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(54) Title: HUMAN XIST ANTISENSE OLIGONUCLEOTIDES FOR X REACTIVATION THERAPY

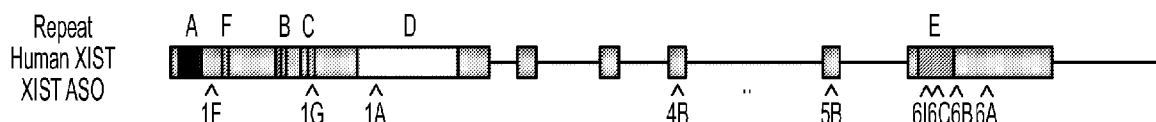


FIG. 1A

(57) Abstract: Antisense Oligonucleotides targeting XIST RNA, and the use thereof for reactivating genes on the inactive X chromosome.



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2021/044824

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12N 15/113 (2022.01)

CPC - C12N 15/113; C12N 2310/113; C12N 2310/14; C12N 2310/315 (2022.01)

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	US 2019/0309291 A1 (THE GENERAL HOSPITAL CORPORATION) 10 October 2019 (10.10.2019) entire document	1-3, 5-7, 10, 12
A ✓	CARRETTE et al. "A mixed modality approach towards Xi reactivation for Rett syndrome and other X-linked disorders" PNAS, Vol. 115(4); 27 December 2017 [retrieved on 08 November 2021]. Retrieved from the internet <URL: https://www.pnas.org/content/pnas/115/4/E668.full.pdf >; Pgs. E668-E675.	1-3, 5-7, 10, 12
A	US 2019/0048339 A1 (THE GENERAL HOSPITAL CORPORATION) 14 February 2019 (14.02.2019) entire document	1-3, 5-7, 10, 12
A	WO 2019/112975 A1 (LEE et al) 13 June 2019 (13.06.2019) entire document	1-3, 5-7, 10, 12

 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

20 January 2022

Date of mailing of the international search report

FEB 15 2022

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2021/044824

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 13ter.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 13ter.1(a)).
 - on paper or in the form of an image file (Rule 13ter.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:

SEQ ID NOs: 1-10 were searched.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2021/044824

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.: 13-29, 32, 33
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 extra sheet(s).

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.:
1-3, 5-7, 10, 12

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/US2021/044824

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 need to be paid.

Group I+: claims 1-12 are drawn to isolated antisense oligonucleotide (ASO) comprising 12-50 consecutive nucleotides of SEQ ID NOs:1-45, or 12-50 consecutive nucleotides of a sequence at or within 100 nts of the binding sites for ASOs comprising SEQ ID NOs:1-45 in 5 XIST.

Group II: Claims 30 and 31 are drawn to an inhibitor of XIST RNA and an inhibitor of an XIST-interacting protein.

The first invention of Group I+ is restricted to an antisense oligonucleotide comprising SEQ ID NO: 1 comprising phosphorothioate internucleotide linkages. It is believed that claims 1-3, 5-7, 10, and 12 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional specific sequence(s) and/or modification(s) for each additional ASO to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected embodiment requires the selection of a single definition for each ASO. An exemplary election would be SEQ ID NO: 2 comprising phosphorothioate internucleotide linkages. Additional embodiment(s) 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:

The special technical features of Group I+, SEQ ID NO: 1, are not present in Group II; the special technical features of Group II, an inhibitor of an XIST-interacting protein, are not present in Group I+.

The Group I+ formulae do not share a significant structural element, requiring the selection of alternatives for an ASO sequence, and accordingly these groups lack unity a priori.

Additionally, even if Group I+ and II were considered to share technical features including: an isolated antisense oligonucleotide (ASO) comprising 12-50 consecutive nucleotides a sequence at or within 100 nts of binding sites in XIST, these shared technical features do not represent a contribution over the prior art, as disclosed by the article "A mixed modality approach towards Xi reactivation for Rett Syndrome and other X-linked disorders" by Carrette, L. et al. (hereinafter, "Carrette").

Specifically, Carrette discloses an isolated antisense oligonucleotide (ASO) comprising 12-50 consecutive nucleotides a sequence at or within 100 nts of binding sites in XIST (a mixed modality approach combining an Xist antisense oligonucleotide and a small-molecule inhibitor of DNA methylation, wherein the antisense oligonucleotide comprises from 15-16 nucleotides in length; abstract, Table S1).

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 feature.