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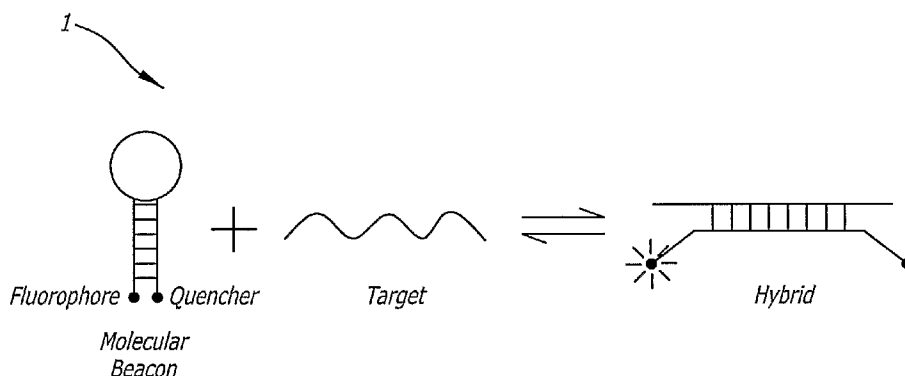
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(88) Date of publication of the international search report:  
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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: METHODS AND SEQUENCES TO PREFERENTIALLY SUPPRESS EXPRESSION OF MUTATED HUNTINGTIN



(57) Abstract: Disclosed herein are methods and sequences to preferentially suppress the expression of the mutated huntingtin ("htt") protein over expression of the normal htt protein. Also disclosed are methods comprising screening an individual for the heterozygous presence of one or more single nucleotide polymorphisms within the individual's Huntington's genes; administering nucleic acid molecules comprising nucleotide sequences that preferentially suppress the expression of amino acid sequences encoding for mutated huntingtin ("htt") over suppressing the expression of amino acid sequences encoding for normal htt by targeting an area of a Huntington's disease gene that is heterozygous for the presence of one or more single nucleotide polymorphisms.

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# INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2006/025638

## A. CLASSIFICATION OF SUBJECT MATTER

INV. 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)

C12N

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, CHEM ABS Data, WPI Data, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                        | Relevant to claim No. |
|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X         | <p>WO 2005/027980 A (UNIV MASSACHUSETTS [US]; ARONIN NEIL [US]; ZAMORE PHILLIP D [US])<br/>31 March 2005 (2005-03-31)<br/>abstract<br/>page 2, line 16 - page 3, line 31<br/>page 35 - page 37; example II<br/>page 37; example III</p> <p style="text-align: center;">-----<br/>-/--</p> | 1-21                  |

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

☒ See patent family 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

9 March 2007

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## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2006/025638

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                       | Relevant to claim No. |
|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A         | MILLER V M ET AL: "Allele-specific silencing of dominant disease genes"<br>PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE, WASHINGTON, DC, US,<br>vol. 100, no. 12,<br>10 June 2003 (2003-06-10), pages<br>7195-7200, XP002278730<br>ISSN: 0027-8424<br>abstract<br>page 7197, column 1, paragraphs<br>ALLELE-SPECIFIC,SILENCING... | 1-21                  |
| A         | LIU W ET AL: "Specific inhibition of Huntington's disease gene expression by siRNAs in cultures cells"<br>PROCEEDINGS OF THE JAPAN ACADEMY. SERIES B, PHYSICAL AND BIOLOGICAL SCIENCES, TOKYO, JP,<br>vol. 79B, no. 10, December 2003 (2003-12),<br>pages 293-298, XP002983007<br>ISSN: 0386-2208<br>the whole document                                                  | 1-21                  |
| A         | WO 2004/047872 A2 (MEDTRONIC INC [US])<br>10 June 2004 (2004-06-10)<br>abstract<br>pages 6,FF.                                                                                                                                                                                                                                                                           | 1-21                  |
| X,P       | WO 2005/078096 A2 (UNIV MASSACHUSETTS [US]; ZAMORE PHILLIP D [US]; ARONIN NEIL [US]; BROD) 25 August 2005 (2005-08-25)<br>abstract<br>figure 4A<br>page 23, line 21 - line 28                                                                                                                                                                                            | 1-21                  |
| X         | LI SHI-HUA ET AL: "Interaction of Huntington disease protein with transcriptional activator Sp1."<br>MOLECULAR AND CELLULAR BIOLOGY MAR 2002,<br>vol. 22, no. 5, March 2002 (2002-03),<br>pages 1277-1287, XP002421817<br>ISSN: 0270-7306<br>abstract<br>page 1278, column 1, paragraph                                                                                  | 9-14                  |

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2006/025638

### Box 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:  
  
Although claims 1-6 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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 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:

see additional 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 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.:

1-21 (partly)

#### 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**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

**Invention 1 (claims 1-21(partly))**

A method comprising administration to an individual nucleic acid molecules comprising nucleotide sequence that preferentially suppresses the expression of amino acid sequences encoding for mutant huntingtin over normal one by targeting an are of a Huntington's disease gene that is heterozygous for the persence of one or more single nucleotide polymorphisms wherein said individual has been screened for the heterozygous presence of one or more SNPs within said gene.

A nucleic acid molecule comprising a nucleotide sequence that preferentially suppresses the expression of amino acid sequences encoding for mutant huntingtin over normal one.

An expression cassette comprising a nucleotide sequence wherein said sequence is a human sequences.

A kit for screening individuals for the heterozygous presence of one or more single nucleotide polymorphisms within said Huntington's gene.

Wherein each of the above subject matters is characterised by SEQ ID NOs: 1.

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**Inventions 2-135 (claims 1-21(partly))**

A method comprising administration to an individual nucleic acid molecules comprising nucleotide sequence that preferentially suppresses the expression of amino acid sequences encoding for mutant huntingtin over normal one by targeting an are of a Huntington's disease gene that is heterozygous for the persence of one or more single nucleotide polymorphisms wherein said individual has been screened for the heterozygous presence of one or more SNPs within said gene.

A nucleic acid molecule comprising a nucleotide sequence that preferentially suppresses the expression of amino acid sequences encoding for mutant huntingtin over normal one.

An expression cassette comprising a nucleotide sequence wherein said sequence is a human sequences.

A kit for screening individuals for the heterozygous presence of one or more single nucleotide polymorphisms within said Huntington's gene.

Wherein each of the above subject matters is characterised by SEQ ID NOs: 2-135, respectively.

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**Inventions 136, 137 (claims 1,4,15,17,20,21(partly))**

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

A method comprising administration to an individual nucleic acid molecules comprising nucleotide sequence that preferentially suppresses the expression of amino acid sequences encoding for mutant huntingtin over normal one by targeting an are of a Huntington's disease gene that is heterozygous for the persence of one or more single nucleotide polymorphisms wherein said individual has been screened for the heterozygous presence of one or more SNPs within said gene.

A kit for screening individuals for the heterozygous presence of one or more single nucleotide polymorphisms within said Huntington's gene.

Wherein each of the above subject matters is characterised by SEQ ID NOs: 136 and 137, respectively.

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2006/025638

| Patent document<br>cited in search report |    | Publication<br>date | Patent family<br>member(s)                                                                | Publication<br>date                                                |
|-------------------------------------------|----|---------------------|-------------------------------------------------------------------------------------------|--------------------------------------------------------------------|
| WO 2005027980                             | A  | 31-03-2005          | CA 2579638 A1<br>EP 1670518 A1                                                            | 31-03-2005<br>21-06-2006                                           |
| WO 2004047872                             | A2 | 10-06-2004          | AU 2003293035 A1<br>CA 2507606 A1<br>EP 1569662 A2<br>JP 2006515864 T<br>US 2004162255 A1 | 18-06-2004<br>10-06-2004<br>07-09-2005<br>08-06-2006<br>19-08-2004 |
| WO 2005078096                             | A2 | 25-08-2005          | NONE                                                                                      |                                                                    |