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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
9 August 2012

(54) Title: METHODS AND COMPOSITIONS FOR THE REGULATION OF RNA

(57) Abstract: The invention relates to compositions and methods of modulating the status, activity or expression of long intervening non-coding RNA transcript (lncRNA) targets.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/46365

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12N 15/11; C07H 21/04 (2012.01)
USPC - 514/44A; 536/24.5
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)
USPC: 514/44A; 536/24.5

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,USOC,EPAB,JPAB); Google; PubMed: lncRNA, lincRNA, long noncoding RNA, dsRNA, siRNA, double-stranded RNA, ligand, conjugated, attached, sense, 2'-o-methyl, overhang, snalp, virus
GenCore 6.3: SEQ ID NO:744297

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GUPTA, et al. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature 15 April 2010, 464(7291):1071-1076; abstract; pg 1071, para 3; Methods pg 1, col 2, para 2	1-11, 13-25
Y	US 2005/0064454 A1 (YOUNG, et al.) 24 March 2005 (24.03.2005) para [0014]; SEQ ID NO:2724	1-11, 13-25
Y	US 2005/0153337 A1 (MANOHARAN) 14 July 2005 (14.07.2005) para [0020], [0030]-[0031], [0069], [0074], [0103], [0332], [0609], [0650], [0900]-[0903], [0907], [1061], [1180]	2-3, 6, 8-11, 20-25
Y	US 2006/0240093 A1 (MACLACHLAN, et al.) 26 October 2006 (26.10.2006) para [0044]-[0045]	16-17
A	KHALIL, et al. Many human large intergenic noncoding RNAs associate with chromatin-modifying complexes and affect gene expression. Proc. Natl. Acad. Sci. USA 2009, 106(28):11667-11672	1-25
A	FORREST, et al. Annotating non-coding transcription using functional genomics strategies. Brief Funct. Genomic Proteomic 2009, 8(6):437-443	1-25
A	US 2006/0134663 A1 (HARKIN, et al.) 22 June 2006 (22.06.2006) SEQ ID NO:27629	12

☐ 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
"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
5 March 2012 (05.03.2012)	16 MAR 2012
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. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/46365

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.: 56
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.

Group I+: claims 1-25, drawn to a double-stranded ribonucleic acid (dsRNA) for inhibiting expression of a lncRNA gene, wherein said dsRNA comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity to a lnc RNA gene listed in Table 2, which antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from one of the antisense sequences listed in Table 1. The first invention is restricted to SEQ ID NO: 744297. Should an additional fee(s) be paid, Applicant is invited to elect an additional SEQ ID NO(s) to be searched.

----------(Continued on extra 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.:
1-25, restricted to SEQ ID NO: 744297

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.

********** Supplemental Sheet **********

Continuation of Box III - observations where unity of invention is lacking:

Group II: claims 26-29, drawn to a vector encoding at least one strand of a dsRNA, wherein said dsRNA comprises a region of complementarity to at least a part of an RNA encoding a lncRNA, wherein said dsRNA is 30 base pairs or less in length, and wherein said dsRNA targets a said lncRNA for cleavage.

Group III: claims 30-39, 49-55, drawn to a method of altering the path of lineage of a cell comprising,
(a) identifying the cell type of a first cell by determining the RNA population signature of said cell,
(b) contacting said first cell with a lncRNA transcript or modified lncRNA transcript and allowing said first cell to undergo cellular division to produce daughter cells,
(c) determining the RNA population signature of the daughter cells produced in (b),
(d) comparing the RNA population signature of the first cell with the daughter cells, wherein a difference in the RNA population signatures between the first cell and the daughter cells indicates an alteration in the path of lineage of said first cell.

Group IV+: claims 40-48, 57-61, drawn to a synthetic isolated lnc RNA transcript variant. The first invention is restricted to SEQ ID NO: 744297. Should an additional fee(s) be paid, Applicant is invited to elect an additional SEQ ID NO(s) to be searched.

The inventions listed as Groups I+ through IV+ 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 inventions of Groups I+ through III do not include the inventive concept of a synthetic isolated lnc RNA transcript variant, as required by Group IV+.

The inventions of Groups I+ through II and IV+ do not include the inventive concept of a method of altering the path of lineage of a cell, required by Group III.

The inventions of Groups I+ and III through IV+ do not include the inventive concept of a vector encoding at least one strand of a dsRNA, wherein said dsRNA comprises a region of complementarity to at least a part of an RNA encoding a lncRNA, wherein said dsRNA is 30 base pairs or less in length, and wherein said dsRNA targets a said lncRNA for cleavage, required by Group II.

The inventions of Group I+ share the technical feature of a dsRNA of claim 1. However, this shared technical feature does not represent a contribution over prior art as being obvious over a paper titled "Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis" by GUPTA et al. (Nature 15 April 2010, 464(7291):1071-1076) (hereinafter"Gupta") that teaches a ribonucleic acid (siRNA) for inhibiting expression of a lncRNA (also referred to as "lincRNA") gene, wherein said siRNA comprises an antisense strand (HOTAIR - abstract; "depletion of HOTAIR by small interfering RNAs (siRNAs) in MCF7, a cell line that expresses endogenousHOTAIR, decreased its matrix invasiveness" - pg 1071, para 3; Methods pg 1, col 2, para 2), the antisense strand comprising a region of complementarity to a lncRNA gene (Methods pg 1, col 2, para 2), which antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from one of the antisense sequences (Methods pg 1, col 2, para 2). Gupta does not teach that the siRNA is double-stranded (dsRNA). However, it was routine in the art to use both single-stranded and double-stranded siRNAs to inhibit gene expression, and it would have been obvious to use a dsRNA comprising the same antisense sequence as taught by Gupta to achieve the same result. As said dsRNA would have been obvious to one of ordinary skill in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

The inventions of Group IV+ share the technical feature of a synthetic isolated lnc RNA transcript variant of claim 40. However, this shared technical feature does not represent a contribution over prior art as being obvious over Gupta, as above, that teaches a synthetic isolated lncRNA (also referred to as "lincRNA") (HOTAIR, abstract; pg 1071, para 3, "Retroviral transduction allowed stable overexpression of HOTAIR of several-hundred-fold compared to vector-transduced cells"). Gupta does not teach that the disclosed lncRNA is a variant. However, it would have been obvious that it was routine in the art to make variants of known sequences (e.g., by making substitutions or deletions) in order to study and/or alter the function of the sequences. As said synthetic isolated lnc RNA transcript variant would have been obvious to one of ordinary skill in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Another special technical feature of the inventions listed as Group I+ and IV+ is the specific nucleic acid recited therein. The inventions do not share a special technical feature, because 1) US 2006/0134663 A1 to HARKIN et al. (hereinafter "Harkin") that teaches a sequence that is 99.2% identical to the reverse sequence of claimed SEQ ID NO:744297 (nucleotides 1-1484 of SEQ ID NO:27629 of Harkin), and which further comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the reverse sequence of claimed SEQ ID NO:744297 (SEQ ID NO:27629 of Harkin) and 2) no significant structural similarities can readily be ascertained among the ligands. Without a shared special technical feature, the inventions lack unity with one another.

Groups I+ through IV+ therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.