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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 May 2023 (11.05.2023)

WIPO | PCT

(10) International Publication Number
WO 2023/081908 A3

(51) International Patent Classification:
C12N 15/113 (2010.01) *A61P 21/00* (2006.01)
A61K 31/7115 (2006.01) *A61P 25/00* (2006.01)
A61K 31/712 (2006.01) *C12N 15/861* (2006.01)
A61K 31/7125 (2006.01)

(21) International Application Number:
PCT/US2022/079444

(22) International Filing Date:
08 November 2022 (08.11.2022)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/276,854 08 November 2021 (08.11.2021) US

(71) Applicant: **UNIVERSITY OF MASSACHUSETTS** [US/US]; One Beacon Street, 31st Floor, Boston, Massachusetts 02108 (US).

(72) Inventors: **KHVOROVA, Anastasia**; 10 Rocklawn Road, Westborough, Massachusetts 01581 (US). **GILBERT, James W.**; 9 Brightwood Avenue, Worcester, Massachusetts 01604 (US). **FERGUSON, Chantal**; 36 Johnson Street, Worcester, Massachusetts 01604 (US). **BROWN, Robert**; 16 Oakland Avenue, Needham, Massachusetts 02492 (US). **WEISS, Alexandra**; 18 Weathers Lane, Bolton, Massachusetts 01740 (US).

(74) Agent: **VELEMA, James H.** et al.; LATHROP GPM LLP, 28 STATE STREET, Boston, Massachusetts 02109 (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, 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,

(54) Title: OLIGONUCLEOTIDES FOR SOD1 MODULATION

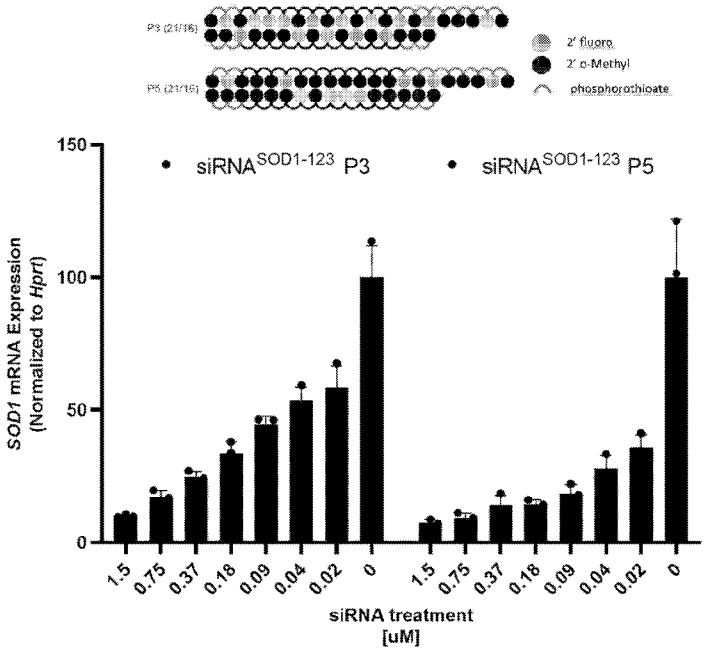

FIG. 19

(57) Abstract: This disclosure relates to novel SOD1 targeting sequences, novel branched oligonucleotides, and expression vector construct that encodes an RNA molecule substantially complementary to a SOD1 nucleic acid sequence. The disclosure further provides a method for inhibiting expression of SOD1 gene in a cell for the treatment of SOD1-related familial amyotrophic lateral sclerosis (ALS).

WO 2023/081908 A3

[Continued on next page]

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

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:
28 September 2023 (28.09.2023)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US22/79444

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. C12N 15/113; A61K 31/7115; A61K 31/712; A61K 31/7125; A61P 21/00; A61P 25/00; C12N 15/861 (2023.01)
ADD.

CPC - INV. C12N 15/1137; A61K 31/7115; A61K 31/712; A61K 31/7125; A61P 21/00; A61P 25/00; C12N 15/861

ADD. C12N 2310/11; C12N 2310/14; C12N 2310/315; C12N 2310/322; C12N 2310/52; C12N 2320/30

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 database consulted during the international search (name of database 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.
X --- Y	US 2020/0157547 A1 (VOYAGER THERAPEUTICS INC.) 21 May 2020; paragraphs [0003], [0018], [0022], [0024], [0027]-[0028], [0101]-[0102], [0127], [0135]	1, 3-5, 78-84, 176 --- 45, 49-50, 87-88, 90, 132, 137-138, 157-159, 162/157-158
Y	US 2020/0385737 A1 (UNIVERSITY OF MASSACHUSETTS) 10 December 2020; paragraphs [0016], [0029]-[0031], [0041], [0048], [0075], [0078], [0100], [0343], [0375], [0377], [0381], [0383], [0396]; tables 6-8; fig 23	45, 49-50, 87-88, 90, 132, 137-138, 157-159, 162/157-158

☐ 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
09 May 2023 (09.05.2023)	JUL 25 2023
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US22/79444

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/US22/79444

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.: 6-44, 52-77, 85-86, 91-131, 139-156, 166-175, 178
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:
-***-Please See Supplemental Page-***-

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.:
Groups I+, Claims 1-5, 45-51, 78-84, 87-90, 132-138, 157-165, 176-177, 179, and SEQ ID NO: 1 (SOD1 nucleic acid sequence), (mX)#(fX)#(mX)(fX)(fX)(fX)(mX)(fX)(mX)(fX)(mX)(fX)(mX)(fX)#(mX)#(fX)#(mX)#(mX)#(mX)#(fX)#(mX) (antisense chemical modification pattern), (mX)#(mX)#(mX)(fX)(mX)(fX)(mX)(fX)(mX)(fX)(mX)(mX)(mX)(fX)#(mX)#(mX) (sense chemical modification pattern), compound of formula I-1 (compound structure), R1 (5' terminal group structure), L1 (linker L structure).

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/US22/79444

-***-Continued From Box No. III: Observations where unity of invention is lacking-***-

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 must be paid.

Groups I+, Claims 1-5, 45-51, 78-84, 87-90, 132-138, 157-165, 176-177, 179, and SEQ ID NO: 1 (SOD1 nucleic acid sequence), (mX)#(fX)#(mX)(fX)(fX)(fX)(mX)(fX)(mX)(fX)(mX)(fX)(mX)(fX)#(mX)#(fX)#(mX)#(mX)#(mX)#(fX)#(mX) (antisense chemical modification pattern), (mX)#(mX)#(mX)(fX)(mX)(fX)(mX)(fX)(mX)(fX)(mX)(mX)(mX)(fX)#(mX)#(mX) (sense chemical modification pattern), compound of formula I-1 (compound structure), R1 (5' terminal group structure), L1 (linker L structure) are directed towards antisense compounds and cells, vectors, and methods associated therewith.

The antisense compounds, cells, vectors, and methods of Claims 1 (in-part), 3-5 (each in-part), 45 (in-part), 49-50 (each in-part), 78 (in-part), 79-81, 82 (in-part), 83-84, 87, 88 (in-part), 90, 132 (in-part), 137-138 (each in-part), 157-159 (each in-part), 162/157-158, 176 (in-part) are believed to encompass the first named invention of Groups I+ and are the claims that will be searched without fee to the extent that they encompass SEQ ID NO: 1 (first exemplary SOD1 nucleic acid sequence), (mX)#(fX)#(mX)(fX)(fX)(fX)(mX)(fX)(mX)(fX)(mX)(fX)(mX)(fX)#(mX)#(fX)#(mX)#(mX)#(mX)#(fX)#(mX) (first exemplary antisense chemical modification pattern), (mX)#(mX)#(mX)(fX)(mX)(fX)(mX)(fX)(mX)(fX)(mX)(mX)(mX)(fX)#(mX)#(mX) (first exemplary sense chemical modification pattern), compound of formula I-1 (first exemplary compound structure), R1 (first exemplary 5' terminal group structure), L1 (first exemplary linker L structure). This first named invention of Group I+ has been selected to encompass the first species of each of the genera found in claims 1, 3-5, 45, 49-50, 78, 82, 88, 132, 137-138, 157-159, 176 based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines.

Applicant is invited to elect additional SOD1 nucleic acid sequence(s), antisense and sense chemical modification pattern(s), compound structure(s), 5' terminal group structure(s), linker L structure(s) to be searched. Additional SOD1 nucleic acid sequence(s), antisense and sense chemical modification pattern(s), compound structure(s), 5' terminal group structure(s), linker L structure(s) will be searched upon the payment of additional fees. Applicants must specify the searchable claims that encompass any additionally elected SOD1 nucleic acid sequence(s), antisense and sense chemical modification pattern(s), compound structure(s), 5' terminal group structure(s), linker L structure(s). Applicants must further indicate, if applicable, the claims which encompass 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. Exemplary elections would be SEQ ID NO: 12 (SOD1 nucleic acid sequence), (mX)#(fX)#(mX)(mX)(mX)(fX)(mX)(mX)(mX)(mX)(mX)(mX)(mX)(fX)#(mX)#(fX)#(mX)#(mX)#(mX)#(fX)#(mX) (antisense chemical modification pattern), (mX)#(mX)#(mX)(mX)(mX)(fX)(fX)(fX)(mX)(fX)(mX)(mX)(mX)(mX)#(mX)#(mX) (sense chemical modification pattern), compound of formula I-2 (compound structure), R2 (5' terminal group structure), L2 (linker L structure).

Groups I+ share the technical features including: a double stranded RNA or dsRNA molecule comprising a sense strand and an antisense strand, wherein the antisense strand comprises a sequence substantially complementary to a SOD1 nucleic acid sequence; a dsRNA comprising an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein: 1. the antisense strand comprises a sequence substantially complementary to a SOD1 nucleic acid sequence; 2. the antisense strand comprises a chemical modification pattern; 3. a portion of the antisense strand is complementary to a portion of the sense strand; and 4. the sense strand comprises a chemical modification pattern, wherein "m" corresponds to a 2'-O-methyl modification; "f" corresponds to a 2'-fluoro modification; "#" corresponds to a phosphorothioate internucleotide linkage; and "X" corresponds to any nucleotide of A, U, G, or C; a vector comprising a regulatory sequence operably linked to a nucleotide sequence that encodes a dsRNA molecule substantially complementary to a SOD1 nucleic acid sequence; a cell comprising the vector; a recombinant adeno-associated virus or rAAV comprising the vector and an AAV capsid; a branched RNA compound comprising: two or more RNA molecules comprising 15 to 35 nucleotides in length, and a sequence substantially complementary to a SOD1 mRNA, wherein the two RNA molecules are connected to one another by one or more moieties independently selected from a linker, a spacer and a branching point; a branched RNA compound comprising two or more dsRNA, said dsRNA comprising an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein: 1. the antisense strand comprises a sequence substantially complementary to a SOD1 nucleic acid sequence; 2. the antisense strand comprises a chemical modification pattern; 3. a portion of the antisense strand is complementary to a portion of the sense strand; and 4. the sense strand comprises a chemical modification pattern, wherein "m" corresponds to a 2'-O-methyl modification; "f" corresponds to a 2'-fluoro modification; "#" corresponds to a phosphorothioate internucleotide linkage; and "X" corresponds to any nucleotide of A, U, G, or C, wherein the two or more dsRNA are connected to one another by one or more moieties independently selected from a linker, a spacer and a branching point; a compound of formula I: L-(N)n, wherein: L comprises an ethylene glycol chain, an alkyl chain, a peptide, an RNA, a DNA, a phosphate, a phosphonate, a phosphoramidate, an ester, an amide, a triazole, or combinations thereof; and N is a double stranded nucleic acid comprising 15 to 35 bases in length comprising a sense strand and an antisense strand; wherein: the antisense strand comprises a sequence substantially complementary to a SOD1 nucleic acid sequence, wherein the sense strand and antisense strand each independently comprise one or more chemical modifications; and wherein n is 2, 3, 4, 5, 6, 7 or 8; a method of treating or managing amyotrophic lateral sclerosis or ALS, comprising administering to a patient in need of such treatment or management a therapeutically effective amount of a double stranded RNA or dsRNA molecule comprising a sense strand and an antisense strand, wherein the antisense strand comprises a sequence substantially complementary to a SOD1 nucleic acid sequence. These shared technical features are previously disclosed by US 2019/0169608 A1 to Phio Pharmaceuticals Corp. (hereinafter "Phio"), as further evidenced by US 2020/0385737 A1 to UNIVERSITY OF MASSACHUSETTS (hereinafter "Massachusetts"), and further in view of Massachusetts.

Phio discloses a double stranded RNA or dsRNA molecule comprising a sense strand and an antisense strand, wherein the antisense strand comprises a sequence substantially complementary to a SOD1 nucleic acid sequence (a dsRNA construct comprising a sense strand and an antisense strand which hybridizes to said sense strand and to mRNA of a target SOD1 gene; paragraphs [0006], [0063], [0091]); a dsRNA comprising an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein: 1. the antisense strand comprises a sequence substantially complementary to a SOD1 nucleic acid sequence; 2. the antisense strand comprises a chemical modification pattern; 3. a portion of the antisense strand is complementary to a portion of the sense strand; and 4. the sense strand comprises a chemical modification pattern, comprising 2'-O-methyl modification, 2'-fluoro modification; and phosphorothioate internucleotide linkage; and nucleotides of A, U, G, or C (a dsRNA construct comprising a sense strand and an antisense strand which hybridizes to said sense strand and to mRNA of a target SOD1 gene, wherein the sense and antisense strands comprise chemical

-***-Continued Within the Next Supplemental Box-***-

-***-Continued from previous Supplemental Box-***-

modifications comprising 2'-O-methyl modification, 2'-fluoro modification; and phosphorothioate internucleotide linkage; and nucleotides of A, U, G, or C; abstract; paragraphs [0006], [0063], [0083], [0091]); a vector comprising a regulatory sequence operably linked to a nucleotide sequence that encodes a dsRNA molecule substantially complementary to a SOD1 nucleic acid sequence (a vector expressing at least one strand of a dsRNA comprising an antisense strand which hybridizes to a sense strand and to mRNA of a target SOD1 gene, which would intrinsically involve a regulatory sequence operably linked to a nucleotide sequence that encodes a dsRNA molecule; paragraphs [0006], [0048], [0063], [0091]); a cell comprising the vector (a cell comprising the vector; paragraph [0049]); a method of treating or managing amyotrophic lateral sclerosis or ALS, comprising administering to a patient in need of such treatment or management a therapeutically effective amount of a double stranded RNA or dsRNA molecule comprising a sense strand and an antisense strand, wherein the antisense strand comprises a sequence substantially complementary to a SOD1 nucleic acid sequence (a method of treating or managing a disease involving faulty SOD1 expression, such as ALS, as shown by the Massachusetts evidentiary reference (SOD1 mutations account for the vast majority of inherited cases of ALS; paragraph [0005]) comprising administering to a patient in need of such treatment or management a therapeutically effective amount of a dsRNA molecule comprising a sense strand and an antisense strand, wherein the antisense strand comprises a sequence substantially complementary to a SOD1 nucleic acid sequence; paragraphs [0006], [0063], [0083], [0091], [0228], [0294]; claims 51, 67, 68).

Phio does not disclose a recombinant adeno-associated virus or rAAV comprising the vector and an AAV capsid; a branched RNA compound comprising: two or more RNA molecules comprising 15 to 35 nucleotides in length, wherein the two RNA molecules are connected to one another by one or more moieties independently selected from a linker, a spacer and a branching point; a branched RNA compound comprising two or more dsRNA, wherein the two or more dsRNA are connected to one another by one or more moieties independently selected from a linker, a spacer and a branching point; a compound of formula I: L-(N)n, wherein: L comprises an ethylene glycol chain, an alkyl chain, a peptide, an RNA, a DNA, a phosphate, a phosphonate, a phosphoramidate, an ester, an amide, a triazole, or combinations thereof; and N is a double stranded nucleic acid comprising 15 to 35 bases in length comprising a sense strand and an antisense strand; wherein: the antisense strand comprises a sequence substantially complementary to a SOD1 nucleic acid sequence, wherein the sense strand and antisense strand each independently comprise one or more chemical modifications; and wherein n is 2, 3, 4, 5, 6, 7 or 8.

Massachusetts discloses a recombinant adeno-associated virus or rAAV comprising the vector and an AAV capsid (rAAVs comprising an AAV capsid are used to deliver ds siRNAs into cells; paragraphs [0009], [0015], [0267], [0426], [0433]); a branched RNA compound comprising: two or more RNA molecules comprising 15 to 35 nucleotides in length, and a sequence substantially complementary to a gene mRNA, wherein the two RNA molecules are connected to one another by one or more moieties independently selected from a linker, a spacer and a branching point (a di-branched RNA compound comprising two RNA molecules that are between 15 and 35 bases in length, comprising a region of complementarity which is substantially complementary to C9ORF72 mRNA, wherein the two RNA molecules are connected to one another by one or more moieties independently selected from a linker, a spacer and a branching point; paragraph [0075]); a branched RNA compound comprising two or more dsRNA, said dsRNA comprising an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein: 1. the antisense strand comprises a sequence substantially complementary to a nucleic acid sequence; 2. the antisense strand comprises a chemical modification pattern; 3. a portion of the antisense strand is complementary to a portion of the sense strand; and 4. the sense strand comprises a chemical modification pattern, comprising 2'-O-methyl modification, 2'-fluoro modification; and phosphorothioate internucleotide linkage; and nucleotides of A, U, G, or C, wherein the two or more dsRNA are connected to one another by one or more moieties independently selected from a linker, a spacer and a branching point (a di-branched RNA compound comprising two dsRNA molecules, each comprising a sense and an antisense strand, wherein the antisense strand comprises a sequence substantially complementary to a target nucleic acid sequence and to a portion of the sense strand, and wherein the antisense and sense strands comprise a chemical modification pattern comprising 2'-O-methyl modification, 2'-fluoro modification; and phosphorothioate internucleotide linkage; and nucleotides of A, U, G, or C, wherein the two or more dsRNA are connected to one another by one or more moieties independently selected from a linker, a spacer and a branching point; paragraphs [0016], [0022], [0023], [0029], [0075], [0098], [0238]); a compound of formula I: L-(N)n, wherein: L comprises an ethylene glycol chain, an alkyl chain, a peptide, an RNA, a DNA, a phosphate, a phosphonate, a phosphoramidate, an ester, an amide, a triazole, or combinations thereof; and N is a double stranded nucleic acid comprising 15 to 35 bases in length comprising a sense strand and an antisense strand; wherein: the antisense strand comprises a sequence substantially complementary to a target nucleic acid sequence, wherein the sense strand and antisense strand each independently comprise one or more chemical modifications; and wherein n is 2, 3, 4, 5, 6, 7 or 8 (a compound of formula I, wherein L is selected from an ethylene glycol chain, an alkyl chain, a peptide, RNA, DNA, a phosphate, a phosphonate, a phosphoramidate, an ester, an amide, a triazole, and combinations thereof, and N is a double stranded nucleic acid comprising 15 to 35 bases in length comprising a sense strand and an antisense strand; wherein: the antisense strand comprises a sequence substantially complementary to a target nucleic acid sequence, wherein the sense strand and antisense strand each independently comprise one or more chemical modifications; and wherein n is 2, 3, 4, 5, 6, 7 or 8; paragraph [0100]).

It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the vector and antisense compound, as previously disclosed by Phio, for the integration of a rAAV comprising the vector and an AAV capsid, and a branched RNA compound comprising two or more dsRNA, wherein the two or more dsRNA are connected to one another by one or more moieties independently selected from a linker, a spacer and a branching point, and a compound of formula I, wherein L comprises an ethylene glycol chain, an alkyl chain, a peptide, an RNA, a DNA, a phosphate, a phosphonate, a phosphoramidate, an ester, an amide, a triazole, or combinations thereof; and N is a double stranded nucleic acid comprising 15 to 35 bases in length comprising a sense strand and an antisense strand; wherein: the antisense strand comprises a sequence substantially complementary to a target nucleic acid sequence, wherein the sense strand and antisense strand each independently comprise one or more chemical modifications; and wherein n is 2, 3, 4, 5, 6, 7 or 8, based on the teachings of Massachusetts, as this modification would provide the capability of generating compounds capable of delivering two or more dsRNA molecules comprising antisense activity against SOD1 mutated gene, wherein the antisense compounds are branched, comprise a well-defined chemical structure, and comprise base and internucleotide linkage modification, thereby providing improved antisense nucleotide compounds with greater structural stability, and therefore greater therapeutic efficacy in diseases, such as ALS, that are caused by SOD1 mutation.

Since none of the special technical features of the Groups I+ inventions are found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Phio and Massachusetts references, unity of invention is lacking.