(54) Title: COMPOSITIONS AND USES FOR TREATMENT THEREOF

(57) Abstract: The invention is directed generally to oligonucleotide compositions for the treatment of DNA repeat expansion diseases. The invention also relates to oligonucleotides directed to subunits of the DNA mismatch repair system.
Designated States (unless otherwise indicated, for every kind of regional protection available):

- Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM)
- European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GR, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, 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:

7 January 2016
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(b.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
   c. [x] furnished subsequent to the international filing date for the purposes of international search only:
      - [x] in the form of an Annex C/ST.25 text file (Rule 13(b.1(a))
      - [ ] on paper or in the form of an image file (Rule 13(b) and Administrative Instructions, Section 713).

2. [x] 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:
   GenCore ver 6.4.1 SEQ ID NOs: 2-4, 29-32
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12N 15/11; C07H 21/04, 21/00 (2015.01)
CPC - C12N 15/13, 21/0315, 2310/0314, 2310/0231, 2310/0323

B. DOCUMENTS CONSIDERED TO BE RELEVANT

CPC: C12N 15/13, 21/0315, 2310/0314, 2310/0231, 2310/0323

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/44A, 536/24.5, 22.1 (text search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Patents, Schol; Google Scholar; Google Patents. Search terms: DNA expansion repeat disorder, DNA mismatch repair system, MSH2, MLH1, oligonucleotide, nuclease resistant, LNA, Phosphoramoimide morpholino (PMO), exon skipping, splice donor, splice acceptor, intron-exon junction

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>US 2002/0068709 A1 (ORMUM et al.) 6 June 2002 (06.06.2002). Especially para [0047], [0057], [0070], [0077], [0082].</td>
<td>1, 3, 4, 11-15, 17, 20</td>
</tr>
<tr>
<td>Y</td>
<td>US 2008/020409 A1 (WILSON et al.) 21 August 2008 (21.08.2008). Especially para [0018], [0029], [0051], [0065], [0077], [0079], [0082]</td>
<td>7, 16, 18, 19, 21-24</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

Earlier application or patent but published on or after the international filing date

Document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation of other special reason (as specified)

Document referring to an oral disclosure, use, exhibition or other means

Document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search
13 October 2015 (13.10.2015)

Date of mailing of the international search report
12 NOV 2015

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-8300

Form PCT/ISA/210 (second sheet) (January 2015)

Authorized officer: Lee W. Young
PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774
INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/29724

Observations where certain claims were found unsearchable (Continuation of first sheet)

<table>
<thead>
<tr>
<th>Box No. II</th>
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<tbody>
<tr>
<td>Observations where certain claims were found unsearchable</td>
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</tbody>
</table>

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).

Observations where unity of invention is lacking (Continuation of first sheet)

<table>
<thead>
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<th>Box No. III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observations where unity of invention is lacking</td>
</tr>
</tbody>
</table>

This International Searching Authority found multiple inventions in this international application, as follows:

---go to Extra Sheet for continuation---

1. H J As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. H 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.: Claims 1-26 limited to the first named mismatch repair complex gene, MSH2 (Claims 1-4, 7, 11-24).

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.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2015)
INTERNATIONAL SEARCH REPORT

— Continuation of Box III (Lack of Unity of Invention) ————

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.

Group I: Claims 1-26, drawn to a composition of at least one nuclease-resistant oligonucleotide comprising a nucleic acid sequence that hybridizes to a complementary target nucleic acid sequence of a gene or gene product encoding a component of a mismatch repair (MMR) complex.

The nuclease-resistant oligonucleotide that will be searched to the extent that it hybridizes to the first named mismatch repair complex gene, MSH2 (claim 4). It is believed that claims 1-4, 7.1-24 read on this first named invention and thus these claims will be searched without fee to the extent that they encompass at least one oligonucleotide that hybridizes to MSH2. Additional mismatch repair complex genes will be searched upon payment of additional fees. Applicant must specify the claims that encompass any additional elected target gene(s). 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. An exemplary election would be: MLH1 (claims 1-3, 4 (in part), 7, 11-24).

Group II: Claims 27-36, drawn to a method for treatment, efficacy of treatment, or monitoring the progression of DNA Repeat Expansion Disease (DRED).


The inventions listed as Groups I, II and III 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:

Group I has the special technical feature of at least one oligonucleotide comprising a nucleic acid sequence that hybridizes to a complementary target nucleic acid sequence of a gene or gene product encoding a component of a mismatch repair (MMR) complex, not required by Groups II or III.

Group II has the special technical feature of a kit not required by Groups I or Group III.

Group III has the special technical feature of a method of treating DNA Repeat Expansion Disease, not required by Group I or II.

Among the inventions listed as Groups I are the specific genes recited therein (MSH2, MSH3, MSH6, MLH1, MLH3, PMS1, PMS2). The inventions do not share a special technical feature, because no significant structural similarities can readily be ascertained among the genes.

Among the inventions listed as Groups II are the specific sequences recited therein. The inventions do not share a special technical feature, because no significant structural similarities can readily be ascertained among sequences (SEQ ID NO: 1) comprising the gene MLH3 contains the complementary sequence of all other named sequences (GenBank Accession No. NG_008649.1 is SEQ ID NO: 1, as admitted by Applicant in instant Specification, para [0007]).

Common Technical Features:

Group I has the common technical feature of an oligonucleotide comprising a nucleic acid sequence that hybridizes to a complementary target nucleic acid sequence of a gene or gene product encoding a component of a mismatch repair (MMR) complex

Group II and III share the common technical feature of claim 1, 21, 22, and 23.

Group I, II and III share the common technical feature of claim 14.

However, said common technical features do not represent a contribution over the prior art, and is obvious over US 2002/0068709 A1 to ORUM et al. (hereinafter "ORUM"), in view of US 2008/0200409 A1 to WILSON et al. (hereinafter "Wilson"). and the publication titled "Structure of the human MSH2 locus and analysis of two Muir-Torre kindreds for msh2 mutations" by KOLODNER et al. (hereinafter "Kolodner") [Genomics December1994 24 No 3 Pages 516-526].

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Concerning Group I, claim 1 [also generic claim for Group II claim 28 and Group III claims 37 and 38], Orum teaches an isolated nuclease-resistant oligonucleotide comprising a nucleic acid sequence that hybridizes to a complementary target nucleic acid sequence of a gene or gene product encoding a component of a mismatch repair (MMR) complex [para [0047]]. The LNA modified antisense oligonucleotide may comprise antisense oligonucleotides specific to [....] DNA repair genes such as MSH2 and MLH1 [para [0051]]; LNA modified antisense oligonucleotides may be used in combinations. For instance, a cocktail of several different LNA modified oligonucleotides, directed against different regions of the same gene, may be administered simultaneously or separately [para [0070]]. Nuclease resistance of LNA-modified oligonucleotides can be further enhanced by providing nuclease-resistant intermolecular linkages. Many such linkages are known in the art, e.g., phosphorothioate [para [0070]].

Concerning Group I, claim 14 [also generic claim for Group III claim 39], Orum teaches a pharmaceutical composition [para [0082]]: "[LNA-modified oligonucleotides of the invention include the pharmaceutically acceptable salts thereof] comprising a nuclease-resistant [para [0070]] oligonucleotide 15 to 30 nucleotide bases in length [para [0077]]. Usually, antisense compounds of the invention have lengths in the range of about 12 to 40 nucleotides. More preferably 30 nucleotides; and most preferably, they have lengths in the range of about 12 to 20 nucleotides" targeted to a complementary nucleic acid sequence of a gene or gene product encoding a MutS subunit [i.e. MSH2] [para [0047], MSH2], wherein the oligonucleotide hybridizes with and decreases the expression of the human MutS subunit by at least 20% [para [0020]]. "It will be particularly preferred where interaction or contact with an LNA-modified oligonucleotide results in complete or essentially complete modulation of expression relative to a control, e.g. at least about a 95%, 97%, 98%, 99% or 100% inhibition of or increase in expression relative to control", and wherein the oligonucleotide comprises at least one modification [para [0047], [0070]].

Concerning Group I claim 21, 22, 23 [also, each is a generic claim for Group II claim 27 and Group III claim 40], Wilson teaches an oligonucleotide complex for modulating the expression or activity of a gene or gene product, the complex comprising a first oligonucleotide and a second oligonucleotide, wherein the first oligonucleotide comprises a sequence complementary to an acceptor region of an exon of a gene [para [0019]]. "According to a first aspect, the invention provides antisense molecules capable of binding to a selected target to induce exon skipping" [para [0018]]. The most obvious or readily defined targets for splicing intervention are the donor and acceptor splice sites [para [0065]]; "There is also provided a combination or "cocktail" of two or more antisense oligonucleotides capable of binding to a selected target to induce exon skipping", and wherein the nucleic acid sequence of the first oligonucleotide comprises a nuclelease-resistant modification [not required in claim 23] [para [0077]]. "The most common method for producing antisense molecules is the methylation of the 2' hydroxylase position and the incorporation of a phosphorothioate backbone produces molecules that superficially resemble RNA but that are more resistant to nuclease degradation", and wherein the second oligornucleotide comprises a sequence complementary to a donor region of an exon [para [0019], [0018], [0065]], and wherein the nucleic acid sequence of the second oligonucleotide comprises a sequence complementary to an acceptor region of an exon of a gene encoding a MutS or MutL subunit [e.g. MSH2], or that the second oligonucleotide is a sequence complementary to a donor region of an exon of a gene encoding a MutS or MutL subunit [e.g. MSH2]. However, Orum teaches multiple antisense oligonucleotides [para [0051]; cocktail of oligos] complementary to the exon coding domains [para [0061] or MSH2 [para [0047]]. In addition, Kolodner teaches the exact exon-intron splice junctions of MSH2 [abstract, "The MSH2 genomic locus has been cloned and shown to cover approximately 73 kb of genomic DNA and to contain 16 exons. The sequence of all the intron-exon junctions has been determined."] it would have been obvious for an artisan of ordinary skill in the art to use the method of Wilson to target MSH2, as taught by Orum, and where the specific exon-intron junctions were known, as taught by Kolodner, in order to design specific first and second oligonucleotides.

As the common technical features were known in the art at the time of the invention, they cannot be considered common special technical features that would otherwise unify the groups. The inventions lack unity with one another.

Therefore, Groups I, II and III lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.