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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))*

— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
26 April 2012

(54) Title: MODULATION OF NUCLEAR-RETAINED RNA

(57) Abstract: Provided herein are methods, compounds, and compositions for reducing expression of a nrRNA in an animal. Also provided herein are methods, compounds, and compositions for treating, ameliorating, delaying or reducing a symptom of a disease or disorder associated with a nuclear-retained RNA in an animal. Such methods, compounds, and compositions are useful to treat, prevent, delay, or ameliorate a disease or condition associated with a nuclear-retained RNA, or a symptom thereof.

WO 2012/012467 A3

INTERNATIONAL SEARCH REPORT

PCT/US2011/044583 01.03.2012

International application No.
PCT/US 11/44583

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12N 15/11, A61K 31/7088 (2012.01)
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

Electronic data base consulted during the international search (name of data base and; where practicable, search terms used)
PubWEST -- PGPB,USPT,USOC,EPAB,JPAB; Dialog Classic Files -- 654, 652, 349, 348, 35, 65, 155; USPTO Web Page; Google Scholar; Search terms -- nuclear RNA reduction, antisense uptake, modified antisense oligonucleotide, complementarity, RNase activation, nuclear-retained RNA, non-coding RNA, enrRNA, DMPK, myotonic dystrophy, DM1

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2010/0016215 A1 (MOULTON et al.) 21 January 2010 (21.01.2010) para [0025], [0026], [0028], [0033], [0055]-[0057], [0108], [0110], [0113], [0176], abstract	1-4, 6
Y	US 2010/0047289 A1 (FAKHARI et al.) 25 February 2010 (25.02.2010) para [0080], [0094]	1-4, 6

☐ 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
18 February 2012 (18.02.2012)	01 MAR 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

2011/044583 01.03.2012

International application No.
PCT/US 11/44583

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.: 5, 7-11, 18-48 and 57-69
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 1-4 and 6, directed to a method of achieving a pharmacologically relevant reduction of a nuclear-retained RNA in a cell or tissue having low antisense oligonucleotide uptake, comprising administering to an animal suspected of having said nuclear-retained RNA a chemically-modified antisense oligonucleotide complementary to said nuclear-retained RNA in an amount effective to activate a nuclear ribonuclease capable of cleaving the nuclear-retained RNA to achieve a pharmacologically relevant reduction.

- Please see extra sheet for continuation -

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.:
1-4 and 6

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.

Continuation of Box III: Lack of Unity of Invention

Group II: claims 12-17 and 49-53, directed to a method of treating, ameliorating, delaying or reducing a symptom of a disease or disorder associated with a nuclear-retained RNA in a tissue having a low antisense oligonucleotide uptake, comprising: a) selecting an animal having a disease or disorder associated with said nuclear-retained RNA in said tissue; and b) administering to said animal a chemically-modified antisense oligonucleotide complementary to said nuclear-retained RNA in an amount effective to activate a nuclear ribonuclease capable of cleaving the nuclear-retained RNA in said pharmacologically relevant amount, thereby treating, ameliorating, delaying or reducing a symptom of said disease or disorder.

Groups III+: claims 54-56, directed to a compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides having a nucleobase sequence comprising at least 12 contiguous nucleobases of any of the sequences of SEQ ID NOs: 92-110, 150-160, and 171-175; wherein the first invention is limited to SEQ ID NO: 92. (applicants may opt for additional sequences to be searched by specifying the SEQ ID NO: and paying an additional invention search fee for each elected sequence).

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 special technical feature of the Group I claims is a method of achieving a pharmacologically relevant reduction of a nuclear-retained RNA in a cell or tissue having low antisense oligonucleotide uptake, comprising administering to an animal suspected of having said nuclear-retained RNA a chemically-modified antisense oligonucleotide complementary to said nuclear-retained RNA in an amount effective to activate a nuclear ribonuclease capable of cleaving the nuclear-retained RNA to achieve a pharmacologically relevant reduction - not required by the claims of any other Group. The special technical feature of the Group II claims is a method of treating, ameliorating, delaying or reducing a symptom of a disease or disorder associated with a nuclear-retained RNA in a tissue having a low antisense oligonucleotide uptake, comprising: a) selecting an animal having a disease or disorder associated with said nuclear-retained RNA in said tissue; and b) administering to said animal a chemically-modified antisense oligonucleotide complementary to said nuclear-retained RNA in an amount effective to activate a nuclear ribonuclease capable of cleaving the nuclear-retained RNA in said pharmacologically relevant amount - not required by the claims of any other Group. The special technical feature of the Groups III+ claims is a compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein each subgroup is directed to a different specific sequence.

There is no common technical element shared by all of the above groups. Groups I and II share the common technical element of being related to providing a modified antisense oligonucleotide to a cell or tissue to achieve a pharmacologically relevant activation of a RNAse in the nucleus of the cells, wherein said nuclease affects a nuclear retained RNA. The claims of Groups III+ share a common technical element of being related to a compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides. These common technical elements do not represent an improvement over the prior art of US 2010/0016215 A1 to Moulton et al., which discloses an antisense compound for use in treating myotonic dystrophy (DM1 or DM2), enhancing antisense targeting to heart and quadricep muscles by conjugating a cell-penetrating peptide to the oligonucleotide (abstract). DM is characterized by expanded repeats in the untranslated regions of the mRNA, which form secondary and higher order structures, accumulate in the nucleus and form foci (para [0026]). The effective compound is a phosphorodiamidate oligonucleotide (PMO) (para [0029]); further wherein the PMO suffers from low delivery efficiency, and the cell-penetrating peptide improves uptake and restores normal levels of dystrophin (a pharmacologically relevant reduction) (para [0176]). Although Moulton does not explicitly recite wherein the antisense is effective to activate a nuclear RNAse, Moulton discloses wherein "the antisense oligonucleotide is complementary to at least 8, typically 9-12 or more, e.g., 15-30 contiguous bases in polyCUG repeats or polyCCUG repeats within the 3' UTR regions of the transcript for dystrophia myotonica protein kinase (DMPK) in muscle cells, and is designed to bind by hybridization to these repeats, blocking binding of splice-associated proteins" (para [0055]). It would have been obvious to a person skilled in the art that enabling splicing of the transcript would have involved an increase in the effective funtion of RNA splicing proteins, which were known to those of skill in the art to include RNAse activity in order to create the splice site. Moulton further teaches modified oligonucleotides having 12-30 nucleobases (para [0054], [0055]). Therefore, the inventions of Groups I - III+ lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.