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C07H 21/04 (2006.01)
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- (81) **Designated States (unless otherwise indicated, for every kind of national protection available):** AE, AG, AL, AM,

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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:**
12 July 2012



WO 2012/068405 A3

(54) **Title:** MODULATION OF ALPHA SYNUCLEIN EXPRESSION

(57) **Abstract:** Disclosed herein are antisense compounds and methods for decreasing alpha-synuclein mRNA and protein expression. Also disclosed herein are methods for treating, preventing, and ameliorating neurodegenerative diseases in an individual in need thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 11/61245

A. CLASSIFICATION OF SUBJECT MATTER
 IPC(8) - C12Q 1/68; C07H 21/04, A61K 48/00 (2012.01)
 USPC - 435/6.16, 536/24.5, 514/44R

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): C12Q 1/68; C07H 21/04, A61K 48/00 (2012.01)
 USPC: 435/6.16, 536/24.5, 514/44R

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
 USPC: 435/6.1, 536/23.1

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

PubWEST;PGPB, USPT, EPAB, JPAB, SureChem, GoogleScholar, Dialog
 alpha-synuclein mRNA, SNCA, a-SYN, 2'-O-methoxyethyl, 2'-MOE, single-stranded, phosphorothioate internucleoside linkage, modified bicyclic sugar, CH(CH3)-O-2' bridge, tetrahydropyran, 5-methylcytosine, neurodegenerative disease, motor coordination, olfaction, spati

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- Y	US 2008/0003570 A1 (ROGERS et al.) Abstract, SEQ ID NO: 21, para[0005], para[0011], para[0012], para[0031], para[0035], para[0036], para[0037], para[0038], para[0073], para[0067], para[0068], para[0074], para[0103], para[0128], para[0134]	1 and 16-21 ----- 2-15
Y	US 2005/0064548 A1 (LINDQUIST et al.) 24 March 2005 (24.03.2005) para[0089], para[0090], para[0096]	2-15
Y	US 2007/0225209 A1 (ROCH et al.) 27 September 2007 (27.09.2007) par[0113], para[0400]	8, 11
Y	US 6,833,361 B2 (HONG et al) 21 December 2004 (21.12.2004) col 2, ln 25-55, col 2, ln 60-67	7, 8
Y	US 2009/0092981 A1 (SWAYZE et al.) 9 April 2009 (09.04.2009) para[0003], para[0060]-para[0062], para[0358]	9, 10
Y	US 2010/0204306 A1 (TAN) 12 August 2010 (12.08.2010) Abstract, para[0008], para[0116]	12, 13
Y	US 7,750,141 B2 (CROOKE et al.) 6 July 2010 (06.07.2010) claim 11	14, 15
Y	US 5,102,785 A (LIVAK et al.) 7 April 1992 (07.04.1992) col 10, ln 5-10, col 13, ln 10-35	14, 15

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

1 May 2012 (01.05.2012)

Date of mailing of the international search report

18 MAY 2012

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 11/61245

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.:
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 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.

-----SEE SUPPLEMENTAL 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 1-21 restricted to SEQ ID NO: 11

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
Information on patent family members

International application No.

PCT/US 11/61245

-----SUPPLEMENTAL SHEET-----

This application contains the following inventions or groups of inventions which are not so linked 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 1-21 are directed to a modified oligonucleotide consisting of 12 to 30 linked nucleosides having a nucleobase sequence comprising at least 12 contiguous nucleobases of a nucleobase sequence selected from among the nucleobase sequences recited in SEQ ID NOs: 11 to 88 and 98 to 136.

Group II claims 22-24 are directed to a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising a portion of at least 8 contiguous nucleobases complementary to an equal length portion of nucleobases 404 to 463 of SEQ ID NO: 1; and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 1.

The inventions listed as Groups I+ and II do not relate to a single inventive concept under Rule 13.1 because under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special shared technical feature of the groups is a modified oligonucleotide consisting at least 8 contiguous nucleobases. However, this is not an improvement over the prior art of US 2008/0003570 A1 to Rogers et al. (hereinafter Rogers) that teaches a modified oligonucleotide (para [0035], [0037], [0038]) consisting of 12 to 30 linked nucleosides having a nucleobase sequence comprising at least 12 contiguous nucleobases of SEQ ID NO: 11 (SEQ ID NO: 21 at 100% homology, para [0011], [0012]). The different nucleotide sequences represented by SEQ ID Nos: 11 to 88, 98 to 136 and SEQ ID NO: 1 are different structures that are not common to one another but are different because they are composed of unique nucleic acid sequences. Therefore the inventions listed as Groups I+ and II do not relate to a single general inventive concept under PCT Rule 13.1 because they do not share a same or corresponding special technical feature. This ISA will establish the ISR for the first group mentioned, specifically, Group I claims 1-21 restricted to SEQ ID NO: 11 without payment of additional fees. In order for all inventions to be examined in Group I+ or Group II, applicants must designate with specificity the particular sequence(s) to be searched and the appropriate examination fees must be paid for each additional sequence.