(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 December 2024 (12.12.2024)

WIPO | PCT

(10) International Publication Number
WO 2024/254092 A3

(51) International Patent Classification:
C12N 15/113 (2010.01) *C07K 14/47* (2006.01)

(21) International Application Number:
PCT/US2024/032449

(22) International Filing Date:
04 June 2024 (04.06.2024)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/471,030 05 June 2023 (05.06.2023) US

(71) Applicant: **TRUSTEES OF TUFTS COLLEGE** [US/US]; Tufts University, Ballou Hall, Medford, MA 02155 (US).

(72) Inventors: **OUDIN, Madeleine**; c/o Trustees of Tufts College, Tufts University, Ballou Hall, Medford, MA 02155 (US). **DAME, Haley**; c/o Trustees of Tufts College, Tufts University, Ballou Hall, Medford, MA 02155 (US).

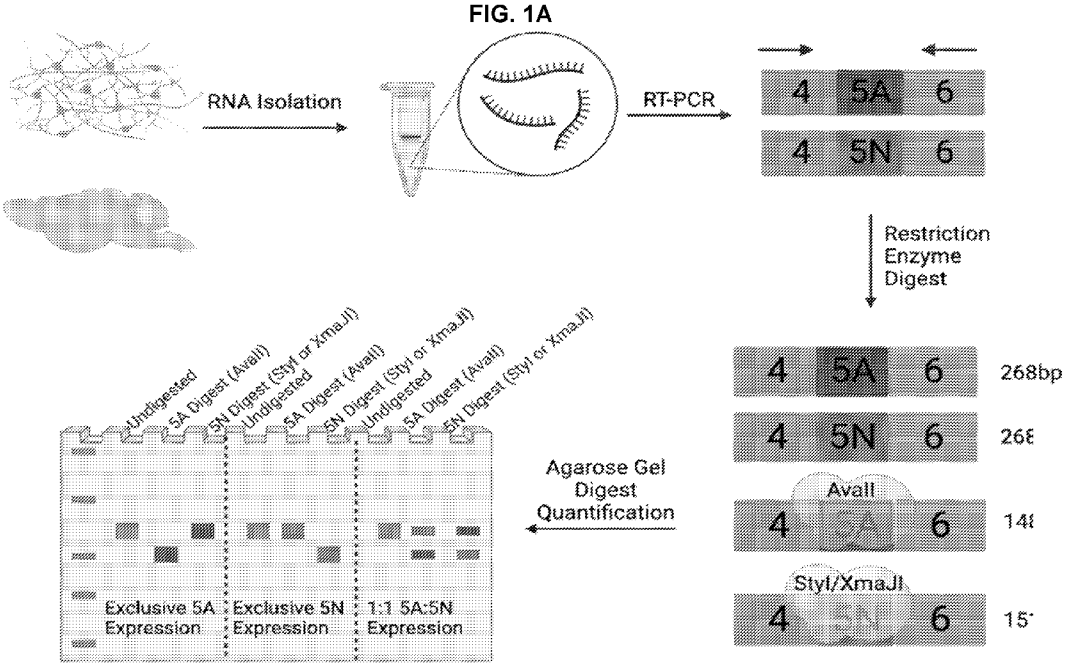
(74) Agent: **HUNTER-ENSOR, Melissa**; Greenberg Traurig, LLP, One International Place, Suite 2000, Boston, MA 02110 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE,

(54) Title: METHODS AND COMPOSITIONS FOR TREATING NEUROLOGICAL DISEASES AND DISORDERS AND CANCERS

FIG. 1A



(57) Abstract: Provided herein are antisense oligonucleotides and therapeutic methods featuring such oligonucleotides. These oligonucleotides and methods are useful for promoting switching of exon isoforms of a gene or polynucleotide encoding a voltage gated sodium ion channel polypeptide and for treating a neurological, neurodevelopmental, or neurodegenerative disorder, disease, or pathology, or a cancer, and/or symptoms thereof in a subject.

[Continued on next page]

WO 2024/254092 A3

SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

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))*

(88) Date of publication of the international search report:
16 January 2025 (16.01.2025)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/032449

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***C12N 15/113*** (2024.01); ***C07K 14/47*** (2024.01)

CPC: ***C12N 15/113; C07K 14/47;*** *C12N 2310/11; C12N 2310/31; C12N 2310/315; C12N 2310/32; C12N 2310/321*

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)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

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

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2020/0123544 A1 (CELEX ONCOLOGY INNOVATIONS LIMITED) 23 April 2020 (23.04.2020) entire document	1-4, 11-16
A	US 2017/0240904 A1 (LIFESPLICE PHARMA LLC) 24 August 2017 (24.08.2017) entire document	1-4, 11-16

☐ 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

"D" document cited by the applicant in the international application

"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
24 October 2024 (24.10.2024)	**17 December 2024 (17.12.2024)**

Name and mailing address of the ISA/US	Authorized officer
COMMISSIONER FOR PATENTS **MAIL STOP PCT, ATTN: ISA/US** **P.O. Box 1450** **Alexandria, VA 22313-1450** **UNITED STATES OF AMERICA**	**TAINA MATOS**
Facsimile No. **571-273-8300**	Telephone No. **571-272-4300**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/032449

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.
   b. ☑ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)),
      ☑ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/032449

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.: **5-10, 17-21, 25-94**
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 need to be paid.

Group I+: claims 1-4 and 11-16 are drawn to antisense oligonucleotides (ASO) and isolated or purified antisense oligonucleotides (ASO) for modifying pre-mRNA splicing of exon 5 in the SCN8A sodium ion channel-encoding gene.

Group II: claims 22-24 are drawn to isolated or purified antisense oligonucleotides (ASO) for modifying pre-mRNA splicing of exon 5 in the SCN5A sodium ion channel-encoding gene.

The first invention of Group I+ is restricted to an SCN8A 5N ASO selected to be ASO-3 with a sequence of SEQ ID NO: 21, an SCN8A 5A ASO selected to be ASO-24 with a sequence of SEQ ID NO: 19, and antisense oligonucleotides and isolated or purified antisense oligonucleotides comprising the same. The first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Specifically, the first named invention was selected based on the first listed SCN8A 5N ASO species and SCN8A 5A ASO species presented in the claims (see claims 12 and 15). It is believed that claims 1-4 and 11-16 read on this first named invention and thus these claims will be searched without fee to the extent that they read on SEQ ID NOs: 19 and 21.

Applicant is invited to elect additional SCN8A 5N ASO's, SCN8A 5A ASO's, and their respective, corresponding, SEQ ID NOs to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be an SCN8A 5N ASO selected to be ASO-8 with a sequence of SEQ ID NO: 8, an SCN8A 5A ASO selected to be ASO-27 with a sequence of SEQ ID NO: 20, and antisense oligonucleotides and isolated or purified antisense oligonucleotides comprising the same. Additional SCN8A 5N ASO's, SCN8A 5A ASO's, and their respective, corresponding, SEQ ID NOs 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:

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

The Group I+ formulas do not share a significant structural element responsible for antisense oligonucleotides for modifying pre-mRNA splicing of an isoform of exon 5 of an SCN8A gene requiring the selection of alternative SCN8A 5N ASO's and SCN8A 5A ASO's where "wherein the ASO is selected from ASO-3, which comprises or consists of nucleic acid sequence ctgcagaatcaaacca; ASO-8, which comprises or consists of nucleic acid sequence gaaagtgcgtagagct; ASO-9, which comprises or consists of nucleic acid sequence ctgaaagtgcgtagag; ASO-10, which comprises or consists of nucleic acid sequence ccctgaaagtgcgtag; ASO- 11, which comprises or consists of nucleic acid sequence accctgaaagtgcgta; ASO-12, which comprises or consists of nucleic acid sequence agtaccctgaaagtgc; or ASO-13, which comprises or consists of nucleic acid sequence ccctcagtaccctgaa" and "wherein the ASO is selected from ASO-24, which comprises or consists of nucleic acid sequence atgttctcagcgctga, or ASO-27, which comprises or consists of nucleic acid sequence ggagaaccctgaatgt."

The special technical features of Group I+, antisense oligonucleotides (ASO) and isolated or purified antisense oligonucleotides (ASO) for modifying pre-mRNA splicing of exon 5 in the SCN8A sodium ion channel-encoding gene, are not present in Group II; the special technical features of Group II, isolated or purified antisense oligonucleotides (ASO) for modifying pre-mRNA splicing of exon 5 in the SCN5A sodium ion channel-encoding gene, are not present in Group I+.

Additionally, even if Groups I+ and II were considered to share the technical features of an antisense oligonucleotide (ASO) comprising 8-20 nucleobases, wherein at least 90% of the nucleobases or more than 8 consecutive nucleobases of the oligonucleotide are complementary to a nucleic acid sequence in an isoform of exon 5 of an SCN8A gene encoding a voltage-gated sodium ion channel polypeptide; an isolated or purified antisense oligonucleotide (ASO) for modifying pre-mRNA splicing of exon 5 in the SCN8A sodium ion channel-encoding gene which specifically modulates splicing of the SCN8A exon 5N transcript; and an isolated or purified antisense oligonucleotide (ASO) for modifying pre-mRNA splicing of exon 5 in the SCN8A sodium ion channel-encoding gene which specifically modulates splicing of the SCN8A exon 5A transcript. However, these shared technical features do not represent a contribution over the prior art.

US 2017/0240904 A1 to Lifesplice Pharma LLC (hereinafter, "Lifesplice") teaches an antisense oligonucleotide (ASO) comprising 8-20 nucleobases (a splice modulating oligonucleotide that specifically binds to a SCN9A pre-miRNA; Para. [0034]; the SMO of the invention may be defined as a oligonucleotide which is capable of hybridizing with the target nucleic acid sequence to exact an antisense activity; Para. [0039]; the SMO sequence is 14 to 26 nucleotides long; Para. [0046]), wherein at least 90% of the nucleobases or more than 8 consecutive nucleobases of the oligonucleotide are complementary to a nucleic acid sequence in an isoform of exon 5 of an SCN8A gene encoding a voltage-gated sodium ion channel polypeptide (the SMO includes a sequence designed to modulate the splicing of an SCN8A pre-mRNA…the SMO includes a sequence that specifically binds to exon 5A or exon 5N; Paras. [0036], [0047]; hybridization of the SMO with a substantially complementary sequence contained within a complementary sequence of a target complementary sequence of the SCN8A pre-mRNA molecule; Para. [0037]; the complementarity to a pre-mRNA by an inventive SMO is 100%; Para. [0038]); an isolated or purified antisense oligonucleotide (ASO) (an SMO is prepared…can be purified; Para. [0077]; the SMO of the invention may be defined as a oligonucleotide which is capable of hybridizing with the target nucleic acid sequence to exact an antisense activity; Para. [0039]) for modifying pre-mRNA splicing of exon 5 in the SCN8A sodium ion channel-encoding gene which specifically modulates splicing of the SCN8A exon 5N transcript (the SMO includes a sequence designed to modulate the splicing of an SCN8A pre-mRNA… the SMO includes a sequence that specifically binds to exon 5A or exon 5N; Para. [0036]; the SMO modulates the splicing of exon 5A/5N in the SCN8A pre-mRNA; Para. [0047]); and an isolated or purified antisense oligonucleotide (ASO) (an SMO is prepared…can be purified; Para. [0077]; the SMO of the invention may be defined as a oligonucleotide which is capable of hybridizing with the target nucleic acid sequence to exact an antisense activity; Para. [0039]) for modifying pre-mRNA splicing of exon 5 in the SCN8A sodium ion channel-encoding gene which specifically modulates splicing of the SCN8A exon 5A transcript (the SMO includes a sequence designed to modulate the splicing of an SCN8A pre-mRNA…the SMO includes a sequence that specifically binds to exon 5A or exon 5N; Para. [0036]; the SMO modulates the splicing of exon 5A/5N in the SCN8A pre-mRNA; Para. [0047]).

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 features.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/032449

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first 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.: **1-4, 11-16**

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.