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Datasheet for the decision of 6 February 2024

Case Number: T 0369/21 - 3.3.08

Application Number: 11004071.4

Publication Number: 2423325

IPC: C12Q1/68

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Title of invention:
Method of preparing libraries of template polynucleotides

Patent Proprietor:
Illumina Cambridge Limited

Opponent:
Kilger, Christian

Headword:
Method of preparing libraries/ILLUMINA CAMBRIDGE

Relevant legal provisions:
EPC Art. 100(a), 100(c)
RPBA 2020 Art. 12(3), 13(1)

Keyword:
Claims as granted - requirements of the EPC met - (yes)

Decisions cited:
G 0002/10, G 0003/14

Catchword:

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Beschwerdekammern

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Case Number: T 0369/21 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 6 February 2024

Appellant: (Opponent)	Kilger, Christian Wachtelstr. 4 14195 Berlin (DE)
Representative:	Kilger, Christian CH Kilger Anwaltspartnerschaft mbB Fasanenstraße 29 10719 Berlin (DE)
Respondent: (Patent Proprietor)	Illumina Cambridge Limited Illumina Centre 19 Granta Park, Great Abington Cambridge, Cambridgeshire CB21 6DF (GB)
Representative:	Westendorp, Michael Hoefer & Partner Patentanwälte mbB Pilgersheimer Straße 20 81543 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 1 April 2021 rejecting the opposition filed against European patent No. 2423325 pursuant to Article 101(2) EPC**

Composition of the Board:

Chair	T. Sommerfeld
Members:	M. Montrone
	K. Kerber-Zubrzycka

Summary of Facts and Submissions

I. An appeal was lodged by the opponent ("appellant") against the decision of an opposition division to reject the opposition against the European patent No. 2 423 325 ("patent"). This patent is based on European patent application No. 11004071.4 ("application") which is a divisional application of the earlier European patent application No. 06794950.3, originally filed as an International patent application published as WO 2007/052006 ("earlier application"). Except for claims 1 to 15 of the application, the contents of the application and of the earlier application are identical, with the original claims of the earlier application being present in the application as "Embodiments" on pages 63 to 69.

II. An opposition was filed against the patent. The opposition proceedings were based on the grounds for opposition in Article 100 (a) EPC, in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC) and Article 100 (c) EPC. The opposition division held that the grounds of opposition did not prejudice the maintenance of the patent as granted and hence rejected the opposition.

III. With their statement of grounds of appeal, the appellant submitted arguments against the subject-matter of claim 1 as granted under added subject-matter (Articles 100(c) and 76(1) EPC) and under lack of novelty and inventive step (Article 100(a) EPC with Articles 54 and 56 EPC).

IV. In reply, the patent proprietor ("respondent") *inter alia* re-submitted auxiliary request 1 and counter arguments.

V. With letter dated 25 November 2021, the appellant submitted *inter alia* a new line of argument under inventive step against the method of claim 1.

VI. In a communication pursuant to Article 15(1) RPBA, the parties were informed of the board's preliminary opinion.

VII. Oral proceedings were held with both parties being represented.

VIII. Claim 1 as granted (main request) reads (designation of the features added between brackets, according to the parties' feature analysis):

"1. A method of generating a library of template polynucleotide molecules

which have common sequences at their 5' ends and common sequences at their 3' ends, the method comprising:

providing one or more blunt end target polynucleotide duplexes, adding a single 'A' deoxynucleotide to both 3' ends of the target polynucleotide duplexes, thereby producing a one-base 3' overhang, ("feature 1.2")

ligating identical mismatched adapter polynucleotides to both ends of each of one or more target polynucleotide duplexes to form one or more adapter-target constructs, ("feature 1.3")

wherein each mismatched adapter is formed from two annealed polynucleotide strands that form a bimolecular complex comprising at least one double-stranded region and an unmatched region, and wherein each mismatched adapter comprises a one-base 3' 'T' overhang on the double-stranded end, which is complementary to the one-base 3' 'A' overhang on the target polynucleotide duplexes, ("feature 1.4")

carrying out an initial primer extension reaction in which a primer oligonucleotide is annealed to an adapter portion of each of the adapter-target constructs and extended by sequential addition of nucleotides to form extension products complementary to at least one strand of each of the adapter-target constructs,

wherein the extension products, and optionally amplification products derived therefrom, collectively provide a library of template polynucleotide molecules which have common sequences at their 5' ends and common sequences at their 3' ends;

wherein the target polynucleotide duplexes to be ligated are a complex mixture of genomic DNA fragments representing a whole or substantially whole genome, and ("feature 1.7")

wherein the library of template polynucleotide molecules generated is representative of the whole or substantially whole genome" ("feature 1.8").

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

D1: US 2004/0067493

D2: US 6,287,825

D8: Lucito R., *et al.*, PNAS, 1998, Vol. 95, 4487-4492

D9: Mead, D. A., *et al.*, Bio/Technology, 1991, Vol. 9, 657-663

D12: US 2003/0013671

D13: US 2004/0209299

D14: Hughes S., *et al.*, Progress in Biophysics & Molecular Biology, 2005, Vol. 88, 173-189

X. The appellant's submissions, insofar as relevant to the present decision, may be summarised as follows:

Main request (claims as granted)

Added subject-matter - claim 1

The terms "*adding a single 'A' deoxynucleotide to both 3' ends of the target polynucleotide duplexes*" in feature 1.2, as well as features 1.4 and 1.8 (see section VIII, above) were not directly and unambiguously disclosed in the application as filed.

Feature 1.8 was not explicitly disclosed in the application as filed. In order to be implicitly disclosed, this feature had to be the direct and unambiguous consequence of the subject-matter explicitly disclosed in the application as filed. According to claim construction, the terms "*representative of the whole or substantially whole genome*" in claim 1 had a narrow meaning in the sense

that the library generated by the claimed method contained 100% of the genomic sequences or almost 100%. However, the application as filed did not intend to generate such a library. Instead libraries with common ends were generated from complex mixtures (page 11, line 27 to page 12, line 15). These libraries were then subjected to whole genome amplification ("WGA").
For generating such a library in a first step adapter sequences were ligated to templates forming thereby adapter-template constructs. The adapters were thus the common sequences at both ends of the constructs. In a second step these constructs were subjected to PCR amplification which enriched certain templates only, i.e. those with ligated adapters (page 27, lines 6 to 19).

Thus the skilled person reading the application as filed as a whole was aware that the library generated according to these instructions did not represent 100% or almost 100% of the genomic sequences but a subset thereof only. Neither was the efficiency of ligating adapters to template molecules 100% nor did the PCR reaction amplify 100% of the sequences. Moreover an example of a library comprising 100% of the genome was not disclosed in the application as filed.
Lastly, also page 40, lines 5 to 13 of the application as filed did not disclose a library representing the whole or substantially whole genome but templates with these properties.

Novelty

The disclosure of document D13 anticipated the subject-matter of claim 1. As regards the "*mismatched adapter*" specified in feature 1.4 of claim 1, adapters with a 5' overhang were novelty destroying, since the single-

stranded overhang had no counterpart on the other strand (document D13, paragraphs [0080] and [0230]). Nor did the result to be achieved as defined in feature 1.8 of claim 1 confer novelty of the claimed method vis-a-vis document D13.

Inventive step

The subject-matter of claim 1 lacked an inventive step over the teaching of document D1 combined with that of document D9, or in light of the combined teaching of documents D12 and D1 or of documents D2 and D9, or over document D13.

The claimed method was directed to an amplification method which comprised a ligation step. This meant that "*what goes in also comes out*" again. Therefore, no surprise or advantageous effect was ascribable to features 1.7 and 1.8 which related to mere results to be achieved.

Document D1 disclosed a method for generating a library of polynucleotide molecules having common sequences at their 5' and 3' ends. These adapters had regions of complementarity and non-complementarity and thus represented mismatched adapters according to features 1.3 and 1.4 (document D1, paragraphs [0022], [0038] to [0041], [0097], [0125] to [0129] and Figure 5). In an embodiment of D1, the library generated was representative of the whole genome (paragraph [0130]). Document D1 disclosed both blunt end ligation and ligation of ends with overhangs. Although T/A cloning was not mentioned, this was a standard technique in the art (document D9, abstract). Thus the skilled person by combining the teaching of document D1 with that of

document D9 would have arrived at the method of claim 1 in an obvious manner.

Document D12 as alternative closest prior art disclosed a method for the generation of genomic DNA libraries that included all sequences of the starting material (paragraphs [0010], [0013] to [0042], [0151] to [0175]). The method of claim 1 differed from that in document D12 only in that it used mismatched forked adapters, i.e. feature 1.4. The skilled person would have turned to document D1 because this document disclosed that the use of forked adapters reduced the intramolecular base-pairing of adaptor-targets compared to non-forked adapters (paragraph [0097]). By combining the teaching of document D12 with that of document D1 the skilled person would have arrived at the method of claim 1 in an obvious manner.

XI. The respondent's submissions, insofar as relevant to the present decision, may be summarised as follows:

Main request (claims as granted)

Added subject-matter - claim 1

The subject-matter of claim 1 did not comprise added subject-matter. Feature 1.2 found basis on page 30, lines 16, 17 and 21 to 25, page 33, lines 17 to 21 and 24 to 29 and *inter alia* Figure 5 of the application as filed. Feature 1.4 was based on the disclosure of claim 1 as filed in combination with page 18, lines 19 to 25, page 30, lines 26 and 27 and *inter alia* Figure 5. Feature 1.8 was based on the disclosure of claim 1 as filed in combination with page 6, lines 3 to 5, page 27, lines 13 to 19 and page 40, lines 4 to 13.

Novelty

Document D13 did not disclose the forked adapters as defined by feature 1.4 (i.e. adapters with asymmetric ends on each strand). The Figures of document D13 solely disclosed adapters with the same ends on both strands. Thus, claim 1 was novel over document D13.

Inventive step

Document D1 did not disclose the same method as that of claim 1 since the templates used for generating the library represented a subset of fragments of defined size only, i.e. the templates were of reduced complexity (abstract and paragraph [0006]). As a consequence thereof the library generated by the method of document D1 was different from that generated by the method of claim 1. The skilled person starting from document D1 had thus no motivation to look for other methods that generated a whole genome library.

Document D12 disclosed a method for generating a library which maintained substantially the copy number of a set of genes or genomic sequences. Such a library was not necessarily a whole genome library. This library was generated by using blunt ended adapters being ligated to fragmented DNA. The resulting adapter-template constructs had a tendency to self-ligate which reduced the overall efficiency of generating a library. The skilled person looking for a solution that increased the efficiency of generating the library of document D12 while maintaining its complexity did not look at the method of document D1 which disclosed a method for generating a library with a reduced complexity.

XII. The appellant requested:

- that the decision under appeal be set aside and that the patent be revoked.

XIII. The respondent requested:

- that the appeal be dismissed and the patent be maintained as granted, or auxiliary that the patent be maintained on the basis of auxiliary request 1.
- that the new lines of argument put forward in the appellant's letter of 25 November 2021 not be admitted into the appeal proceedings.

Reasons for the Decision

Main request (claims as granted)

Claim construction - claim 1

1. Claim 1 is directed to a method of generating a library of template polynucleotide molecules which have common sequences at their 5' and 3' ends. The method comprises several process steps which following the parties' feature analysis (see section VIII, above) *inter alia* specify that:

- the "*mismatched adapter*" is "*formed from two annealed polynucleotide strands that form a bimolecular complex comprising at least one double-stranded region and an unmatched region*" and in that this adapter comprises "*a one-base 3' 'T' overhang on the double-stranded end, which is*

complementary to the one-base 3' 'A' overhang on the target polynucleotide duplexes" (feature 1.4),

- "*wherein the target polynucleotide duplexes to be ligated*" (i.e. the start material for preparing the library) are "*a complex mixture of genomic DNA fragments representing a whole or substantially whole genome*" (feature 1.7), and

- "*wherein the library of template polynucleotide molecules generated is representative of the whole or substantially whole genome*" (feature 1.8). In other words, the composition of the final library of template molecules corresponds to the composition of the start material, i.e. the duplexes of target polynucleotides.

2. The definition of the "*mismatched adapter*" in feature 1.4 above implies a forked structure at the 5'-end or a mismatched region within this molecule with an additional one T overhang at its 3' double stranded end (see e.g. Figures 1 c) and 8 e) of the patent).

3. As regards the construction of the features "*representing a*"/"*representative of*" the "*whole or substantially whole genome*" in features 1.7 and 1.8 of claim 1, the following is relevant.

3.1 These features encompass two alternatives:
(1) representative of the whole genome and
(2) representative of substantially the whole genome.

3.2 It is established case law that terms in a claim must be given their normal meaning, unless the description gives them a special meaning. Furthermore, the description and drawings may be used to interpret the

claims and identify their subject-matter, in case of unclear terms in the claims (see Case Law of the Boards of Appeal of the EPO, 10th edition 2022, ("Case Law"), II.A.6.3.1 and II.A.6.3.3).

3.3 As regards the terms "*representative of the whole or substantially whole genome*" of feature 1.8 (identical considerations apply for feature 1.7), these terms could be construed narrowly in that they encompass the complete genome or close thereto, i.e. 100% or substantially 100% thereof, or more broadly to include any representative percentage of the whole genome, for example, a subset comprising, for example, 70% or 75% of the genomic sequences (see e.g. document D8, title and page 4487, left column, penultimate paragraph and document D1, paragraphs [0057] and [0101]).

3.4 While the normal meaning of the term "*whole genome*" relates to a complete genome or 100% of the genome, the term "*substantially*" in conjunction with a *"whole genome*" has no defined boundaries. The normal meaning of "*substantially*" used as an adjective in feature 1.8 defines that the library generated represents the whole genome in substance, i.e. to a high extent.

3.5 The meaning of "*representative*" differs depending on the context in which the term is used. It includes for example, constituting, amounting to, or being present in something to a particular degree. Looking at feature 1.8 in the context of claim 1 it is difficult to ascribe "*representative*" only one of these different meanings.

3.6 In such a situation the case law has established that the patent may be consulted for interpreting the subject-matter claimed. The patent is silent on any

definition of "*whole genome*" or "*substantially whole genome*", as well as on a definition of subsets/parts of genomic sequences being representatives of the whole genome. Instead the description discloses that libraries prepared by the method of the invention are *inter alia* used as template *"for whole genome amplification*" (see paragraphs [0016], [0027] and [0093]). This purpose is achievable only if the sequences in the library comprise the whole genome or an almost complete genome. Accordingly, libraries are prepared from a "*complex mixture of whole genome fragments*" (see paragraph [0016]). In view thereof genomic DNA fragments, or representative libraries of the whole or substantially whole genome as disclosed in paragraph [0094] of the patent constitute the genome as a whole or to an almost complete extent.

3.7 If the patent mentions subsets of the whole genome, these subsets are indicated as such, for example, as "*mixtures of cDNAs*", see paragraph [0013]). The description defines these subsets not as representatives of the whole genome. This is different from the prior art. Document D8, for example, mentions that the "*representations*" generated comprise a subset of the genome, i.e. about 70% thereof (see abstract, page 4487, left column, penultimate paragraph), and not the whole genome or substantially whole genome, which according to another document would be "[*t]he ideal situation*" (see document D14, page 174, last sentence). Similar observations apply to document D1 (see paragraph [0057]).

3.8 In view of the considerations above, the terms "*representing*"/"*representative*" of the "*whole*" or "*substantially whole genome*" in the context of claim 1 have a narrow meaning, as likewise corroborated by the

description. This means that the genomic DNA fragments used for generating the template library, or the library of template polynucleotides generated by the method of claim 1 comprise the complete genome or the complete genome in substance, and not a mere representative subset thereof.

3.9 Features 1.7 and 1.8 of claim 1 are directed to separate process steps. Since these steps have to be carried out by the method of claim 1, both features have a limiting meaning.

4. The appellant submitted that feature 1.8 being directed to a result to be achieved was not relevant for assessing inventive step. In their statement of grounds of appeal, point 7.2.5, reference was made to the Guidelines F.IV.4.10. In essence the appellant argued that feature 1.8 was not allowable since it defined the invention by a result to be achieved which amounted to claiming the underlying technical problem.

4.1 The Guidelines referred to by the appellant relate to clarity. However, contested feature 1.8 is present in granted claim 1 and hence this feature is not open to this objection (see G 3/14, OJ 2015, 102: catchword). Furthermore, the contested feature (here: the library generated "*is representative of the whole or substantially whole genome*") is a functional feature of the claim. Functional features *per se* are not necessarily unclear. Rather the question is whether this feature implies properties of the product (here the library generated) that differentiate the product from those products prepared by other methods of the prior art (see Case Law, I.C.5.2.5).

4.2 As set out above, a library generated from fragments that represent the whole or substantially whole genome differs from a library that is generated from fragments that are a representative subset of genomic sequences only.

4.3 Furthermore, there are no indications on file that the process steps defined in claim 1 are not suitable to generate a library that represents the whole or substantially whole genome.

5. The appellant further submitted that a purpose in a method directed to the production of a product cannot confer novelty or inventive step.

5.1 The board agrees with the appellant in so far as it is established case law that the indication of a purpose in a claim directed to the production of a product (here "*generating a library of template polynucleotide molecules which have common sequences at their 5' ends and common sequences at their 3' ends*") is limiting for this method insofar only as the method as defined by its process steps has to be suitable for that purpose (here generation of a library with the properties as defined in claim 1) (see Case Law, I.C.8.1.3a).

5.2 For the reasons set out above, a library comprising the whole genome or substantially whole genome as defined in claim 1 is different from a library that comprises a fraction of the genome only, even if this fraction comprises a representative 70% or 75% of the genome (see document D1, paragraph [0057] and document D8, page 4487, left column, penultimate paragraph).

Added subject-matter - claim 1

6. In the following reference to the application as filed / claims as filed is to the earlier application, WO 2007/052006.

7. The appellant submitted that features 1.2, 1.4 and 1.8 (see section VIII, above) of claim 1 as granted comprised added subject-matter.

8. As regards features 1.2 and 1.4 in claim 1, the appellant merely submitted that the application as filed did not directly and unambiguously disclose these features, without however providing reasons why the opposition division erred in this respect (decision under appeal, points 4.22.1 to 4.22.3). In the absence of any substantiation, the board has no reasons for overturning the opposition division's conclusions that these two features have a basis in Figure 2a and page 30, line 16 *et seq.* of the application as filed.

9. Since feature 1.8 of claim 1 is not explicitly disclosed in the application as filed, the question is whether this feature is implicitly disclosed therein. The case law has held that an implicit disclosure must be the clear and unambiguous consequence of what is explicitly mentioned in the application as filed (see Case Law, II.E.1.3.3). The respondent in support of a basis for feature 1.8 referred *inter alia* to the disclosure on page 40, lines 4 to 13 of the application as filed in conjunction with claim 1 as filed.

9.1 The first sentence on page 40, lines 4 to 13 of the application as filed starts with "*Template libraries prepared according to the method of the invention*" (emphasis added), i.e. the method of claim 1 as filed. This sentence further mentions the libraries' suitability for *"whole-genome"* amplification starting

from "*a complex mixture of genomic DNA fragments representing a whole or substantially whole genome*". The second sentence defines "*whole-genome amplification*" as an amplification of "*the template*" (i.e. "*the target polynucleotide duplexes to be ligated*" of feature 1.7) which comprises "*a complex mixture of nucleic acid fragments representative of a whole (or substantially whole genome)*".

9.2 Since the amplification of template sequences derived from a mixture of genomic fragments representing a whole or substantially whole genome as start material necessarily results in a library with the same properties as the start material, the passage on page 40 of the application as filed indicated above implicitly discloses feature 1.8 of claim 1. This seems indirectly to be confirmed by the appellant's own submission in the context of inventive step where it was asserted that since the claimed method was directed to an amplification method which comprised a ligation step, the mere result of the claimed method was that "*what goes in also comes out*" again.

10. The appellant in essence submitted that feature 1.8 was not implicitly disclosed in the application as filed because the application as filed did not intend to generate a whole genome library, but rather a template library that was suitable for whole genome amplification, as was apparent from page 11, line 27 to page 12, line 15. The skilled person, however, based on common general knowledge was aware that such a library did not cover 100% of the genome since this was technically not feasible. In fact, only certain templates would be enriched when subject to PCR amplification (page 27, lines 6 to 19).

11. The board is not convinced by the appellant's arguments, because in essence this argument is directed to sufficiency of disclosure (Article 100(b) EPC), i.e. the skilled person based on the teaching of the application as filed and common general knowledge would be aware that a library containing 100% of the genomic sequence cannot be generated. However, Article 100(b) EPC has not been relied on in these proceedings as ground of opposition and its criteria cannot be applied in assessing the requirements of Article 100(c) EPC. Instead the relevant question here is whether feature 1.8 remains within the limits of what a skilled person would derive directly and unambiguously, using common general knowledge, from the whole of the application as filed ("gold standard" of G 2/10, OJ 2012, 376). This includes any implicit disclosure, for example, that of page 40, lines 4 to 13 of the application as filed (see point 9.1, above).

12. The subject-matter of claim 1 as granted, and the claims as granted as a whole thus comply with Article 100(c) (Articles 123(2) and 76(1)) EPC).

Novelty

13. The appellant submitted that the disclosure of document D13 anticipated the subject-matter of claim 1. As regards the "*mismatched adapter*" specified in features 1.3 and 1.4 of claim 1 (see section VIII, above), the appellant referred to claims 50 and 51, paragraph [0080], pages 20 to 21 and pages 71 and 72 (claims) of document D13.

14. The board agrees with the respondent that document D13 is silent on the disclosure of a "*mismatched adapter*" as defined in feature 1.4 of claim 1 (see claim

construction, points 1 and 2, above). The references in document D13 relied on by the appellant disclose an overhang at the 5'-end of the adapter. However, feature 1.4 requires as unmatched region not only, for example, an overhang at the 5'-end of the adapter, but in addition, a single T overhang at the 3'-end of the adapter. There is no mentioning of such a mismatched adapter in claims 50 and 51, paragraph [0080] and pages 20, 21, 71 and 72 of document D13.

15. Accordingly, the subject-matter of the claims as granted is novel over document D13 (Article 100(a) EPC, Article 54 EPC).

Inventive step

16. In the appealed decision, the opposition division concluded that the claimed subject-matter was inventive over the combinations of documents D1 and D9, D2 and D9 and D12 and D1. In the grounds of appeal, the appellant maintained the objections based on these three combinations of documents. However the appellant did not provide any substantiation as regards the combination of documents D2 and D9. In a later letter, the appellant raised a new objection for lack of inventive step, starting from document D13 as closest prior art.

Documents D1 and D9

17. The board does not agree with the appellant's arguments for the following reasons:

18. Document D1 discloses a method that provides a library with reduced genomic complexity based on amplifying a subset of genomic fragments of a certain size (see

abstract, paragraphs [0006], [0009], [0057] and Example 1). This library of reduced complexity is generated to provide a fast and cost effective exploration of complex samples of nucleic acids, particularly genomic DNA (see paragraphs [0004] to [0006]).

18.1 As set out in the decision under appeal (point 6.3.4), the method of claim 1 differs from that in document D1 in:

- blunt-ending the nucleic acid fragments (feature 1.2, see section VIII, above)
- generation of an A-overhang (feature 1.2)
- ligation with adapters having a T-overhang as defined by feature 1.4.

18.2 The generation of A-overhangs and the ligation to adapters with a corresponding T-overhang as defined by features 1.2 and 1.4 of claim 1 may likewise be referred to as "*T/A cloning*" (see e.g. grounds of appeal, page 14, last paragraph to page 15, line 1). A 3'-overhang of a single A on the target polynucleotide and a corresponding 5'-overhang of a single T on the mismatched adapter molecule increase the ligation efficiency between both molecules, i.e. the formation of adapter-target constructs and hence, the efficiency in generating a genomic library.

18.3 While it is uncontested that document D1 does not disclose feature 1.2, the appellant submitted that feature 1.4 relating to mismatched adapters was disclosed in document D1. This is not convincing. Although Figure 5 in conjunction with paragraph [0097] of document D1 disclose mismatched adapters, these adapters do not disclose a one-base 3'-T overhang on their double-stranded ends as requested by feature 1.4 of claim 1 too.

18.4 It is further contested whether or not features 1.7 and 1.8 of claim 1 (see section VIII, above) are distinguishing technical features that can be taken into account for assessing inventive step.

18.5 Claim 1 uses for generating a library with the properties defined by feature 1.8 "*target polynucleotide duplexes*" for ligation that are "*a complex mixture of genomic DNA fragments representing a whole or substantially whole genome*" (i.e. feature 1.7).

18.6 Contrary thereto, the method of document D1 selects genomic fragments of a particular size range after digesting the genome with a restriction enzyme or combination of these enzymes. This sample of selected genomic fragments (i.e. target polynucleotide duplexes) in document D1 is then used to generate the second sample, i.e. the library. Since the library is the cloned and amplified product of the first sample, the library comprises necessarily a reduced content of genomic sequences (see paragraphs [0006], [0009] and [0057]). Thus the starting material used for generating the library according to the claimed method (i.e. feature 1.7) and that of document D1 is different.

18.7 The appellant submitted that document D1 disclosed as an embodiment a library representing the genome as a whole since the library's splitting up into subsets for analysis purposes happened after its generation (see paragraphs [0057] in conjunction with [0125] to [0130]).

18.7.1 The board does not agree. Paragraphs [0125] to [0130] of document D1 disclose how "*a collection of human SNPs*

present on XbaI fragments of 400 to 1,000 base pairs" is generated, using "*human genomic*" DNA as start material (see paragraph [0125] and last sentence of paragraph [0130])). This "*collection*" of sequence fragments of a selected size range (i.e. a subset of the genome) forms the library and not the randomly "*DNase*" fragmented and labelled PCR sample disclosed in paragraph [0129] of document D1.

18.7.2 That the "*collection*" of "*XbaI fragments of 400 to 1,000*" base pairs in paragraph [0130] of document D1 relates to a representative subset of the genome and not to the genome as a whole is also derivable from document D1's teaching as a whole which refers to a "*collection of target sequences in a nucleic acid sample*" (see abstract) for which novel methods "*that reduce the complexity*" of the human genome are required (see paragraph [0004] and claim 1). In this context document D1 states, for example, that "*[I]n order to interrogate a whole genome it is often useful to amplify and analyze one or more representative subsets of the genome. ... Subsets can be defined by many characteristics of the fragments. In a preferred embodiment of the current invention, the subsets are defined by the proximity to an upstream and downstream restriction site and by the size of the fragments resulting from restriction enzyme digestion. Useful size ranges may be from 100, 200, 400, 700 or 1000...*" (see paragraphs [0101], emphasis added and [0057]). The board thus agrees with the opposition division's conclusion on this issue (decision under appeal, point 6.3.7).

18.8 Feature 1.8 as a result to be achieved defines that the library generated by the method of claim 1 is "*representative of the whole or substantially whole*

genome". These properties of the generated library are the result of the other process steps in claim 1 and hence define a technical feature which differs from the "*representative subset*" being solely "*a fraction of a genome*" as generated by the method of document D1 (see paragraphs [0057] and [0101]).

18.9 The technical effects ascribable to these differences are that a more complete library is generated with improved efficiency.

19. The technical problem to be solved thus resides in the provision of a method for generating a more complete library of template polynucleotide molecules with improved efficiency. This problem is solved by the method of claim 1.

20. As regards obviousness, the skilled person starting from document D1 would have no motivation to generate a more complete library. Libraries having an increased size slow down sample analysis at higher costs (see document D1, paragraphs [0004] to [0006]). The generation of a library containing a more complete genome goes thus against the declared aim of document D1's teaching. Irrespective thereof document D9 is silent on generating a more complete genomic library. Thus even if the skilled person would have combined the teaching of documents D1 and D9, he/she would not have arrived at subject-matter falling within the scope of claim 1. Accordingly, the subject-matter of claim 1 is not obvious over the combined teaching of documents D1 and D9.

Documents D12 and D1

21. Document D12 as alternative closest prior art discloses a method that generates a library which comprises the whole or substantially whole genome (see paragraphs [0010] and [0011]).

22. As set out in the decision under appeal (point 6.3.23) the method of claim 1 differs from that in document D12 in:
- the generation of an A-overhang (feature 1.2)
- the ligation with adapters having a T-overhang and
- the ligation with identical forked mismatched adaptor polynucleotides as specified in claim 1 (feature 1.4).

23. The appellant submitted that the method of claim 1 differed from document D12 as disclosed in paragraphs [0013] to [0042] and [0151] to [0175] solely in feature 1.4.

23.1 The board does not agree. The paragraphs cited by the appellant in document D12 solely disclose a ligation between an adapter molecule and "*blunt-ended DNA*" (see e.g. paragraph [0158]), but not the other two distinguishing features of the claimed method indicated in point 22 above.

23.2 As set out in point 18.2 above, the first two differences in point 22 above are known as "*T/A cloning*" and have the effect that the ligation efficiency is increased thereby improving the efficiency in generating a genomic library.

23.3 The third difference (i.e. feature 1.4 of claim 1) reduces the self complementarity between the identical adapter molecules at both ends of the adapter-target constructs (decision under appeal, point 6.3.25, and

patent, paragraphs [0036] and [0048]). Document D12 in contrast thereto ligates identical, fully complementary adapter molecules (i.e. adapters without mismatches) to both ends of the genomic DNA fragments (see, for example, paragraph [0103] and Example 1, paragraph [0158]). The adapter-constructs generated in document D12 have a tendency to self-anneal which reduces genomic sequences required for generating a library. Since this tendency is reduced by using the adapters as defined in feature 1.4 of claim 1, the efficiency in generating a library representing the whole or substantially whole genome is increased.

24. In view thereof, the objective technical problem to be solved resides in the provision of a method with improved efficiency in generating a library of template polynucleotide molecules being representative of the whole genome or of substantially the whole genome. This problem, although worded differently, is in effect identical to that defined by the opposition division (decision under appeal, point 6.3.26). The method of claim 1 solves this problem.

25. The appellant has not defined a technical problem starting from document D12 as closest prior art. Since moreover, the technical problem as defined in the decision under appeal has not been contested, it can be assumed that the appellant agrees with it.

26. As regards obviousness, the appellant submitted that the skilled person in "*search for a solution to this problem*" would have turned to a document in the related art (statement of grounds of appeal, page 38, first paragraph), i.e. document D1. This document disclosed in paragraph [0097] in conjunction with Figure 5 advantages in using forked adapters, i.e. mismatched

adapters in generating a genomic library because they reduced "*intra molecular base-pairing of the adaptor-targets*", i.e. "*the same effect also sought by the opposed patent*" (statement of grounds of appeal, page 38, fifth to seventh paragraph).

27. It is established case law that in applying the could-would approach, the relevant issue is not whether the skilled person could have consulted a document (here: D1), but rather whether the skilled person would have done so in the expectation of solving the underlying technical problem or in the expectation of some improvement or advantage based on conclusive reasons (see Case Law, I.D.5).

27.1 As regards document D1, this document is not concerned with the generation of whole genome libraries or substantially whole genome libraries, but with libraries that have a reduced complexity/coverage (see paragraphs [0006], [0009], [0057]).

27.2 The respondent submitted that the method of claim 1 as solution to the problem identified above was not obvious because in light of document D12's teaching "*the skilled person looking to increase efficiency of a method that maintains complexity of a library would not look to D1, as D1 is concerned with a method of obtaining a library of reduced complexity*" (reply to appeal, page 19, eight paragraph). The board agrees to this.

27.3 Irrespective thereof, document D1 is silent on T/A cloning (see point 18.2 above). Since document D12 is likewise silent on T/A cloning (see point 23.2 above), the combined teaching of documents D12 and D1 cannot result in a method that falls within the scope of

present claim 1 either. Thus the subject-matter of claim 1 is not obvious over the combined teaching of documents D12 and D1.

Documents D9 and D2

28. The appellant submitted in the context of inventive step *inter alia* that the method of claim 1 was not inventive in light of document D2 combined with document D9 without providing any substantiation. Since the appellant merely referred to their previous submissions during the opposition proceedings, their opinion is that arguments put forward in opposition proceedings form automatically part of the appeal proceedings. This understanding is not correct.

28.1 The statement of grounds of appeal and the reply must contain a party's complete case (Article 12(3) RPBA). This is not fulfilled by a passing reference to the arguments put forward in opposition proceedings (see Case Law, V.A.2.6.3.f) and V.A.2.6.5). It is not for the board to identify the issues that may still be a matter of dispute among those raised in each and every submission in the previous proceedings, nor to identify the arguments as to why the impugned decision is incorrect. The parties are required to bring forward in their statement of grounds of appeal and in their reply their line(s) of argument and all the facts and evidence on which they rely in appeal proceedings.

28.2 Consequently, any arguments based on documents D2 combined with D9 for assessing inventive step of the method of claim 1 do not form part of the appeal proceedings.

Document D13 as closest prior art

29. In their submission dated 25 November 2021, the appellant submitted for the first time that document D13 was suitable as closest prior art too.

29.1 This line of arguments is new to the proceedings and hence represents an amendment of the appellant's case which may be admitted only at the discretion of the board (Article 13(1) RPBA).

29.2 Reasons have not been provided by the appellant why this line of argument has been submitted at this late stage of the proceedings only, although the contested subject-matter has not changed since the onset of the opposition proceedings.

29.3 As regards the use of document D13 as new closest prior art, the appellant referred in general to the duty of the EPO to examine facts of its own motion.

29.4 This understanding of the appellant is not correct. As set out in Article 12(2) RPBA, the primary object of appeal proceedings is to review the decision under appeal in a judicial manner. Accordingly a party's appeal case shall be directed to the requests, facts, objections, arguments and evidence on which the decision under appeal was based. Appeal proceedings are not a continuation of the opposition proceedings. Consequently, this new line of argument is not admitted into the appeal proceedings and any of the appellant's submissions based on document D13 under inventive step are disregarded (Article 13(1) RPBA).

30. The method of claim 1 and thus the claims as granted comply with the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

L. Malécot-Grob T. Sommerfeld

Decision electronically authenticated