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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:
27 January 2011

(54) Title: PEPTIDE DICER SUBSTRATE AGENTS AND METHODS FOR THEIR SPECIFIC INHIBITION OF GENE EXPRESSION

(57) Abstract: This invention relates to compounds, compositions, and methods useful for reducing a target RNA and protein levels via use of Dicer substrate siRNA (DsiRN A) -peptide conjugates.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/37265

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/713, C07H 21/00 (2010.01)
USPC - 514/44A
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

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic data bases searched: PubWEST (PGPB, USPT, EPAB, JPAB); Google Search; GenCore Sequence Search (AA)
Search terms: Dicer, Dicer substrate RNA peptide conjugate, double stranded RNA (dsRNA), PAR$, IGF-1 or insulin, LDL, growth factor, anticancer, toxin , delivery peptide; SEQ ID NOs: 1, 16, 31, 46

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y --- A	US 2008/0076701 A1 (QUAY et al.) 27 March 2008 (27.03.2008). Especially [0010], [0016], [0018],[0020], [0034], [0055], [0058], [0074], [0079], [0119], [0134], [0137], [0141], [0218], [0247], [0330], [0333]	1,3-28, 33-52,60-71, 73-76,78,79, 80A-83A, 80B-82B --- 29-32, 53-55, 72,77 --- 56-59
Y	US 2003/0130186 A1 (VARGEESE et al.) 10 July 2003 (10.07.2003). Especially para [0165], [0173], [0174], [0284], [0304].	29-32
Y --- A	KIM et al., Synthetic dsRNA Dicer substrates enhance RNAi potency and efficacy. Nat Biotechnol, February 2005, Vol 23, No 2, Pages 222-226. Especially pg 223 left col para 2.	53-55 --- 56-59
Y	ROSE et al., Functional polarity is introduced by Dicer processing of short substrate RNAs. Nucl Acids Res , 26 July 2005, Vol 33, No 13, Pages 4140-4156. Especially abstract, pg 4141 right col para 3.	72
Y	US 2009/0035822 A1 (FOSTER et al.) 5 February 2009 (05.02.2009). Especially SEQ ID NO: 104.	77

☐ 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
4 November 2010 (04.11.2010)	18 NOV 2010

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. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/37265

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.: 83B and 84
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:
Group I: Claims 1, 3-79, 80A-83A, and 80B-82B, drawn to an isolated double stranded ribonucleic acid composition, wherein a peptide is conjugated to said dsRNA, wherein said dsRNA-peptide conjugate binds to a target, and wherein a delivery peptide has an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 16, 31, 46.

Group II+: Claims 1 , 3-79, 80A-83A, and 80B-82B, drawn to an isolated double stranded ribonucleic acid composition, wherein a peptide is conjugated to said dsRNA, wherein said dsRNA-peptide conjugate binds to a target, and wherein a delivery peptide has an amino acid sequence selected from the group consisting of SEQ ID NOs: 2-15, 17-30, 32-45, 47-89. If Applicant elects to have this group searched, Applicant must specify the specific amino acid sequence(s) to be searched. Each structurally unrelated amino acid sequence constitutes an inventive concept.

---please see coninuation 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.:
1 and 3-82, limited to SEQ ID NOs:1, 16, 31, 46

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.:

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.

Continuation of:
Box No. III Observations where unity of invention is lacking

Group III+: Claims 2-79, 80A-83A, and 80B-82B, drawn to an isolated double stranded ribonucleic acid composition, wherein a peptide is conjugated to said dsRNA, wherein said dsRNA-peptide conjugate is internalized by a target cell, and wherein a delivery peptide has an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-89. If Applicant elects to have this group searched, Applicant must specify the specific amino acid sequence(s) to be searched. Each structurally unrelated amino acid sequence constitutes an inventive concept.

The inventions listed as Groups I-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:

The technical feature shared by the groups listed as Groups I, II+, and III+ is an isolated double stranded ribonucleic acid (dsRNA) composition comprising a first oligonucleotide strand having a 5' terminus and a 3' terminus and a second oligonucleotide strand having a 5' terminus and a 3' terminus, wherein said first strand and said second strand have a length that is at least 16 and at most 50 nucleotides in length, wherein said peptide is conjugated to said dsRNA. This shared technical feature does not provide a contribution over the prior art, as evidenced by US 2008/0076701 A1 to Quay et al. (published March 27, 2008; hereinafter 'Quay'). Quay teaches an isolated double stranded ribonucleic acid (dsRNA) composition (para [0010]) comprising a first oligonucleotide strand having a 5' terminus and a 3' terminus and a second oligonucleotide strand having a 5' terminus and a 3' terminus (para [0010]), wherein said first strand and said second strand have a length that is at least 16 and at most 50 nucleotides in length (para [0010]), wherein said peptide is conjugated to said dsRNA (para [0010]). Quay further teaches that the dsRNA-peptide conjugate binds to a target (para [0029]), and that the dsRNA-peptide conjugate is internalized by a target cell (para [0030]). Finally, Quay teaches that the composition may comprise a delivery peptide (para [0029]). In the absence of a contribution over the prior art, the shared technical feature is not a shared special technical feature. Without a shared special technical feature, the inventions lack unity with one another.

A further special technical feature of each of the inventions listed as Groups I, II+ and III+ is the specific amino acid sequence recited therein. Significant structural similarities cannot readily be ascertained among the sequences. Without significant structural similarities, the sequences do not have a shared special technical feature. In the absence of a shared special technical feature, the inventions lack unity with one another. In this case, the first named structurally related sequences that will be searched without additional fees are SEQ ID NOs: 1, 16, 31, 46. In order for more sequences to be examined, the appropriate additional examination fees must be paid and the desired sequences to be searched clearly identified.