

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
8 December 2005 (08.12.2005)

PCT

(10) International Publication Number
WO 2005/116226 A3

(51) International Patent Classification:

C12N 15/88 (2006.01) A61K 51/12 (2006.01)
A61K 47/48 (2006.01) A61K 49/18 (2006.01)
A61K 49/00 (2006.01) G01N 33/58 (2006.01)

(21) International Application Number:

PCT/GB2005/002058

(22) International Filing Date: 24 May 2005 (24.05.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/573,805 24 May 2004 (24.05.2004) US
0411537.4 24 May 2004 (24.05.2004) GB

(71) Applicant (for all designated States except US): MIDAT-
ECH LTD [GB/GB]; 4 & 5 Dunmore Court, Wootton
Road, Abingdon, Oxford Oxfordshire OX13 6BH (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): RADEMACHER,

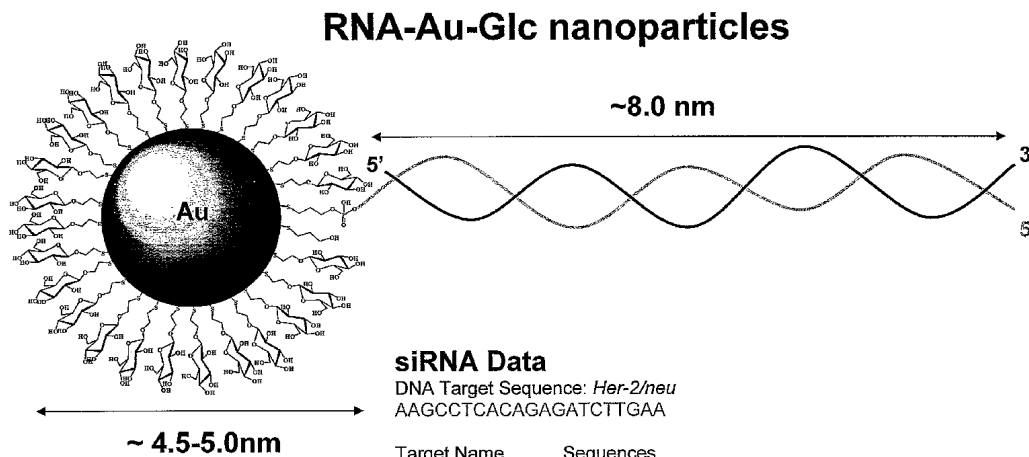
Thomas, William [US/GB]; c/o Midatech Ltd, 4 & 5 Dun-
more Court, Wootton Road, Abingdon, Oxford Oxfordshire
OX13 6BH (GB). GUMAA, Khalid, [GB/GB]; c/o Mi-
datech Ltd, 4 & 5 Dunmore Court, Wootton Road, Abing-
ton, Oxford Oxfordshire OX13 6BH (GB). MARTIN-LO-
MAS, Manuel [ES/ES]; c/o Consejo Superior De Investi-
gaciones Cientificas, Calle Serrano, E-113 28006, Madrid
(ES). PENADES, Soledad [ES/ES]; c/o Consejo Super-
ior De Investigaciones Cientificas, Calle Serrano, E-113
28006, Madrid (ES). OJEDA, Rafael [ES/ES]; c/o Con-
sejo Superior De Investigaciones Cientificas, Calle Ser-
rano, E-113 28006, Madrid (ES). BARRIENTES, Africa
G. [ES/ES]; c/o Consejo Superior De Investigaciones Ci-
entificas, Calle Serrano, E-113 28006, Madrid (ES).

(74) Agents: KIDDLE, Simon et al.; Mewburn Ellis LLP, York
House, 23 Kingsway, London Greater London WC2B 6HP
(GB).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,

[Continued on next page]

(54) Title: NANOPARTICLES COMPRISING RNA LIGANDS



(57) Abstract: Broadly, the present invention relates to nanoparticles comprising having a core including metal and/or semiconductor atoms, the core being linked to RNA ligands. The RNA ligands are typically short RNA sequences designed to mimic small interfering RNA (siRNA) and micro-RNA sequences (miRNA). The nanoparticles can be used to deliver the RNA ligands and have applications in a wide range of applications, in vitro systems and for therapeutic or diagnostic applications. By way of example, the nanoparticles of the present invention may be employed (1) for targeted transcriptional gene silencing, (2) for targeted mRNA degradation, (3) for imaging mRNA, (4) for inhibiting pathways by employing a plurality of RNA ligands on the same or different nanoparticles, (5) for aerosol delivery, e.g. to the lungs, (6) in combination with mRNA silencing for targeting siRNA resistant mRNA and (7) for use as a tool in functional genomics.

WO 2005/116226 A3



KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

- (84) Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

- (88) Date of publication of the international search report:**
29 November 2007

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2005/002058

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C12N15/88 A61K47/48 A61K49/00 A61K51/12 A61K49/18
 G01N33/58

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)
 C12N A61K G01N C12Q

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 practical, search terms used)
 EPO-Internal, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 249 502 A (HITACHI SOFTWARE ENG [JP]) 16 October 2002 (2002-10-16) abstract paragraph [0040] - paragraph [0045] claims ----- -/--	1,2, 4-13, 20-26, 28-31, 33,34, 39-52, 55-60, 67,68,70

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 *E* earlier document 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
9 May 2007	27/09/2007

Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Dullaart, Anwyn
---	---

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2005/002058

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/00876 A1 (MIRKIN CHAD A [US]; LETSINGER ROBERT L [US]; MUCIC ROBERT C [US]; STOR) 4 January 2001 (2001-01-04) examples 1-3 claims 100,101	1,2, 4-13, 20-26, 28-31, 33,34, 39-52, 55-60, 67,68,70
X	----- WO 02/32404 A (CONSEJO SUPERIOR INVESTIGACION [ES]; KIDDLE SIMON JOHN [GB]; PENADES S) 25 April 2002 (2002-04-25) cited in the application page 1 page 25, paragraph EXPERIMENTAL - page 31 claims	1,2, 4-13, 20-26, 28-31, 33,34, 39-52, 55-60, 67,68,70
X	----- WO 98/04740 A (UNIV NORTHWESTERN [US]; MIRKIN CHAD A [US]; LETSINGER ROBERT L [US]; M) 5 February 1998 (1998-02-05) examples claims	1,2, 4-13, 20-26, 28-31, 33,34, 39-52, 55-60, 67,68,70
X	----- EP 0 990 903 A1 (MASSACHUSETTS INST TECHNOLOGY [US]) 5 April 2000 (2000-04-05) example 9	1,2, 4-13, 20-26, 28-31, 33,34, 39-52, 55-60, 67,68,70
X	----- WO 01/51665 A2 (NANOSPHERE INC [US]) 19 July 2001 (2001-07-19) examples claims ----- -/--	1,2, 4-13, 20-26, 28-31, 33,34, 39-52, 55-60, 67,68,70

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2005/002058

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>PATOLSKY F ET AL: "Dendritic amplification of DNA analysis by oligonucleotide-functionalized Au-nanoparticles"</p> <p>CHEMICAL COMMUNICATIONS - CHEMCOM, vol. 6, no. 12, 21 June 2000 (2000-06-21), pages 1025-1026, XP002229552 ISSN: 1359-7345 the whole document</p> <p>-----</p>	<p>1,2, 4-13, 20-26, 28-31, 33,34, 39-52, 55-60, 67,68,70</p>
Y	<p>MATZKE M ET AL: "RNAi extends its reach"</p> <p>SCIENCE, vol. 301, no. 5636, 22 August 2003 (2003-08-22), pages 1060-1061, XP002432809 ISSN: 0036-8075 the whole document</p> <p>-----</p>	<p>1,2, 4-13, 20-26, 28-31, 33,34, 39-52, 55-60, 67,68,70</p>
Y	<p>MIYAGISHI M ET AL: "Comparison of the suppressive effects of antisense oligonucleotides and siRNAs directed against the same targets in mammalian cells"</p> <p>ANTISENSE AND NUCLEIC ACID DRUG DEVELOPMENT, vol. 13, no. 1, 2003, pages 1-7, XP002432810 ISSN: 1087-2906 abstract figures</p> <p>-----</p>	<p>1,2, 4-13, 20-26, 28-31, 33,34, 39-52, 55-60, 67,68,70</p>
Y	<p>CHOUDHURY A ET AL: "Small interfering RNA (siRNA) inhibits the expression of the Her2/Neu gene, upregulates HLA class I and induces apoptosis of Her2/Neu positive tumor cell lines"</p> <p>INTERNATIONAL JOURNAL OF CANCER, vol. 108, no. 1, 1 January 2004 (2004-01-01), pages 71-77, XP002432811 ISSN: 0020-7136 abstract page 71, paragraph SIRNA page 72; table 1 page 73, paragraph RESULTS figures</p> <p>-----</p>	<p>1,2, 4-13, 20-26, 28-31, 33,34, 39-52, 55-60, 67,68,70</p>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2005/002058

Box 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:

Although claims 55 and 57-60 are directed to a method of treatment of the human/animal body, a search has been carried out, based on the alleged effects of the compound/composition.
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 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:

see additional 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.:

see annex

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 4-13, 20-26, 28-31, 33, 34, 40-45, 70 in part, 1-2, 39, 46-52, 55-60, 67 and 68

Nanoparticles as defined in these claims, containing only an RNA ligand, and (methods for) their therapeutic use.

2. claims: 4-13, 20-26, 28-31, 33-35, 40-45, 70 in part, 3 and 36-38

Nanoparticles, methods and use as defined in these claims, containing an RNA ligand and a carbohydrate.

3. claims: 14, 15, 20-26, 28-31, 33, 34, 40-45, 61-66, 70 in part, 16 and 32

Nanoparticles, methods and use as defined in these claims, containing an RNA ligand and a label which is fluorescent or a dye.

4. claims: 14, 15, 20-26, 28-31, 33, 34, 40-45, 53, 54, 61-66, 70 in part, and 17

Nanoparticles, methods and use as defined in these claims, containing an RNA ligand and a radionuclide.

5. claims: 14, 15, 20-26, 28-31, 33, 34, 40-45, 61-66, 70 in part, 18, 19 and 27

Nanoparticles, methods and use as defined in these claims, containing an RNA ligand and a magnetic or nmr active label.

6. claims: 20-26, 28-31, 33-35, 40-45 and 70 in part

Nanoparticles, methods and use as defined in these claims, containing an RNA ligand and a protein or protein domain.

7. claims: 20-26, 28-31, 33, 34, 40-45, 53, 54 and 70 in part

Nanoparticles, methods and use as defined in these claims, containing an RNA ligand and a drug other than previously defined.

8. claim: 69

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

The use of a nanoparticle as defined as tool for functional
genomics

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2005/002058

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 1249502	A	16-10-2002	JP	2002311027 A	23-10-2002
			US	2003190628 A1	09-10-2003
WO 0100876	A1	04-01-2001	AU	784040 B2	19-01-2006
			AU	5637800 A	31-01-2001
			CA	2376623 A1	04-01-2001
			EP	1198591 A1	24-04-2002
			JP	2003503699 T	28-01-2003
WO 0232404	A	25-04-2002	AT	319436 T	15-03-2006
			AU	9406801 A	29-04-2002
			CA	2424734 A1	25-04-2002
			DE	60117828 T2	16-11-2006
			EP	1326589 A2	16-07-2003
			EP	1671625 A1	21-06-2006
			ES	2262684 T3	01-12-2006
			JP	2004511511 T	15-04-2004
			US	2004052729 A1	18-03-2004
WO 9804740	A	05-02-1998	AU	4043497 A	20-02-1998
			CA	2262018 A1	05-02-1998
			EP	0918885 A1	02-06-1999
			JP	2000516460 T	12-12-2000
			JP	2004194669 A	15-07-2004
EP 0990903	A1	05-04-2000	AT	234468 T	15-03-2003
			DE	69905832 D1	17-04-2003
			DE	69905832 T2	05-02-2004
			GB	2342651 A	19-04-2000
			US	2001023078 A1	20-09-2001
WO 0151665	A2	19-07-2001	AU	774593 B2	01-07-2004
			AU	3279501 A	24-07-2001
			CA	2396113 A1	19-07-2001
			EP	1294930 A2	26-03-2003
			JP	2004501340 T	15-01-2004