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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))*

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(88) Date of publication of the international search report:
19 July 2012

(54) Title: COMPOSITIONS AND METHODS FOR SPECIFIC CLEAVAGE OF EXOGENOUS RNA IN A CELL

(57) Abstract: There are provided compositions for cleaving an exogenous RNA of interest only in the presence of an endogenous signal RNA sequence, thereby activating expression of a polynucleotide of interest only in the presence of the endogenous signal RNA sequence. There are provided methods for the preparation of the composition and uses thereof in treatment and diagnosis of various conditions and disorders, for example by selectively activating expression of a toxin only in specific target cell populations.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL 11/00827

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07H 21/00 (2012.01)
USPC - 536/24.1
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)
IPC(8): C07H 21/00 (2012.01)
USPC:536/24.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 536/23.1

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); USPTO Patent Full-Text and Image Database (US, AppFT), Google Scholar, Google Patents
Search Terms Used: dicer, siRNA, miRNA, integrated, genome, nonsense mediated decay, ubiquitin, protein, degradation, initiation, start, stop codon, ricin, abrin, diptheria, saporin, momordin, IRES, Abitbol, Nanodoc

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 2009/0234109 A1 (HAN et al.) 17 September 2009 (17.09.2009) esp: paras [0008], [0069], [0032] [0051], [0189], [0342], [0397], [0469], [0372], [0072], [0445], [0160], [0331], [0398], [0413] -[0416], [0423], [0137], [0192], [0202], [0203], [0388], [0059], [0145], [0140], [0148], [0420], [0390], [0428], [0311], [0205], [0444], [0205], [0227], Fig. 1, Fig. 2, Fig. 3, Fig. 6.	1-15, 18, 26-35, 37-50, 52-65, 67-69 --- 16, 17, 19-25, 36, 51, 66
Y	US 2005/0246794 A1 (KHVOROVA et al.) 3 November 2005 (03.11.2005) esp: para [0379]	16, 17, 51, 66
Y	US 2006/0094055 A1 (DING et al.) 4 May 2006 (04.05.2006) esp: [0010], [0025], [0031], [0049], [0050], [0123].	19-25
Y	US 2008/0214488 A1 (PIERCE et al.) 4 September 2008 (04.09.2008) esp: para [0112].	23
Y	US 2009/0169638 A1 (DAVIS et al.) 2 July 2009 (02.07.2009) esp: paras [0006], [0207].	25
Y	US 2006/0293262 A1 (LIEBERMAN et al.) 28 December 2006 (28.12.2006) esp: para [0049].	36

☐ 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
11 May 2012 (11.05.2012)	21 MAY 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

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL 11/00827

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 examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-38, drawn to a polynucleotide for directing specific cleavage of an exogenous RNA of interest.

Group II: Claims 39-69, drawn to a polynucleotide for directing specific expression of an exogenous protein of interest.

---please see 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.:

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/IL 11/00827

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

The inventions listed as 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 shared technical feature of the inventions listed as Groups I and II is a polynucleotide that directs specific cleavage of an exogenous RNA. This shared technical feature fails to provide a contribution over the prior art, as evidenced by US 2009/0234109 A1 to Han et al. (published 17 September 2009; hereinafter 'Han'). Han discloses one or more polynucleotides for directing specific cleavage of an exogenous RNA of interest (para [0008], [0069] - "signal-activated polynucleotide construct") at a specific target site (para [0008], [0069] - "a duplex region that can either become or be cleaved by Dicer"), the cleavage taking place only in the presence of an endogenous signal RNA in a cell the endogenous signal RNA being an RNA molecule which comprises a signal sequence (para [0069] - "in the presence of the signal polynucleotides, the signal detecting polynucleotides hybridize with the signal polynucleotides, and allow the formation of the duplex region for the generation of the siRNA or the miRNA (e.g., by Dicer cleavage)"), the signal sequence being any predetermined sequence of from 18 to 25 nucleotides in length (para [0051] - "In certain embodiments, the signal polynucleotides comprise . . . an miRNA, an siRNA" which one of ordinary skill in the art recognizes are short RNA molecules generally no more than 25 nucleotides in length) whereby introduction of said composition into a cell comprising said endogenous signal RNA (para [0122]-[0123]) directs the cleavage of said exogenous RNA of interest at the specific target site that is located within a specific sequence (para [0069] Dicer cleavage) which is of sufficient complementarity to hybridize with the predetermined signal sequence (para [0069] - "one or more signal detecting polynucleotides, each capable of hybridizing with one or more signal polynucleotides"). In the absence of a contribution over the prior art, the shared technical feature is not a shared special technical feature.

Further, the special technical feature of the inventions listed as Group II is expression of an exogenous protein of interest within a cell. This special technical feature is not shared by the inventions of Group I.

Unity of invention exists only when the same or corresponding technical feature is shared by the claimed inventions. Without a shared special technical feature, the inventions of Groups I and II lack unity with one another.