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(54) Title: METHODS AND COMPOSITIONS FOR THERAPEUTIC USE OF RNA INTERFERENCE

(57) Abstract: The present invention provides methods and compositions for attenuating expression of a target gene *in vivo*. In general, the method includes administering RNAi constructs (such as small-interfering RNAs (i.e., siRNAs) that are targeted to particular mRNA sequences, or nucleic acid material that can produce siRNAs in a cell), in an amount sufficient to attenuate expression of a target gene by an RNA interference mechanism, e.g., in a sequence-dependent, PKR-independent manner. In particular, the subject method can be used to alter the growth, survival or differentiation of cells for therapeutic and cosmetic purposes.



WO 2004/033620 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/35453

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : CO7H 21/02; CO7H 21/04; A61K 48/00

US CL : 536/23.1, 24.5; 514/44

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)

U.S. : 536/23.1, 24.5; 514/44

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)

Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,858,784 (DEBS et al) 12 January 1999 (12.01.1999), see entire document.	1-3, 13-16, 19, 21 and 23
Y	US 5,801,154 (BARACCHINI et al) 1 September 1998 (01.09.1998), see entire document.	1, 13, 17, 18 and 21-23
A	ELBASHIR et al., RNA interference is mediated by 21- and 22-nucleotide RNAs. Genes & Development. January 2001, Vol. 15, ages 188-200.	1
P, X	US 2002/0150945 A1 (FINNEY et al) 17 October 2002 (17.10.2002), see pages 26 and 28 especially.	1, 13, 17, 18, and 21-23
P, X	WO 02/48310 A2 (PITTMAN et al) 20 June 2002 (20.06.2002), see entire document.	1
Y	DELIE et al., Comparison of two methods of encapsulation of an oligonucleotide into poly(D,L-lactic acid) particles. February 19,2001, Vol. 214, pages 25-30.	4, 5, 8, 9 and 13
Y	POHLMANN et al. Spray-dried indomethacin-loaded polyester nanocapsules and nanospheres: development, stability evaluation and nanostructure models. European Journal of Pharmaceutical Sciences. 2002, Vol. 16, pages 305-312.	4-9

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

"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

"E" earlier application or patent published on or after the international filing date

"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

"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)

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

PCT/US02/35453

Continuation of B. FIELDS SEARCHED Item 3:
DIALOG, WEST, PubMed
(RNAi, siRNA, antisense, respiratory formulations, aerosol)

INTERNATIONAL SEARCH REPORT

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CAVALLI et al. Solid lipid nanoparticles as carriers of hydrocortisone and progesterone complexes with B-cyclodextrins. International Journal of Pharmaceutics. May 1999, Vol. 182, pages 59-69.	8-12

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/35453

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claim 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. Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation 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 an additional fee, this Authority did not invite payment of any additional fee.
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.: 1-19 and 21-23

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

- I. Claims 1-19 and 21-23, drawn to a stable respiratory formulation comprising RNAi constructs, a pharmaceutical preparation comprising the formulation, an aerosol dispenser and a pharmaceutical package comprising the pharmaceutical preparation.
- II. Claim 20, drawn to a method for affecting systemic administration of an RNAi construct by way of pulmonary administration.
- III. Claims 24-38, drawn to a composition comprising one or more RNAi constructs formulated in a supramolecular complex.
- IV. Claims 39-44 and 46-53, drawn to a method of attenuating expression of a target gene in vivo, comprising administering an RNAi construct formulated in a supramolecular complex, a pharmaceutical preparation and packaging thereof.
- V. Claims 57-64, drawn to a coating for use on a surface of a medical device comprising a polymer matrix having RNAi constructs dispersed therein.
- VI. Claims 65-73, drawn to a method for coating a medical device with one or more RNAi constructs.
- VII. Claims 74-89, drawn to a composition comprising one or more RNAi constructs formulated for percutaneous intrapericardial delivery.
- VIII. Claims 90-107, drawn to a method for percutaneous intrapericardial delivery of one or more RNAi constructs in vivo, pharmaceutical compositions, and packaging thereof.
- IX. Claims 111-119 and 129-131, drawn to a composition comprising one or more RNAi constructs formulated in liposomes, a pharmaceutical composition and packaging thereof.
- X. Claims 120-128, drawn to a method for attenuating expression of a target gene of cells in a patient comprising administering RNAi constructs formulated in liposomes.
- XI. Claims 132-135 and 140-142, drawn to a composition comprising one or more RNAi constructs formulated for electroporation into cells in vivo, a pharmaceutical preparation and packaging thereof.
- XII. Claims 136-139, drawn to a method of delivering one or more RNAi constructs to a patient by electroporation.
- XIII. Claims 143-168 and 195-197, drawn to a composition comprising one or more formulated RNAi constructs to reduce expression of a target gene essential to mitosis, a pharmaceutical preparation and packaging thereof.
- XIV. Claims 169-194, drawn to a method of inhibiting unwanted cell growth comprising administering a RNAi construct to reduce the expression of a target gene essential to mitosis.
- XV. Claim 198, drawn to a cosmetic preparation comprising RNAi constructs.
- XVI. Claims 199-209, drawn to a method of inducing cell death comprising the administration of a double stranded RNA or an expression vector capable of transcribing a double stranded RNA.
- XVII. Claims 210-212, drawn to a method of conducting a pharmaceutical business.

The inventions listed as Groups I-XVIII below 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 feature of claim 1 is drawn to a respiratory formulation comprising RNAi constructs formulated for pulmonary or nasal delivery to the lungs of patients. Claim 1 broadly reads on all RNAi constructs delivered via respiration. Pittman et al. (WO 02/48310 A2) teach the introduction of antisense nucleic acids, ribozymes or siRNAs into cells via various methods including injection, inhalation, or insufflation. This meets the limitations of claim 1 and is considered to have the functionality recited therein. Therefore, there is no special technical feature.

Claims 45, 54-56 and 108-110 are considered unsearchable due to improper dependency. Claim 45 is drawn to the composition of claim 39, although 39 is not a composition claim. Claim 39 is drawn to a method. Claims 54-56 are drawn to a pharmaceutical preparation comprising the composition of claims 39-43, although claims 39-43 are method claims. Claims 108-110 are drawn to the composition of claim 90, although claim 90 is drawn to a method. These claims improperly depend from other claims.