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(71) Applicant (for all designated States except US): MAS-

SACHUSETTS INSTITUTE OF TECHNOLOGY
[US/US]; 77 Massachusetts Avenue, Cambridge, MA
02139 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): LEE, Hyukjin

[KR/US]; 217 Thorndike Street, Apt. 202, Cambridge, MA
02141 (US). LYTTON-JEAN, Abigail, K.r. [US/US];
124a Oxford Street, #8, Cambridge, MA 02140 (US).
PARK, Angela, Inok [US/US]; 500 Memorial Drive,
Cambridge, MA 02139 (US). LANGER, Robert, S.
[US/US]; 98 Montvale Road, Newton, MA 02459 (US).
ANDERSON, Daniel, G. [US/US]; 28 Red Oak Drive,
Sudbury, MA 01776 (US).

(74) Agents: NUZZI, Paul A et al.; Choate, Hall & Stewart

LLP, Two International Place, Boston, MA 02210 (US).

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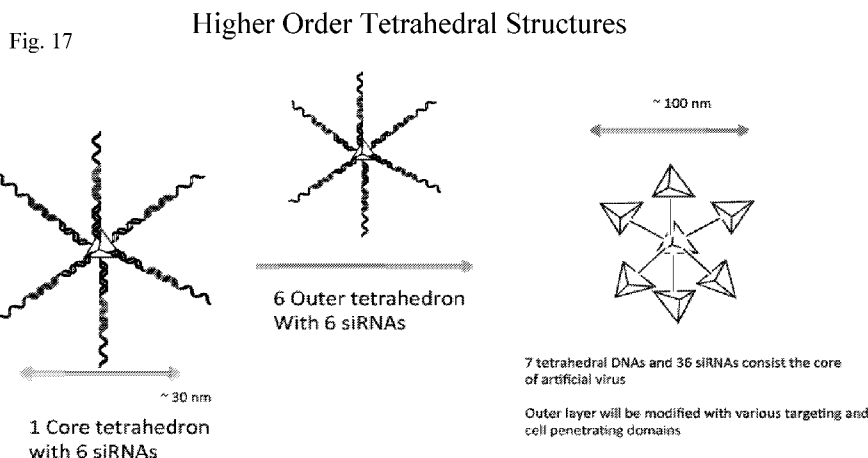
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(15) Information about Correction:

Previous Correction:

see Notice of 13 June 2013

(54) Title: DELIVERY SYSTEM



(57) Abstract: Three-dimensional, nanoscale delivery systems, constructed from, particularly well adapted for delivery of, nucleic acids and/or nucleic acid associated entities are disclosed.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/29571

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/70 (2012.01)

USPC - 514/44R; 977/773

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) - A61K 31/70 (2012.01)

USPC - 514/44R; 977/773

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

IPC(8) - A61K 31/70 (2012.01), USPC - 514/44R; 977/773, 424/450, 536/23.1, 506/13, 506/16, 977/840: keyword search, as below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

USPTO PubWEST(databases: PGPB,USPT,USOC,EPAB,JPAB), Google Scholar -- Search Terms: hybridized, annealed, complementary, oligonucleotide, dna, ma, nucleic acid, nanostructure, structure, tetrahedron, tetrahedral, Langer, Lee, overhang, polyhedron, nanoparticle, particle, payload, deliver, tether, sticky, pyramid, self-assembly

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009/0227774 A1 (TURBERFIELD et al.) 10 September 2009 (10.09.2009) Fig. 1; Fig. ; para [0001]; [0004]; [0005]; [0010]; [0040]; [0041]; [0052]; [0058]; [0061]; [0066]; [0044]; [0127]; [0141]; [0142]; [0130]; [0137]; [0147]	1-10
A	US 2011/0033706 A1 (KRISHNAN) 10 February 2011 (10.02.2011)	1-10
A	US 6,072,044 A (SEEMAN et al.) 6 June 2000 (06.06.2000)	1-10

☐ 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

29 August 2012 (29.08.2012)

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Authorized officer:

Lee W. Young

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/29571

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 1-10, directed to a delivery system comprising:

a nanoparticle comprised of a plurality of DNA oligonucleotides, each of which has a structure comprising:
a first portion that is complementary to a first portion of another oligonucleotide in the plurality such that the plurality of oligonucleotides self-assembles to form the nanoparticle, which is a three-dimensional tetrahedral structure comprising a plurality of faces defined by substantially double stranded arms, wherein at least some oligonucleotides within the plurality have a structure that further comprises:
a second portion that does not hybridize with another oligonucleotide in the plurality, so that such second portions comprises a ligand hybridization element, available for hybridization to a ligand associated with a payload moiety.

- 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.:
1-10

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: Lack of Unity of Invention

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 1-10, directed to a delivery system comprising:

a nanoparticle comprised of a plurality of DNA oligonucleotides, each of which has a structure comprising:

a first portion that is complementary to a first portion of another oligonucleotide in the plurality such that the plurality of oligonucleotides self-assembles to form the nanoparticle, which is a three-dimensional tetrahedral structure comprising a plurality of faces defined by substantially double stranded arms, wherein at least some oligonucleotides within the plurality have a structure that further comprises: a second portion that does not hybridize with another oligonucleotide in the plurality, so that such second portions comprises a ligand hybridization element, available for hybridization to a ligand associated with a payload moiety.

Group II: claims 11, 12 and 16-40, directed to a delivery system comprising:

a nanoparticle comprised of a plurality of oligonucleotides, each of which has a structure comprising:

a first portion that is complementary to a first portion of another oligonucleotide in the plurality such that the plurality of oligonucleotides self-assembles to form the nanoparticle, which has a three-dimensional structure comprising a plurality of faces defined by substantially double stranded arms, wherein at least some oligonucleotides within the plurality have a structure that further comprises:

a second portion that does not hybridize with another oligonucleotide in the plurality, so that such second portions are ligand hybridization elements, available for hybridization to complementary ligands, oligonucleotides within the plurality being designed and constructed such that the nanoparticle includes at least three ligand hybridization elements.

Group III, claims 13, 16-35, 39 and 40, directed to a delivery system comprising:

a nanoparticle comprised of a plurality of oligonucleotides, each of which has a structure comprising:

a first portion that is complementary to a first portion of another oligonucleotide in the plurality such that the plurality of oligonucleotides self-assembles to form the nanoparticle, which has a three-dimensional structure comprising a plurality of faces defined by substantially double stranded arms, wherein at least some oligonucleotides within the plurality have a structure that further comprises:

a second portion that does not hybridize with another oligonucleotide in the plurality, so that such second portions are single stranded ligand hybridization elements, available for hybridization to complementary ligands, which ligand hybridization elements have a sequence comprising poly T or poly A.

Group IV: claims 14-40, and 48-54 directed to a delivery system comprising:

a nanoparticle comprised of a plurality of oligonucleotides, each of which has a structure comprising:

a first portion that is complementary to a first portion of another oligonucleotide in the plurality such that the plurality of oligonucleotides self-assembles to form the nanoparticle, which has a three-dimensional structure comprising a plurality of faces defined by substantially double stranded arms, wherein at least some oligonucleotides within the plurality have a structure that further comprises:

a second portion that does not hybridize with another oligonucleotide in the plurality, so that such second portions are single stranded ligand hybridization elements, available for hybridization to complementary ligands, oligonucleotides within the plurality being designed and constructed such that at least one ligand hybridization element is or comprises a single stranded sequence with a 5' end.

Group V: claims 41-47, directed to a method for generating a delivery system comprising the steps of:

(a) providing a plurality of oligonucleotides, each of which has a structure comprising a first portion that is complementary to a first portion of another oligonucleotide in the plurality such that the plurality of oligonucleotides self-assembles to form a three-dimensional structure whose arms are substantially double stranded, wherein at least some oligonucleotides within the plurality have a structure that further comprises a second portion comprising a ligand hybridization element;

(b) combining said plurality of oligonucleotides in a reaction buffer to form a reaction mixture;

(c) maintaining the combination for a time and under conditions sufficient to permit self-assembly of the nanoparticles.

The inventions listed as Groups I - V 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 features of the claims of Groups I-V are disclosed in the Group descriptions, above.

The common technical elements shared by the above groups is that they are related to a delivery system comprising:

a nanoparticle comprised of a plurality of oligonucleotides, each of which has a structure comprising:

a first portion that is complementary to a first portion of another oligonucleotide in the plurality such that the plurality of oligonucleotides self-assembles to form the nanoparticle, which has a three-dimensional structure comprising a plurality of faces defined by substantially double stranded arms, wherein at least some oligonucleotides within the plurality have a structure that further comprises:

a second portion that does not hybridize with another oligonucleotide in the plurality, so that such second portions are ligand hybridization elements, available for hybridization to complementary ligands, oligonucleotides within the plurality being designed and constructed such that the nanoparticle includes at least three ligand hybridization elements.

- Please see next extra sheet for continuation -

Continuation of: First Extra Sheet: Box No. III Lack of Unity of Invention

These common technical elements do not represent an improvement over the prior art of US 2009/0227774 A1 to Turberfield et al., which discloses a delivery system (a nucleic acid polyhedron having a moiety contained therein; para [0004] - The structure of the nucleic acid polyhedron is preferably modified to allow for release of the moiety; para [0041]) comprising: a nanoparticle (nanoparticle; para [0001]) comprised of a plurality of DNA oligonucleotides (para [0005]), each of which has a structure comprising:

a first portion that is complementary to a first portion of another oligonucleotide in the plurality such that the plurality of oligonucleotides self-assembles to form the nanoparticle (each oligonucleotide comprising subsequences that hybridize to subsequences on the same oligonucleotide or a different oligonucleotide to allow the oligonucleotide(s) to form the polyhedron; para [0005]), which is a three-dimensional tetrahedral structure (DNA tetrahedron; para [0010]) comprising a plurality of faces defined by substantially double stranded arms (Fig 1). Although Turberfield does not explicitly recite wherein at least some oligonucleotides within the plurality have a structure that further comprises:

a second portion that does not hybridize with another oligonucleotide in the plurality, so that such second portions comprises a ligand hybridization element, available for hybridization to a ligand associated with a payload moiety, Turberfield teaches wherein at least some oligonucleotides comprise a second portion that hybridizes with a different oligonucleotide (Each oligonucleotide comprises one, two or more subsequences optionally having linkers there between; para [0058] - The subsequences are selected such that each subsequence hybridizes to another subsequence on the same oligonucleotide or a different oligonucleotide; para [0061] - Each oligonucleotide can comprise three or more subsequences having linkers there between; para [0066]), so that such second portions comprise a ligand hybridization element, available for hybridization to a ligand associated with a payload moiety (The mixing step and the heating and cooling steps of they are performed are carried out in such a manner that the moiety is contained inside the polyhedron. The moiety is preferably attached to or bound to one of the oligonucleotides before it is mixed with the other oligonucleotides forming the nucleic acid polyhedron. The moiety can be attached to or bound to the oligonucleotide in any manner. For example, the moiety can be attached to or bound to the oligonucleotide through an ionic interaction or a covalent linkage. The moiety may be attached or bound to the oligonucleotide via one or more linker molecules. Suitable attachment or binding methods include covalently linking the moiety to the oligonucleotide using bifunctional cross-linker molecules, an aptamer or a poly-histidine tag. The attachment or binding may be reversible or irreversible. The link attaching the moiety to the oligonucleotide can be broken or cleaved after the polyhedron has formed; para [0127]). It would have been obvious to a person skilled in the art to select the oligonucleotide bearing the payload, as taught by Turberfield, so as to not specifically comprise 'a member of the plurality' of sequences that specifically form the nanoparticle structure in order to enable flexible tethering of the payload to be present either within (the moiety is contained inside the nucleic acid polyhedron or encapsulated by the nucleic acid polyhedron; para [0044]) or outside the tetrahedon (para [0142]), potentially attaching the 'second portion' of the oligonucleotide to the first using at least one linker which may be an oligonucleotide (aptamer), as taught by Turberfield (para [0127]). Turberfield further does not limit the structure of the nanoparticle to a tetrahedron (nucleic acid polyhedron; para [0004] - the nucleic acid polyhedron can be designed to have 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or more faces; para [0040]).

Therefore, the inventions of Groups I-V lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.