(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 February 2010 (11.02.2010)

PCT

(10) International Publication Number
WO 2010/017152 A3

(51) **International Patent Classification**:
A61K 31/7088 (2006.01) ***C07H 21/00*** (2006.01)

(21) **International Application Number**:
PCT/US2009/052624

(22) **International Filing Date**:
4 August 2009 (04.08.2009)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
61/086,017 4 August 2008 (04.08.2008) US

(71) **Applicant** *(for all designated States except US)*: **IDERA PHARMACEUTICALS, INC.** [US/US]; 167 Sidney Street, Cambridge, MA 02139 (US).

(72) **Inventors; and**

(75) **Inventors/Applicants** *(for US only)*: **KANDIMALLA, Ekambar** [US/US]; 3 Overlook Road, Hopkinton, Massachusetts 01748 (US). **PUTTA, Mallikarjuna** [IN/US]; 824 Arboretum Way, Burlington, MA 01803 (US). **BHAGAT, Lakshmi** [IN/US]; 1550 Worcester Street, Suite 605, Framingham, MA 01702 (US). **WANG, Daqing** [CN/US]; 7 Selfridge Road, Bedford, MA 01730 (US). **YU, Dong** [CN/US]; 25 Indian Pond Road, Westboro, MA 01581 (US). **AGRAWAL, Sudhir** [US/US]; 61 Lamplighter Drive, Shrewsbury, MA 01545 (US).

(74) **Agent**: **OSLICK, Sherri, L.**; McDonnell Boehnen Hulbert & Berghoff LLP, 300 South Wacker Drive, 32nd Floor, Chicago, Illinois 60606 (US).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) **Date of publication of the international search report**:
12 January 2012

WO 2010/017152 A3

(54) **Title**: MODULATION OF TOLL-LIKE RECEPTOR 8 EXPRESSION BY ANTISENSE OLIGONUCLEOTIDES

(57) **Abstract**: Antisense oligonucleotide compounds, compositions and methods are provided for down regulating the expression of TLR8. The compositions comprise antisense oligonucleotides targeted to nucleic acids encoding TLR8. The compositions may also comprise antisense oligonucleotides targeted to nucleic acids encoding TLR8 in combination with other therapeutic and/or prophylactic compounds and/or compositions. Methods of using these compounds and compositions for down-regulating TLR8 expression and for prevention or treatment of diseases wherein modulation of TLR8 expression would be beneficial are provided.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/52624

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/7088, C07H 21/00 (2011.01)
USPC - 514/44A
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)
USPC: 514/44A

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/44A; 536/24.5 (text search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic data bases: PubWEST (PGPB, USPT, EPAB, JPAB); Google Scholar, GenCore sequence search (NT)
Search terms: Toll-like receptor 8 (TLR8) RNAi, interference, antisense, siRNA, gene silencing, LNA, 2'-MOE, phosphorothioate, administer, disease, treat, prophylactic

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/085443 A2 (CHEN et al.) 15 September 2005 (15.09.2005). Especially para [0008], [00202], [00202].	1-18
A	WO 2008/048410 A2 (CASHMAN et al.) 24 April 2008 (24.04.2008). Especially SEQ ID NO: 6	1-18
A	US 2004/0053248A1 (TANG et al.) 18 March 2004 (08.03.2004) Especially SEQ ID NO: 133	1-18

☐ Further documents are listed in the continuation of Box C. ☐

* 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 application or patent 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	Date of mailing of the international search report
7 November 2011 (07.11.2011)	18 NOV 2011

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/52624

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.: 19-25
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:
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: Claims 1-18, drawn to a synthetic antisense oligonucleotide 20 to 50 nucleotides in length targeted to TLR8 mRNA, as well as compositions and methods related thereto, wherein the antisense oligonucleotide has a sequence comprising SEQ ID NO: 26.

Group II+: Claims 1-18, drawn to a synthetic antisense oligonucleotide 20 to 50 nucleotides in length targeted to TLR8 mRNA, as well as compositions and methods related thereto, wherein the antisense oligonucleotide has a sequence selected from any of SEQ ID NOs: 46, 53, 84, 85, 91, 102, 116, 131, 143, 146, 152, 157, 180, 182, 189 and 197. If Applicant elects to have this group searched, Applicant must specify the specific oligonucleotide sequence to be searched. Each unique oligonucleotide sequence constitutes an inventive concept.

----------continued on Extra 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 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.:
Claims 1-18 limited to SEQ ID NO: 26

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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/52624

Continuation of Box III (Lack of Unity of Invention):

Group III: Claims 26-27, drawn to a method for inhibiting TLR8 expression and activity in a mammal.

The inventions listed as Groups I - III 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:

The shared technical feature of the inventions listed as Groups I, II+ and III is an antisense oligonucleotide complementary to TLR8 mRNA. This shared technical feature fails to provide a contribution over the prior art, as evidenced by WO 2005/085443 A2 to Chen et al. (published September 15, 2005). Chen discloses a synthetic antisense oligonucleotide 20 to 50 nucleotides in length (para [0008] - "RNAi agents targeted to any of a variety of transcripts . . . the siRNA comprises two RNA strands having a region of complementarity approximately 19 nucleotides in length, but ranging in length between 17 and 29 nucleotides") targeted to TLR8 mRNA (para [0079] - "Tables 1-26 list sequences of preferred target portions of transcripts encoding . . . TLR8"; para [00202] - Table 21-TLR8 Target Portions and RNAi Agent Sense Strand Sequences - "HTLR8-2763: ACUGGGAUGUUUGGUUUAU (SEQ ID NO: 244)"). Further, the sequence of TLR8 mRNA (SEQ ID NO:223) was known in the art, as evidenced by WO 2008/048410 A2 to Cashman et al. (published Aoruk 24m 2008), which teaches the sequence for TLR8 (para [0098], SEQ ID NO: 6). In the absence of a contribution over the prior art, the shared technical feature is not a shared special technical feature. Without a shared special technical feature, the inventions lack unity with one another.

Additionally, the special technical feature of each of the inventions listed as Group I and II+ is the specific oligonucleotide sequence recited therein. Significant structural similarities cannot readily be ascertained among the unique oligonucleotide sequences. Without significant structural similarities, the polypeptides do not have a shared special technical feature. In the absence of a shared special technical feature, the inventions lack unity with one another.