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- with sequence listing part of description (Rule 5.2(a))

(88) Date of publication of the international search report:

18 November 2021 (18.11.2021)

(54) Title: ANTISENSE SEQUENCES FOR TREATING AMYOTROPHIC LATERAL SCLEROSIS

(57) Abstract: The present invention relates to antisense sequences, nucleic acid constructs and vectors comprising said antisense sequences, and their use for treating a C9orf72 hexanucleotide repeat expansion associated disease such as amyotrophic lateral sclerosis or frontotemporal dementia.



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INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. C12N15/113 A61K31/7088
ADD. A61P21/00

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 A61K

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)

EPO-Internal, BIOSIS, COMPENDEX, EMBASE, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/167780 A1 (IONIS PHARMACEUTICALS INC [US]) 20 October 2016 (2016-10-20) page 61 - page 66; example 4; table 3; sequences 73-75 -----	1-10, 12-17
X	GIULIETTA RIBOLDI ET AL: "Antisense Oligonucleotide Therapy for the Treatment of C9ORF72 ALS/FTD Diseases", MOLECULAR NEUROBIOLOGY, vol. 50, no. 3, 1 December 2014 (2014-12-01), pages 721-732, XP055508816, US ISSN: 0893-7648, DOI: 10.1007/s12035-014-8724-7 page 726 - page 727 ----- -/-	1,4-10, 12-17



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 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

6 October 2021

Date of mailing of the international search report

18/10/2021

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	MIS MARIA SARA ET AL: "Development of Therapeutics for C9ORF72 ALS/FTD-Related Disorders", MOLECULAR NEUROBIOLOGY, HUMANA PRESS, US, vol. 54, no. 6, 28 June 2016 (2016-06-28), pages 4466-4476, XP036276831, ISSN: 0893-7648, DOI: 10.1007/S12035-016-9993-0 [retrieved on 2016-06-28] page 4468 -----	1,4-10, 12-17
X	JIANG JIE ET AL: "Gain of Toxicity from ALS/FTD-Linked Repeat Expansions inC9ORF72Is Alleviated by Antisense Oligonucleotides Targeting GGGGCC-Containing RNAs", NEURON, CELL PRESS, US, vol. 90, no. 3, 21 April 2016 (2016-04-21), pages 535-550, XP029531466, ISSN: 0896-6273, DOI: 10.1016/J.NEURON.2016.04.006 page 1124 -----	1,4-10, 12-17
A	CAPPELLA M ET AL: "AAV-mediated expression of antisense oligonucleotides for the treatment of C9orf72-ALS", RVSV(M DELTA 51)-M3 IS AN EFFECTIVE AND SAFE ONCOLYTIC VIRUS FOR CANCER THERAPY; 27TH ANNUAL CONGRESS OF THE EUROPEAN SOCIETY OF GENE AND CELL THERAPY BRITISH SOCIETY FOR GENE THERAPY, ESGCT 2019 20191022 TO 20191025 BARCELONA,, vol. 30, no. 11, 1 November 2019 (2019-11-01), page A98, XP009522981, ISSN: 1557-7422, DOI: 10.1089/HUM.2019.29095.ABSTRACTS -----	1-17
X	WO 2019/032607 A1 (WAVE LIFE SCIENCES LTD [SG]; DODART JEAN COSME [US] ET AL.) 14 February 2019 (2019-02-14) page 396, paragraph 551 - paragraph 768 -----	4-7,9, 10,12-17
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/059313

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHRISTOPHER J. DONNELLY ET AL: "RNA Toxicity from the ALS/FTD C9ORF72 Expansion Is Mitigated by Antisense Intervention", NEURON, vol. 80, no. 2, 1 October 2013 (2013-10-01), pages 415-428, XP055649589, US ISSN: 0896-6273, DOI: 10.1016/j.neuron.2013.10.015 -----	1-17
A	Christopher J. Donnelly ET AL: "RNA Toxicity from the ALS/FTD C9ORF72 Expansion Is Mitigated by Antisense Intervention. Supplemental Information", Neuron, 16 October 2013 (2013-10-16), XP055508871, Retrieved from the Internet: URL:https://ars.els-cdn.com/content/image/1-s2.0-S0896627313009185-mmcl.pdf [retrieved on 2018-09-21] -----	1-17
A	C. LAGIER-TOURENNE ET AL: "Targeted degradation of sense and antisense C9orf72 RNA foci as therapy for ALS and frontotemporal degeneration", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (PNAS), vol. 110, no. 47, 19 November 2013 (2013-11-19), pages E4530-E4539, XP055228419, US ISSN: 0027-8424, DOI: 10.1073/pnas.1318835110 -----	1-17
X	WO 2015/057727 A1 (ISIS PHARMACEUTICALS INC [US]) 23 April 2015 (2015-04-23) page 54 - page 55; example 1; table 6; sequences 22,40-42,44,58-61 -----	1-17
X	WO 2015/054676 A2 (ISIS PHARMACEUTICALS INC [US]) 16 April 2015 (2015-04-16) SEQ ID NO:21,26-31,33-39,47,60,67-69,75,81; page 77 - pages 78,81; tables 6-8,16,20,23,25,26,27,28,39; sequences 123-124,138-146,170-190,715-737,754-776,908-931 -----	1-17
X	WO 2014/062736 A1 (ISIS PHARMACEUTICALS INC [US]; UNIV JOHNS HOPKINS [US]) 24 April 2014 (2014-04-24) page 85; claim 99; figure 5; example 7; table 20; sequence 22 -----	1-17
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International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/024205 A1 (PFIZER [US]) 18 February 2016 (2016-02-18) page 65, paragraph 79 - page 66; claim 2; table 4; sequences 62-65, 79-80, 123-125, 189-193 -----	1-17
X	WO 2016/112132 A1 (IONIS PHARMACEUTICALS INC [US]) 14 July 2016 (2016-07-14) page 65 - page 78; compounds 68257-687260, 730401, 730407-730408; sequences 46-49, 85, 91-93 -----	4-10, 12-17
X	WO 2018/064600 A1 (REGENERON PHARMA [US]) 5 April 2018 (2018-04-05) claim 43; sequence 45 -----	4-7
X	WO 2019/094694 A1 (UNIV MASSACHUSETTS [US]) 16 May 2019 (2019-05-16) figure 4; sequence 185 -----	4-7

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Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
- a. ☒ forming part of the international application as filed:
- ☒ in the form of an Annex C/ST.25 text file.
- ☐ on paper or in the form of an image file.
- b. ☐ furnished together with the international application under PCT Rule 13~~ter~~.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
- c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
- ☐ in the form of an Annex C/ST.25 text file (Rule 13~~ter~~.1(a)).
- ☐ on paper or in the form of an image file (Rule 13~~ter~~.1(b) and Administrative Instructions, Section 713).
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

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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:

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 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.:

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-4, 11(completely); 8-10, 12-17(partially)

Antisense nucleic acid molecule targeting a C90RF72 transcript, wherein the antisense nucleic acid molecule is able to reduce the level of sense C90RF72 RNA foci and antisense C90RF72 RNA foci; uses and products derived therefrom.

1.1. claims: 1-3, 8-10, 12-17(all partially)

Antisense nucleic acid molecule targeting a C90RF72 transcript and comprising SEQ ID NO:1;

1.2. claims: 1-3, 8-10, 12-17(all partially)

Antisense nucleic acid molecule targeting a C90RF72 transcript and comprising SEQ ID NO:2;

1.3. claims: 1-3, 8-10, 12-17(all partially)

Antisense nucleic acid molecule targeting a C90RF72 transcript and comprising SEQ ID NO:4;

1.4. claims: 1-3, 8-17(all partially)

Antisense nucleic acid molecule targeting a C90RF72 transcript and comprising SEQ ID NO:6;

1.5. claims: 4(completely); 8-17(partially)

Antisense nucleic acid molecule targeting a C90RF72 transcript and comprising SEQ ID NO:3;

2. claims: 5(completely); 8-10, 12-17(partially)

Antisense nucleic acid molecule targeting a C90RF72 transcript and comprising SEQ ID NO:5; uses and products derived therefrom.

3. claims: 6(completely); 9, 10, 12-17(partially)

Antisense nucleic acid molecule targeting a C90RF72 transcript and comprising SEQ ID NO:21; uses and products derived therefrom.

4. claims: 7(completely); 9, 10, 12-17(partially)

Antisense nucleic acid molecule targeting a C90RF72 transcript and comprising SEQ ID NO:22; uses and products

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

derived therefrom.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2021/059313

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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