novelty-destroying for the claims.

Document D5

13. The respondent also cited documents D5 as being novelty-destroying for the claims. This document discloses an oligonucleotide bearing both a naphthalene isocyanate and an anthracene isocyanate group directly attached at its 5'-OH and 3'-OH extremities (see point 5 supra).

14. The claims of Auxiliary Request I relate to labelled oligo- and polynucleotide probes. Hence, the question arises whether or not the labeled oligonucleotide described in document D5 can be used as a probe. When used as a probe, a labeled oligonucleotide probe must be free to rotate in order to hybridize to a complementary DNA motif through hydrogen bonding between the bases. However, according to page 1272, line 7 from the bottom and page 1273, lines 1-3 of document D5, compound V is so sterically hampered that it is not free to rotate. Hence, it must be concluded that compound V disclosed in document D5 is not (and cannot behave as) an "oligonuclotide probe" as recited in the claims of Auxiliary Request I.

This conclusion also extends to longer chain oligonuclotides obtainable by the synthesis method described on page 1262 of document D5 (under "Chemical Synthesis").

Therefore, document D5 does not affect the novelty of the claims of this request.

Documents A and D4

15. As regards these documents, none of them disclose any labeled oligo- or polynucleotide probes bearing a non-radioactive label **directly** attached to **both** the 3'- and 5'-ends. In fact, all the prior art documents other than document D5 (which does not disclose any probe) relate to oligo- or polynucleotide probes wherein the non-radioactive label is always indirectly attached to the oligonucleotide's 3'- and 5'-ends via at least one linker.

16. Finally, no document of the prior art discloses an oligo- or a polynucleotide having biotin-11-dUMP attached to both its 5’- and 3’-ends, according to claim 1, part (b).

17. In conclusion, the claims of the Auxiliary Request I are novel.

Inventive step

18. In its communication, the board expressed its intention to deal with the issue of inventive step, given that the priority on which the patent in suit relied dated back to 1988. In spite of this, the appellant decided not to attend the oral proceedings and not to provide any further arguments in support of an inventive step. The board, in the light of the fact that the question of inventive step was already discussed in detail during the examination and opposition procedures, will therefore rely on the written submissions on file relating to this issue.

Closest prior art and problem to be solved

19. In simple terms claim 1, part (a) covers polynucleotide probes characterized by (i) the direct attachment of the non-radioactive labels and by (ii) attachment of said labels at each of the 3'- and 5'-ends of the oligo- or polynucleotide.

20. Document D2 suggests that polynucleotides can be labeled at both 5'- and 3'-termini (see page 4, lines 43-45). This document teaches on page 9, lines 35-41 that nucleotides having a "directly" attached label (e.g., 3'-dimethylaminonaphthoyl-ATP and -CTP) can be enzymatically incorporated at the 3'-terminus of a polynucleotide by means of terminal deoxynucleotidyl transferase (TdT). As regards the 5'-terminus, instructions are given (see bottom of page 9) to use H_2N-CH_2CH_2-NH_2 as a linker to bind the activated fluorophore to the polynucleotide. This suggestion in document D2 to prepare polynucleotide probes wherein the 5'-label is linked through a linker, while the 3'-label is directly attached to the polynucleotide thus represents the closest prior art to the subject-matter of claim 1, part (a).

Problem to be solved

21. The appellant maintains that the problem to be solved lies with the provision of labeled oligo- and polynucleotide probes for the detection of nucleic acids endowed with enhanced sensitivity, while avoiding problems of hybrid instability due to diminished hybridization (see also page 2, lines 1-5 and 42-44 and page 9, line 57 to page 10, line 3 of the patent). It

is the appellant's view that the problem above is solved by labeled oligo- and polynucleotide probes exhibiting the following features (see claim 1(a)): (i) the direct attachment of the non-radioactive labels and (ii) attachment of said labels occurs at each of the 3'- and 5'-ends of the oligo- or polynucleotide.

22. However, as regards feature (i) above, the board observes that probes with label moieties **directly** attached to both the 3’- and the 5’-ends (but even to only one end) are not disclosed. Therefore, no technical information can be derived from the patent in suit that the direct attachment of the non-radioactive labels exerts a beneficial effect on the sensitivity/stability of probes compared to indirect attachment. In conclusion, feature (i) above cannot be taken into account for deciding the inventive step.

23. As for the question whether or not feature (ii) above (each of the 3'- and 5'-ends are labeled) achieves any increase in sensitivity/hybridization stability of the probes, compared to attachment to one end only, there is a statement on page 10, lines 1-3 of the patent:

"Thus, multiple labelings at both the 3’ and the 5’ termini of oligonucleotides generate synthetic probes that are more sensitive than those labeled with single biotins at the 3’ and 5’ termini."

In the board's opinion, this passage merely focuses on the multiple versus single labeling issue, in the sense that multiple labeling, regardless of the oligonucleotide extremity, increases sensitivity compared to single labeling. This increase in

sensitivity is indeed illustrated in Table 1 on page 7 of the patent, upon comparison of the relative signal strengths of probes 15 and 9. However, the technical effect invoked by the appellant, namely a higher signal/stability due to the presence of labels at both ends of a probe (compared with a probe having a label at one end only) cannot be derived from this statement.

24. Example 1 of the patent relates to a series of experiments in which a number of indirectly labeled oligonucleotides have been synthesized and their respective sensitivities have been compared on the basis of the signal strength which was generated (see Table 1 on page 7). The board notes that although several oligonucleotides with biotin labels at different positions on the chain are tested and the signals generated are compared, none of the oligonucleotides has a biotin group attached at both the 3’ end and the 5’ end. Nor are said probes with label moieties attached to each of the 5'- and 3'ends disclosed elsewhere in the patent. Hence, the technical effect invoked by the appellant, namely a higher signal/stability due to the presence of labels at both ends of a probe, compared with a probe with a label at one end only, cannot be derived from the patent in suit. In conclusion, feature (ii) also cannot be taken into account when assessing inventive step.

25. The board also notes in passing that the experimental results in Table 1 on page 7 of the patent and its counterpart on page 8, lines 6-22 of the description do not go beyond those already expected from the prior art.

From the Table on page 7, the technical effect which emerges is that the signal of the labeled oligonucleotides increases with the number of labels when these are placed at the ends (see compounds 13 and 15) or at the penultimate 5'- and 3' nucleotides (see compound 12), rather at the centre (see compounds 10 and 14) of the oligonucleotide.

However, according to document A (see page 3, line 49), multiple labeling was indeed known to increase sensitivity (see page 3, line 49). Document A (see page 3, lines 45-46) and document D9 (see page 2, lines 42-45) also recommended to avoid label positions which could cause a change in the T_m value or interfere with normal base pairing.

26. In view of the foregoing, the board does not agree that the problem to be solved is the one argued by the appellant (see point 21 supra). Rather, starting from document D2 as the closest prior art (see point 20 supra), the problem to be solved lies in the provision of further alternative oligo- and polynucleotide probes. The solution to this problem are oligo- and polynucleotide probes bearing a non-radioactive label directly attached at each of their 3'- and 5'-ends.

27. The relevant question is whether or not the solution to this problem proposed in claim 1 (a) follow from the prior art in an obvious way. These oligo- and polynucleotide probes exhibit the following features: (i) the direct attachment of the non-radioactive labels and (ii) attachment of said labels occurs at each of the 3'- and 5'-ends of the oligo- or polynucleotide.

28. As regards feature (i) above relating to the direct attachment of the non-radioactive labels, the board is of the opinion that direct attachment of a label was an obvious alternative to indirect attachment (see e.g., document D9, page 6, last line). Moreover, as emphasized under point 2 supra, the skilled person could easily prepare oligo- and polynucleotides having "directly attached" labels at both ends by relying on the then available DNA labeling chemistry.

29. As for feature (ii) above, according to which attachment of said labels occurs at each of the 3'- and 5'-ends of the oligo- or polynucleotide, the board observes that several prior art documents (in addition to document D2 dealt with under point 20 supra) already proposed oligonucleotide probes bearing non-radioactive labels at both their 5'- and 3'-ends. Document A disclosed such probes labeled via a lysine linker (see page 2, lines 40-41 (c.f. the term "both"), compounds 20 and 21 in Table 1 on page 8 and compound 33 on page 9, line 53). Document D9 described the preparation of a "Biotin Label" (see Example 4 on page 19) consisting in adding a "long chain" N-hydroxysuccinimidyl biotin to the N^4-(2-aminoethyl)-deoxycytidine (see Example 2), to be incorporated into synthetic probes. It is stated on page 10, lines 51-55 of this document that biotin labels could be attached to both 5'- and 3'-ends of an oligonucleotide using conventional methods.

30. In summary, the prior art provided an incentive for the skilled person to synthesise polynucleotide probes bearing a non-radioactive label directly attached at

both their 3'- and 5'-ends, according to present claim 1, part (a).

31. In conclusion, claim 1 of Auxiliary Request I does not fulfil the requirements of Article 56 EPC and this request must thus be refused.

Auxiliary Request II
Article 123(2) EPC

32. The claims of this request differs from those of the Main Request in that the non-radioactive detection moiety in clause (a) of claim 1 has been further defined to comprise biotin or a biotin analogue. This feature is based on claim 2 of the Main Request. Furthermore, the back-references of the remaining claims have been adapted. These amendments do not contravene Article 123(2)(3) EPC.

Novelty (Article 54 EPC)

33. The conclusion arrived at by the board under point 17 supra also applies to the claims of this request, as no prior art before the board discloses oligo- or polynucleotides having at least one biotin or a biotin analogue directly attached to each of the 5′ and 3′ end nucleotides thereof, or having biotin-11-dUMP attached to each of the 5′ and 3′ ends.

Inventive step

34. Starting from document D2 as the closest prior art (see point 20 supra), the problem to be solved by the subject-matter of claim 1 (a) of this request lies in

the provision of further alternative oligo- and polynucleotide probes. The solution to this problem are oligo- and polynucleotide probes bearing at least one biotin, or a biotin analogue, directly attached to each of the 5’ and 3’ end nucleotides thereof.

35. As highlighted under point 30 supra, the prior art provided an incentive for the skilled person to synthesise polynucleotide probes bearing a non-radioactive label directly attached at both their 3'- and 5'-ends, such label being any non-radioactive label moiety or a biotin label. A reagent for directly labeling with biotin, namely biotin-N-succinimide (see document A, page 6, lines 18-19) was also available to the skilled person. Therefore, the selection of a biotin label as a non-radioactive detection moiety as done in present claim 1, part (a), does not render the claim inventive.

For these reasons, it is concluded that the subject-matter of claim 1 lacks inventive step and Auxiliary Request II is also refused for failing to fulfil the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

P. Cremona R. Gramaglia