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(71) Applicant (for all designated States except US): NUGEN TECHNOLOGIES, INC. [US/US]; 821 Industrial Road, San Carlos, CA 94070 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): KURN, Nurith [IL/US]; 2876 Ramona Street, Palo Alto, CA 94306 (US).

(74) Agents: POLIZZI, Catherine, M. et al.; Morrison & Foerster LLP, 755 Page Mill Road, Palo Alto, CA 94304-1018 (US).

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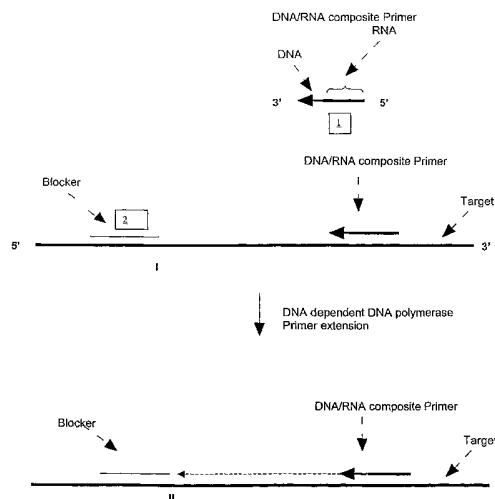
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[Continued on next page]

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



(57) Abstract: Methods for isothermal exponential amplification of a target polynucleotide are disclosed. The methods employ two transcription modules, the first module providing linear amplification resulting in RNA transcripts, and a second module providing for further (generally cyclical) amplification resulting in more RNA transcripts. In one aspect, the amplification for the first module is composite primer based. In a second aspect, the amplification of the first module is based on target switching to generate a primer extension product comprising a promoter sequence. In all aspects, the RNA transcripts of the first transcription module are subjected to further amplification by creating an intermediate product comprising a double stranded promoter region from which transcription can occur. The invention further provides compositions and kits for practicing said methods, as well as methods which use the amplification results.



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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/20660

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12Q1/68

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)

IPC 7 C12Q

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

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

EPO-Internal, BIOSIS, EMBASE, MEDLINE, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WANG ENA ET AL: "High-fidelity mRNA amplification for gene profiling" NATURE BIOTECHNOLOGY, NATURE PUBLISHING, US, vol. 18, April 2000 (2000-04), pages 457-459, XP002211679 ISSN: 1087-0156 abstract page 459, column 1, paragraph 2	17-30, 32, 33, 35, 37-40, 45-53, 56-60, 64, 65
X	US 5 744 308 A (CLEUZIAT PHILIPPE ET AL) 28 April 1998 (1998-04-28) abstract column 11, line 3 -column 13, line 4; figure 1 column 14, line 7 -column 63	54, 55, 57-63
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "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)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" 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
- "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
- "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.
- "&" document member of the same patent family

Date of the actual completion of the international search

4 March 2003

Date of mailing of the international search report

7 8. 03. 03

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Tilkorn, A-C

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 962 272 A (CHENCHIK ALEX ET AL) 5 October 1999 (1999-10-05) abstract column 6, line 6 -column 7, line 3 column 10, line 23 - line 40 column 9, line 66 -column 11, line 45; examples 1-4 ---	64, 65
A	US 5 824 517 A (CLEUZIAT PHILIPPE ET AL) 20 October 1998 (1998-10-20) abstract column 3, line 1 - line 22 column 6, line 28 -column 8, line 46; claims 1,13; example 4 ---	1-16,30, 31,33, 34,36, 38-55, 57-63
A	US 5 766 849 A (MCDONOUGH SHERROL H ET AL) 16 June 1998 (1998-06-16) abstract column 10, line 28 -column 12, line 20 column 9, line 56 -column 10, line 19; claims 1-53 ---	1-16,30, 31,33, 34,36, 38-55, 57-63
A	US 5 169 766 A (BERNINGER MARK S ET AL) 8 December 1992 (1992-12-08) column 5, line 30 -column 6, line 31; figure 1 column 7, line 4 -column 8, line 44; claims 1-13 ---	1-16,30, 31,33, 34,36, 38-55, 57-63
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A	ORITA M ET AL: "RAPID AND SENSITIVE DETECTION OF POINT MUTATIONS AND DNA POLYMORPHISMS USING THE POLYMERASE CHAIN REACTION" GENOMICS, ACADEMIC PRESS, SAN DIEGO, US, vol. 5, 1989, pages 874-879, XPO00606223 ISSN: 0888-7543 the whole document --- -/--	40

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Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	RAMSAY G: "DNA CHIPS: STATE-OF-THE ART" NATURE BIOTECHNOLOGY, NATURE PUBLISHING, US, vol. 16, 1998, pages 40-44, XP000198575 ISSN: 1087-0156 the whole document	45
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P, X	WO 00 70095 A (DADE BEHRING INC) 23 November 2000 (2000-11-23) abstract page 7, line 20 -page 9, line 10 page 19, line 5 -page 25, line 2; claims 1-51	17-30, 32, 33, 35, 37, 40, 56-60, 64, 65
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INTERNATIONAL SEARCH REPORT

national application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 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.: 66, 67
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:
see FURTHER INFORMATION sheet PCT/ISA/210

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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional 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 an additional fee, this Authority did not invite payment of any additional fee.

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.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-7,10-16, 31,34,36,41-44,54,55,61-63 (completely),
8,9,30,33,38-40,45-53,57-60 (partially)

Methods systems and kits that involve a composite primer comprising an RNA portion and a 3'DNA portion, a DNA-dependent DNA polymerase, an enzyme that cleaves RNA from an RNA/DNA hybrid, a propromoter polynucleotide an RNA-dependent DNA polymerase and an RNA polymerase.

2. Claims: 17-29,32,35,37,56,64,65 (completely),8,9,30,33,
38-40,45-53,57-60 (partially)

Methods, systems and kits involving a propromoter template switch oligonucleotide (TSO), an oligonucleotide, a DNA-dependent DNA polymerase, an RNA-dependent DNA polymerase, an enzyme that cleaves RNA from a RNA/DNA hybrid and an RNA polymerase.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 66,67

Claims 66 and 67 are so unclear that no meaningful search can be carried out (Art 6 PCT):

Claim 66 pertains to a method of determining a sequence, but the claim does not contain a technical feature that contributes to determine a sequence.

Similarly, claim 67 is directed to method of detecting the presence of a nucleic acid sequence in a sample, but the claim lacks technical features that are actually needed for the detection.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No

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