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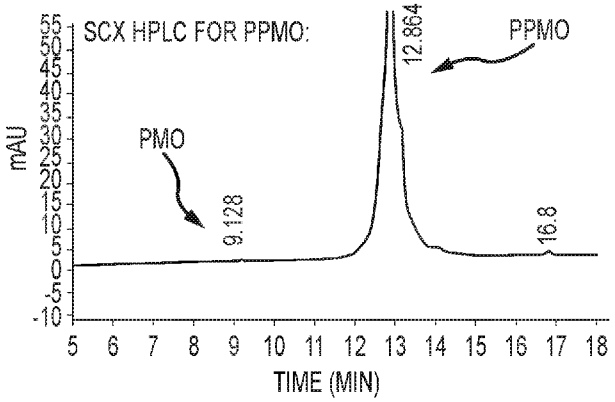


FIG.7B

(57) Abstract: A modified antisense oligonucleotide of about 10 to about 40 nucleobases is disclosed. The oligonucleotide comprises a targeting sequence having a region complementary to at least one string of three or more identical contiguous nucleobases in a target sequence, wherein the target sequence comprises at least one additional nucleobase compared to the region of the targeting sequence and the at least one additional nucleobase has no complementary nucleobase in the region of the targeting sequence, and wherein the targeting region complementary to the at least one string of three or more identical contiguous nucleobases is internal to the targeting sequence.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/56572

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12N 15/113, C12N 15/11 (2019.01)
CPC - C12N 15/113, C12N 2320/30, C12N 2310/33, C12N 2310/11, C12N 2310/3513

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.
X --- Y	US 2003/0045488 A1 (BROWN et al.) 6 March 2003 (06.03.2003) Abstract, Claim 7, Figures 1 and 3, SEQ ID NO: 27, para [0017], [0019], [0022], [0026], [0029], [0034], [0037], [0047], [0075 - 0076], [0079]	1-4 ------- 5-8
Y	US 2005/0288246 A1 (IVERSEN et al.) 29 December 2005 (29.12.2005) para [0002]	5
Y	US 2017/0029818 A1 (BIOMARIN TECHNOLOGIES B.V.) 2 February 2017 (02.02.2017) para [0003], [0073-0074], [0089-0090], [0099], [0116]	6-8, 17
Y	GenBank Accession No: CP018606.1, 07 February 2017 [online]. [Retrieved 17 February 2019]. Retrieved from the internet <URL: https://www.ncbi.nlm.nih.gov/nuccore/CP018606.1/ > entire document	8, 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	Date of mailing of the international search report
17 February 2019	06 MAY 2019

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/56572

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 as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

----------Continued on 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.:
1-8, 17, limited to SEQ ID NO: 2

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/US 18/56572

Continuation of Box III Observations where unity of invention is lacking:

Group I+: Claims 1-18 directed to a modified antisense oligonucleotide of about 10 to about 40 nucleobases comprising: a targeting sequence having a region complementary to at least one string of three or more identical contiguous nucleobases in a target sequence, wherein the targeting sequence has one fewer nucleobases than the target, and wherein the targeting region complementary to the string of three or more identical contiguous nucleobases is internal to the targeting sequence. The modified antisense oligonucleotide will be searched to the extent that the target sequence comprises an exon 44 sequence in human dystrophin (preprocessed) mRNA associated with Duchenne muscular dystrophy, and the targeting sequence of the oligonucleotide comprises SEQ ID NO: 2. It is believed that claims 1-8 and 17, limited to a modified antisense oligonucleotide having an exon 44 target of dystrophin pre-mRNA comprising SEQ ID NO: 2 encompass this first named invention, and thus these claims will be searched without fee to the extent that the modified antisense oligonucleotide encompasses SEQ ID NO: 2. Additional modified antisense oligonucleotides will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected modified antisense oligonucleotides. 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. An exemplary election would be a modified antisense oligonucleotide wherein the target sequence comprises an exon 7 target in human SMN2 pre-processed mRNA associated with spinal muscular atrophy, and the targeting sequence comprises SEQ ID NO: 9 (claims 1-5, 11-13 and 17).

The inventions listed as Groups I+ 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:

Special Technical Features

No technical features are shared between the modified antisense oligonucleotide sequencess of Groups I+ and, accordingly, these groups lack unity a priori.

Additionally, even if the inventions listed as Group I+ were considered to share technical features, these shared technical features are previously disclosed by the prior art, as further discussed below.

Common Technical Features

The feature shared by the inventions listed as Group I+ is a modified antisense oligonucleotide of about 10 to about 40 nucleobases comprising: a targeting sequence having a region complementary to at least one string of three or more identical contiguous nucleobases in a target sequence, wherein the targeting sequence has one fewer nucleobases than the target, and wherein the targeting region complementary to the string of three or more identical contiguous nucleobases is internal to the targeting sequence. However, these shared technical features do not represent a contribution over prior art, because the shared technical features are made obvious by US 2013/0131312 A1 to Iversen et al. (hereinafter 'Iversen'). Iversen teaches modified antisense oligomers of 10 to 40 nucleobases having strings of three or more bases (para [0046] ""An antisense oligomer compound" or "antisense oligomer analog" or antisense compound" ... refer to a substantially uncharged nucleic acid analog, typically having a length between 8 and 40 bases, and having a base sequence that is complementary or substantially complementary to a single-stranded target nucleic acid, e.g., a processed or preprocessed mRNA transcript", para [0015] "In some antisense applications, the optimal targeting sequence against which the oligomer antisense is directed may include a run of four of more cytosine bases, in which case the oligomer will contain a corresponding string of four or more complementary guanine bases", Table 1 shows oligos wherein said strings of guanine bases are internal to the targeting sequence (first oligo-AVI-4126), para [0018] "The improvement includes substituting an inosine base for at least one guanine base in the string of bases in the compound so as to limit the number of contiguous guanine bases in the string to three or fewer, preferably two or fewer.", para [0019] "Where the target nucleic acid region includes the start codon in an mRNA, the improvement may be effective to enhance the ability of the conjugate to block translation of the protein encoded by the mRNA .... Where the target nucleic acid region includes a donor or acceptor splice site in an preprocessed mRNA, the improvement may be effective to enhance the ability of the conjugate to mask mRNA splicing at the target region", para [0073] "the antisense oligomer compound is a synthetic oligomer ... an antisense oligonucleotide analog. Such analogs, in which the backbone structure, ring structure, or, less frequently, base structure of natural polynucleotides is modified"). Iversen does not expressly teach that the targeting sequence having a region complementary to at least one string of three or more identical contiguous nucleobases in a target sequence has one fewer nucleobases than the target, however, Iversen teaches that strings of guanosine residues in the modified antisense have substitutions in the complement sequence to the three or more identical contiguous nucleobases in a target sequence, which effectively reduce the paired nucleotide string length. Based on Iversen's teaching, an artisan of ordinary skill would have readily appreciated that a substitution or a deletion of a nucleotide from the antisense oligo would prevent strings of 3 or 4 consecutive guanosines, which would result in improvements in the function of the oiligonucleotide sequences, as discussed above by Iversen, thus, it would have been obvious for said artisan to delete or substitute said nucleotides from said modified antisense oligonucleotides.

As the technical feature was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the inventions.

Group I+ therefore lack unity under PCT Rule 13 because they do not share the same or corresponding special technical feature.