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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:
18 May 2012

(54) Title: COMPOSITIONS AND METHODS FOR DELIVERING NUCLEIC ACID MOLECULES AND TREATING CANCER

(57) Abstract: Compositions and methods for the delivery of nucleic acids to a cell and methods for the treatment of a disease or disorder, particularly cancer, are provided. The compositions may include an inhibitory nucleic acid molecule and a poly(propyleneimine) (PPI) dendnmer.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/48078

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/7088;C12N 15/11(2006.01)
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: 514/44A (keyword limited; terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (USPT, PGPB, EPAB, JPAB), Google Patents/Scholar
Search Terms Used: PPI dendrimer, siRNA, antisensse, chemotherapeutic, contrast agent, multidrug resistance

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	WO 2007/006700 A1 (Tack et al.) 18 January 2007 (18.01.2007) pg 5, ln 2-21, pg 7, ln 9-14, pg 22, ln 2-17, pg 23, ln 10-29	1-5, 16 ---------- 6-15, 17-21
Y	US 2008/0112916 A1 (Wagner et al.) 15 May 2008 (15.05.2008) para [0020], [0031]-[0033], [0056],	6-9
Y	US 2008/0280813 A1 (Minko et al.) 13 November 2008 (13.11.2008) para [0003]-[0004], [0008], [0017], [0026], [0029], [0037]-[0038], [0049], [0062], Fig. 6, SEQ ID NO: 3	8-12, 17-21
Y	US 2008/0193384 A1 (Willard et al.) 14 August 2008 (14.08.2008) para [0021]-[0022], Fig. 9	13-15

☐ 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
02 March 2012 (02.03.2012)	**23 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

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/48078

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 1-21, directed to a method for delivering an siRNA or antisense molecule to a cell, comprising: a) forming a complex comprising at least one siRNA or antisense molecule and a poly(propyleneimine)(PPI) dendrimer; and b) contacting a cell with said complex.

Group II: claims 22-35, directed to a method of treating cancer, comprising administering to said patient at least two chemotherapeutic agents with different mechanisms of action and at least two inhibitors of cellular drug resistance.

- Please see extra sheet for continuation -

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.:
1-21

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 III: Lack of Unity of Invention

Group III: claims 36-42, directed to a compound comprising a polyamidoamine dendrimer, polyethylene glycol, and poly-L-lysine.

Group IV: claims 43-53, directed to a composition comprising at least one liposome or dendrimer comprising at least two chemotherapeutic agents with different mechanisms of action and at least two inhibitors of cellular drug resistance and at least one pharmaceutically acceptable carrier.

The inventions listed as Groups I - 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 special technical feature of the Group III claims is a compound comprising a polyamidoamine dendrimer, polyethylene glycol, and poly-L-lysine - not required by the claims of any other Group. The special technical feature of the Group I claims is a method for delivering an siRNA or antisense molecule to a cell, comprising: a) forming a complex comprising at least one siRNA or antisense molecule and a poly(propyleneimine)(PPI) dendrimer; and b) contacting a cell with said complex - not required by the claims of any other Group. The special technical feature of the Group IV claims is a composition comprising at least one liposome or dendrimer comprising at least two chemotherapeutic agents with different mechanisms of action and at least two inhibitors of cellular drug resistance and at least one pharmaceutically acceptable carrier - not required by the claims of any other Group.

There is no common technical element shared by all of the above groups. Groups I, III and IV share the common technical element of being related to a dendrimer This common technical element does not represent an improvement over the prior art of US 2007/0231378 A1 to Chang et al., which discloses a targeted complex (para [0126]) for delivering an agent (para [0127]) to a cell (para [0126]), comprising an antibody for fragment thereof and a liposome or polymer, wherein the polymer is further mixed with a therapeutic agent which may be an siRNA or antisense molecule (para [0127]), wherein suitable polymers are DNA binding cationic polymer, preferably polyethyleneimine, or polylysine, protamine or polyamidoamine dendrimers. (para [0125]). Although Chang does not explicitly disclose a polypropyleneimine dendrimer, since Chang discloses cationic polymer dendrimers and similar polymers (PEI), it would have been obvious to a person skilled in the art to use PPI dendrimer for the same purpose, based on the teaching of Chang. Groups II and IV share the common technical elements of being related to at least two chemotherapeutic agents with different mechanisms of action and at least two inhibitors of cellular drug resistance. These common technical elements do not represent an improvement over the prior art of US 2007/0243548 A1 to Georges teaches the use of at least two anti-drug resistance agents (polyclonal antibodies; para [0102], wherein "As used herein, the term "polyclonal antibodies" means a population of antibodies that can bind to multiple epitopes on an antigenic molecule. A polyclonal antibody is specific to a particular epitope on an antigen, while the entire pool of polyclonal antibodies can recognize different epitopes. In addition, polyclonal antibodies developed against the same antigen can recognize the same epitope on an antigen, but with varying degrees of specificity"; para [0098]) and anti-cancer drugs in combination with each other (para [0022]). Although Georges does not explicitly state wherein the chemotherapuetic agents must function by different mechanisms, it would have been obvious to a person skilled in the art, when combining chemotherapeutic agents as taught by Georges, to use agents functioning by at least two different mechanisms in order to increase the efficacy of the treatment by inhibiting the growth of the cancer cells using more than one pathway, and by using compounds with different molecular characteristics that would have been less likely to be reduced in effectiveness by a single drug resistance mechanism. Therefore, the inventions of Groups I-IV lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.