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(54) Title: METHODS AND COMPOSITIONS FOR NUCLEIC ACID AMPLIFICATION

(57) Abstract: Compositions that are used in nucleic acid amplification in vitro are disclosed, which include a target specific uni-
versal (TSU) promoter primer or promoter provider oligonucleotide that includes a target specific (TS) sequence that hybridizes
specifically to a target sequence that is amplified and a universal (U) sequence that is introduced into the sequence that is amplified,
by using a primer for the universal sequence. Methods of nucleic acid amplification in vitro are disclosed that use one or more TSU
oligonucleotides to attached a U sequence to a target nucleic acid in a target capture step and then use a primer for a U sequence
in subsequent amplification steps performed in substantially isothermal conditions to make amplification products that contain a U
sequence that indicates the presence of the target nucleic acid in a sample.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US07/88473

A. CLASSIFICATION OF SUBJECT MATTER

IPC: C12P 19/34(2006.01)

USPC: 435/91.2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/91.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched EAST database

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	Becker et al. (US PG pub 2006/0046265 A1 published March 2, 2006)	1-2, and 12 ----- 9 and 11
Y	Langmore et al. (US patent 6,828,098 B2 issued December 7, 2004)	9 and 11

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents		"T"
"A"	document defining the general state of the art which is not considered to be of particular relevance	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier application or patent published on or after the international filing date	"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed	

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **Claims Nos.:**
because they relate to subject matter not required to be searched by this Authority, namely:

2. **Claims Nos.:**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. **Claims Nos.:**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-2, 9, 11-12 (group I claims that read upon species Ia)

- Remark on Protest**
- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-15, drawn to a composition (product).

Group II, claim(s) 16-23, drawn to a method (process).

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

1. Species of means of joining (claim 1 is generic)
 - a. Covalent linkage (claim 2)
 - b. Non covalent linkage (claim 5)
 - c. Direct joining via hybridization complex (claim 6)
 - d. Indirect joining via hybridization complex that includes S-oligonucleotide (claim 7)
2. Species of Covalent linkage (claim 2 is generic)
 - e. Linkage via a polynucleotide linker sequence (claim 3)
 - f. Linkage via a non-nucleotide abasic linker compound (claim 4)
3. Species of promoter primer (claim 1 is generic)
 - g. comprising a universal promoter primer made up a 5' promoter sequence and a 3' universal sequence that is the same as the universal sequence of the TSU promoter oligonucleotide. (claim 10)
 - h. comprising at least one universal promoter primer made up of a 5' promoter sequence and a 3' U1 sequence and at least one target specific primer (TSP) made up of a sequence that is complementary to a sequence contained in an RNA transcript made from a double stranded DNA that contains a cDNA sequence made from synthetic extension of the 3' end of the TSU promoter primer oligonucleotide (claim 15).
4. Species of methods of amplifying a target gene
 - i. Method comprising steps recited in claims 16-17
 - j. Method comprising steps recited in claims 18-19
 - k. Method comprising steps recited in claims 20-21
 - l. Method comprising steps recited in claims 22-23

If no additional fees are paid the search will be restricted to group I invention (claims 1-15) first recited in the claims. Within that group the search will be further restricted to the claims that read upon the first species recited.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Becker et al. (US PG Pub. 20060046265 A1 published March 2, 2006) teaches

a composition (see page 4 par. 0022 where reaction mixture—composition is taught) comprising:

a TSU promoter oligonucleotide that includes a 5' promoter sequence, an internal first universal sequence (U1), and a 3' first target specific sequence (TS1) that binds specifically to a target sequence contained in a target nucleic acid, wherein the TSU promoter oligonucleotide is a TSU promoter primer that has a 3' terminus that is capable of being extended by a polymerase, or is a TSU promoter provider oligonucleotide that has a blocked 3' terminus that is incapable of being extended by a polymerase (see page 25 example 1 par. 0185 where both kinds of promoter primers recited above are taught. In SEQ ID No 5, the 5' promoter sequence is underlined, the 3' first target specific sequence (TS1) is the last part of oligo and 10 nt inbetween the 5' and 3' end is the internal sequence that is equivalent, of the first universal sequence (U1) recited in instant claim),

a TSU non-promoter primer oligonucleotide made up of a 5' second universal sequence (U2) and a 3' second target specific sequence (TS2) which is different from the TS1 (see page 26 par. 0185 where priming oligonucleotide taught is nonpromoter primer. See page 4 par. 0018 where insertion sequence taught are universal sequence (U2) recited in instant claims), and

a means for directly or indirectly joining the TSU promoter oligonucleotide to the TSU non-promoter primer oligonucleotide, thereby forming a target specific universal (TSU) primer complex (see page 26 par 0185 where hybridization to target is taught as a means for joining the TSU promoter oligonucleotide to the TSU non-promoter primer oligonucleotide, thereby forming a target specific universal (TSU) primer complex).

Thus Becker et al. taught the composition of claim 1 to one of ordinary skill at the time of the invention. Hence composition of claim 1 was known to one of one of ordinary skill at the time of the invention. Hence the composition of group I invention does not share the same or corresponding special technical features as method of group II invention. Therefore unity is lacking.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: 1) The species of means of joining recited have different characteristics associated with them; 2) Species of Covalent linkage recited are mutually exclusive; 3) Species of promoter primer recited have different attributes; 4) the methods of target amplifications differ in the types of primers that are required for the amplification.