

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
29 April 2004 (29.04.2004)

PCT

(10) International Publication Number
WO 2004/035819 A3

- (51) International Patent Classification⁷: **C12Q 1/68**, C07H 21/00, C12N 15/11
- (74) Agent: INSPICOS A/S; Bøge Alle 3, P.O. Box 45, DK-2970 Hørsholm (DK).
- (21) International Application Number: PCT/DK2003/000715
- (22) International Filing Date: 21 October 2003 (21.10.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/420,278 21 October 2002 (21.10.2002) US
PA 2003 00752 19 May 2003 (19.05.2003) DK
- (71) Applicant (for all designated States except US): **EXIQON A/S** [DK/DK]; Bygstubben 9, DK-2950 Vedbaek (DK).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **KAUPPINEN, Sakari** [FI/DK]; Norskekrogen 12, DK-2765 Smørum (DK). **ALSBO, Carsten** [DK/DK]; Rasmussensvej 4, DK-4600 Køge (DK). **NIELSEN, Peter, Stein** [DK/DK]; Fyrrebakken 4, DK-3460 Birkerød (DK). **JEFFARES, Daniel, Charlton** [NZ/DK]; Borups Allé 13, 1. th., dk-2200 Copenhagen N (DK). **MOURIER, Tobias** [DK/DK]; Tibirkegade 4, 1. tv., DK-2200 Copenhagen N (DK). **MØRK, Søren** [DK/DK]; Fengersvej 3, DK-2500 Valby (DK). **ARCTANDER, Peter** [DK/DK]; Ympelhavevej 4, DK-4792 Askeby (DK). **TOMMERUP, Niels** [DK/DK]; Herstedøstervej 64 C, DK-2620 Albertslund (DK). **TOLSTRUP, Niels** [DK/DK]; Bellevuevej 7, 1. th., DK-2930 Klampenborg (DK). **VISSING, Henrik** [DK/DK]; Virumstræde 13A, DK-2830 Virum (DK).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, EG, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- (88) Date of publication of the international search report: 26 August 2004
- (15) Information about Correction:
Previous Correction:
see PCT Gazette No. 29/2004 of 15 July 2004, Section II
- 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.

(54) Title: OLIGONUCLEOTIDES USEFUL FOR DETECTING AND ANALYZING NUCLEIC ACIDS OF INTEREST

(57) Abstract: The invention features improved non-naturally occurring nucleic acids with higher melting temperature than control nucleic acid with 2' deoxynucleotides, and methods for expression profiling of mRNAs, identifying and profiling of particular mRNA splice variants, and detecting mutations, deletions, or duplications of particular exons or other splice variants, e.g., alterations associated with a disease such as cancer, in a nucleic acid sample, e.g., a biological sample or a patient sample.



WO 2004/035819 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 03/00715

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68 C07H21/00 C12N15/11

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 C07H C12N G01N

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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | WO 01 81632 A (BALABAN DAVID ;AFFYMETRIX INC (US)) 1 November 2001 (2001-11-01) page 33, line 14 - line 18 page 38, line 17 - line 19; claims --- -/-- | 1-156, 160-184 |

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

18 June 2004

Date of mailing of the international search report

19 JUL 2004

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

PATRICK ANDERSSON /ELY

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00715

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|---|---|
| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | WO 99 14226 A (WENGEL JESPER ;EXIQON A S (DK); NIELSEN POUL (DK)) 25 March 1999 (1999-03-25) | 1-112, 115-138, 141,142, 145,159, 166-179, 182-184 |
| Y | page 60, line 1 - line 9 page 65, line 9 - line 16 | 113,114, 139,140, 143,144, 148, 160-165, 180,181 |
| Y | --- WO 02 061387 A (JAKOBSEN MOGENS HASTEEN ;EXIQON AS (DK); KONGSBK LARS (DK)) 8 August 2002 (2002-08-08) | 113,114, 139,140, 143,144, 148, 160-165, 180,181 |
| A | --- DWAINE A. BRAASCH ET AL: "Locked nucleic acid (LNA): fine-tuning the recognition of DNA and RNA" CHEMISTRY & BIOLOGY, vol. 8, 2001, pages 1-7, XP002285000 the whole document | 1-184 |
| P,X | --- NIELS TOLSTRUP ET AL: "OligoDesign: optimal design of LNA (locked nucleic acid) oligonucleotide capture probes for gene expression profiling" NUCLEIC ACIDS RESEARCH, vol. 31, no. 13, 2003, pages 3758-3762, XP002285001 the whole document ----- | 1-184 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 03/00715

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.: **1-6, 16-17, 19-21**
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:

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

Continuation of Box I.2

Claims Nos.: 1-6,16-17,19-21

Present claims 1-6, 16-17 and dependent claims relate to a compounds defined either by these two parameters:

P1: having a melting temperature at least 3 degrees C higher than that of a corresponding control nucleic acid, or

P2: having a capture efficiency that is at least 10% greater than that of a corresponding control nucleic acid .

The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to any non-naturally occurring nucleic acid.

Moreover, claims 19-21 depending on claims 1-9 can be considered unclear since claims 1-9 relates to nucleic acids with two capture regions, whereas nucleic acids of claims 19-21 explicitly are limited to be capable of hybridizing to either only one intron or exon. The nucleic acids of claims 19-21 are interpreted as being capable of hybridizing to one exon and one intron region.

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

Information on patent family members

International Application No

PCT/DK 03/00715

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|----------------------------|---------------------|
| WO 0181632 | A | 01-11-2001 | AU 5723901 | A 07-11-2001 |
| | | | CA 2406402 | A1 01-11-2001 |
| | | | EP 1285089 | A1 26-02-2003 |
| | | | JP 2003530894 | T 21-10-2003 |
| | | | WO 0181632 | A1 01-11-2001 |
| ----- | | | | |
| WO 9914226 | A | 25-03-1999 | AU 9063398 | A 05-04-1999 |
| | | | CA 2303299 | A1 25-03-1999 |
| | | | CN 1279687 | T 10-01-2001 |
| | | | WO 9914226 | A2 25-03-1999 |
| | | | EP 1015469 | A2 05-07-2000 |
| | | | JP 2002521310 | T 16-07-2002 |
| | | | NZ 503765 | A 26-04-2002 |
| | | | US 2003134808 | A1 17-07-2003 |
| | | | US 2002068708 | A1 06-06-2002 |
| | | | US 2003144231 | A1 31-07-2003 |
| | | | US 6670461 | B1 30-12-2003 |
| ----- | | | | |
| WO 02061387 | A | 08-08-2002 | EP 1337826 | A2 27-08-2003 |
| | | | WO 02061387 | A2 08-08-2002 |
| | | | WO 02097398 | A2 05-12-2002 |
| | | | US 2002187485 | A1 12-12-2002 |
| | | | US 2003152927 | A1 14-08-2003 |
| ----- | | | | |