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Published:

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— *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))*

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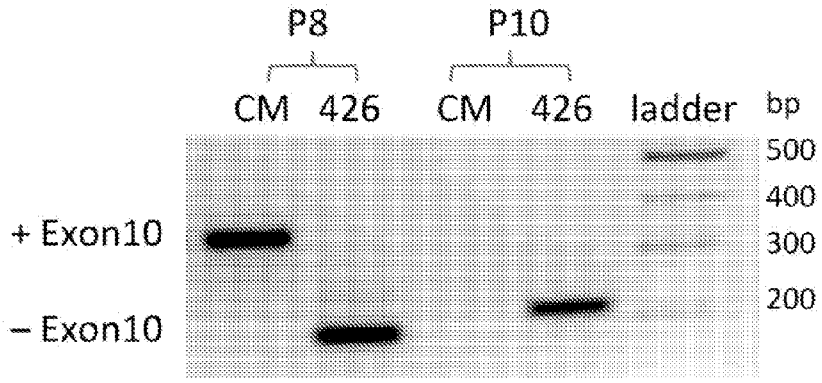

Figure 1

(57) Abstract: Described are compounds and methods useful for the treatment and investigation of diseases and disorders associated with expanded repeat-containing RNA molecules. In certain embodiments, compounds and methods useful for the modulation of ATXN-3 pre-mRNA are described. In certain embodiments, compounds and methods useful for the modulation of ATN-1 mRNA are described.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/049197

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 471/04 (2015.01)
CPC - C07D 471/04 (2014.11)
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(8) - A61K 31/675; C07D 471/04, 473/34 (2015.01)
CPC - C07D 471/04, 473/34; C07H 19/06 (2014.11) (keyword delimited)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 536/18.7, 22.1, 23.1 (keyword delimited)

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

Orbit, Google Patents, STN, Google Scholar, Google, PubChem.
Search terms used: oligonuleotide, repeat containing, single strained, target rna, isis pharmaceutical

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/033223 A1 (ISIS PHARMACEUTICALS INC et al) 07 March 2013 (07.03.2013) entire document	1-5
A	WO 2013/096679 A1 (ALIOS BIOPHARMA INC) 27 June 2013 (27.06.2013) entire document	1-5
A	US 2009/0253583 A1 (YOGANATHAN) 08 October 2009 (08.10.2009) entire document	1-5
A	US 2013/0059902 A1 (ISIS PHARMACEUTICALS INC) 07 March 2013 (07.03.2013) entire document	1-5

☐ 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
05 January 2015	04 FEB 2015
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: Blaine R. Copenheaver 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/US2014/049197

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.: 6-165, 168, 169
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:
Claims 1-5 have been analyzed subject to the restriction that the claims read on the Formula I as described in the Lack of Unity of Invention (See Extra Sheet). The claims are restricted to a compound comprising a single-stranded oligonucleotide consisting of 13 to 30 linked nucleosides and having a nucleobase sequence complementary to a repeat region of an expanded repeat-containing target RNA, wherein the 5' -terminal nucleoside of the single-stranded oligonucleotide comprises a phosphate moiety and an internucleoside linking group linking the 5' -terminal nucleoside to the remainder of the oligonucleotide wherein the 5'-terminal nucleoside of the single-stranded oligonucleotide has Formula I: wherein T1 is a phosphorous moiety; T2 is an internucleoside linking group linking the 5'-terminal nucleoside of Formula I to the remainder of the oligonucleotide; A has a formula of the first shown structure of the instant invention; Q1 and Q2 are each independently selected from H; M3 is O; BX2 is not present, then Bx1 is a nucleobase, where the nucleobase is uracil; each of J4, J5, J6, J7 is independently H; and G is H.

See 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.:
1-5

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/US2014/049197

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 need to be paid.

Group I+: claims 1-5 are drawn to a compound comprising a single-stranded oligonucleotide.

Group II: claims 166 and 167 are drawn to methods modulating splicing of a ATXN-3 or mutant ATXN-3 pre-mRNA.

The first invention of Group I+ is restricted to a compound comprising a single-stranded oligonucleotide consisting of 13 to 30 linked nucleosides and having a nucleobase sequence complementary to a repeat region of an expanded repeat-containing target RNA, wherein the 5' -terminal nucleoside of the single-stranded oligonucleotide comprises a phosphate moiety and an internucleoside linking group linking the 5' -terminal nucleoside to the remainder of the oligonucleotide wherein the 5'-terminal nucleoside of the single-stranded oligonucleotide has Formula I: wherein T1 is a phosphorous moiety; T2 is an internucleoside linking group linking the 5'-terminal nucleoside of Formula I to the remainder of the oligonucleotide; A has a formula of the first shown structure of the instant invention; Q1 and Q2 are each independently selected from H; M3 is O; BX2 is not present, then Bx1 is a nucleobase, where the nucleobase is uracil; each of J4, J5, J6, J7 is independently H; and G is H. It is believed that claims 1-5 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. An exemplary election would be a compound comprising a single-stranded oligonucleotide consisting of 13 to 30 linked nucleosides and having a nucleobase sequence complementary to a repeat region of an expanded repeat-containing target RNA, wherein the 5' -terminal nucleoside of the single-stranded oligonucleotide comprises a phosphate moiety and an internucleoside linking group linking the 5' -terminal nucleoside to the remainder of the oligonucleotide wherein the 5'-terminal nucleoside of the single-stranded oligonucleotide has Formula I: wherein T1 is a phosphorous moiety; T2 is an internucleoside linking group linking the 5'-terminal nucleoside of Formula I to the remainder of the oligonucleotide; A has a formula selected from the second shown structure of the instant invention; Q1 and Q2 are each independently selected from H; M3 is O; BX2 is not present, then Bx1 is a nucleobase, where the nucleobase is uracil; each of J4, J5, J6, J7 is independently H; and G is H. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in 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:

The special technical features of Group I+, a compound comprising a single-stranded oligonucleotide consisting of 13 to 30 linked nucleosides and having a nucleobase sequence complementary to a repeat region of an expanded repeat-containing target RNA, wherein the 5' -terminal nucleoside of the single-stranded oligonucleotide comprises a phosphate moiety and an internucleoside linking group linking the 5' -terminal nucleoside to the remainder of the oligonucleotide, are not present in Group II; and the special technical features of Group II, methods modulating splicing of a ATXN-3 or mutant ATXN-3 pre-mRNA, are not present in Group I+.

The Groups I+ formulae do not share a significant structural element, requiring the selection of alternatives for the compound variables T1, T2, A, M3, Bx1, J4, J5, J6, J7, and G.

The Groups I+ and II share the technical features of a compound comprising a single-stranded oligonucleotide consisting of 13 to 30 linked nucleosides and having a nucleobase sequence complementary to a repeat region of an expanded repeat-containing target RNA, wherein the 5' -terminal nucleoside of the single-stranded oligonucleotide comprises a phosphate moiety and an internucleoside linking group linking the 5' -terminal nucleoside to the remainder of the oligonucleotide. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2009/0253583 A1 to Yoganathan teaches a compound comprising a single-stranded oligonucleotide consisting of 13 to 30 linked nucleosides and having a nucleobase sequence complementary to a repeat region of an expanded repeat-containing target RNA, wherein the 5' -terminal nucleoside of the single-stranded oligonucleotide comprises a phosphate moiety and an internucleoside linking group linking the 5' -terminal nucleoside to the remainder of the oligonucleotide (Para. [0046], The polynucleotides may be single- or double-stranded...covalent internucleoside (backbone) linkages...; Para. [0053], the polynucleotide sequence is identical to all or a portion of the complementary strand of a reference polynucleotide sequence.; Para. [0171], Other testing methods can include additional steps, such as reverse transcription, RT-PCR and/or PCR (including multiplex PCR); Para. [0176], ...the probes incorporated into the array are 30-mers; Paras. [0086]-[0087]).

Additionally, WO 2013/096679 A1 to Beigelman et al. teach a compound having the core structure of Formula I comprising a oligonucleotide (Para. [0065], Additionally, a nucleoside can be incorporated into larger DNA and/or RNA polymers and oligomers) wherein the 5'-terminal nucleoside has Formula I: wherein T1 is a phosphorus moiety; A is the first shown structure of the instant invention; Q1 and Q2 are each independently H; M3 is O; BX1 is a nucleobase; J4 is substituted C1-C6 alkyl; J5 is H; J6 is H; J7 is halogen; and G is H (Para. [0170]; Further examples of a compound of Formula (III) include, but are not limited to the following:...see first shown structure...).

The inventions listed in Groups I+ and II therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.