(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 June 2009 (11.06.2009)

PCT

(10) International Publication Number
WO 2009/073193 A3

(51) International Patent Classification:
A61K 9/127 (2006.01)

(21) International Application Number:
PCT/US2008/013336

(22) International Filing Date:
3 December 2008 (03.12.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/005,228 3 December 2007 (03.12.2007) US
61/093,619 2 September 2008 (02.09.2008) US

(71) Applicant *(for all designated States except US)*: **THE JOHNS HOPKINS UNIVERSITY** [US/US]; 3400 N. Charles Street, Baltimore, MD 21218 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BARNETT, Bradley, Powers** [US/US]; 501 Saint Paul Street, Apt. #1101, Baltimore, MD 21202 (US). **GESCHWIND, Jeffrey** [US/US]; 600 N. Wolfe Street, Blalock 545, Baltimore, MD 21287 (US).

(74) Agents: **CORLESS, Peter, F.** et al.; Edwards Angell Palmer & Dodge LLP, P.o. Box 55874, Boston, MA 02205 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, 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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, 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 (Art. 21(3))*

(88) Date of publication of the international search report:
23 December 2009

(54) Title: METHODS OF SYNTHESIS AND USE OF CHEMOSPHERES

(57) Abstract: The present invention provides, in general, compositions comprising a hydrogel and an agent, for example a therapeutic agent or an imaging agent, for locoregional delivery. In certain preferred embodiments of the invention, the hydrogel compositions are detectable by Magnetic Responance and CT Scan and are used for locoregional delivery of therapeutic agents, for example chemotherapeutic agents. The invention also features polymer matrix compositions comprising nanoparticles that can be loaded after polymerization with bioactive agents, for example a diagnostic agent or therapeutic agent.

WO 2009/073193 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/13336

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 9/127 (2009.01)
USPC - 424/450, 489; 428/402.24
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 - 424/450, 489; 428/402.24

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 424/450, 489, 449, 649; 514/75, 540, 554, 559, 34, 27, 110, 274, 449, 49, 492, 283, 64; 977/906; 427/212 428/323, 407, 499, 551 (text search - see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,OC,EPAB,JPAB); DialogPro (General Research); Google Patents
polymer, matrix, nanoparticle, load, polymerize, bioactive, irreversible, reversible, react, interact, metal, decorate, streptavidin, conjugate, biotin, radioisotope, entrapment, encapsulation, microsphere, silica, SiO2, phosphorylate, bind, kit

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 2007/0148251 A1 (HOSSAINY et al.) 28 June 2007 (28.06.2007), abstract, para [0001]-[0011], [0015]-[0019], [0028], [0043], [0051]-[0055], [0061] and [0064]-[0066].	1, 2, 5-7, 11 and 12 --- 3, 4, 8-10 and 30-36
Y	US 2007/0202342 A1 (WHITEFORD et al.) 30 August 2007 (30.08.2007), abstract, para [0159], [0196]-[0198], [0212], [0240]-[0242], [0379], [0539] and [0540].	3 and 4
Y	US 2005/0107870 A1 (WANG et al.) 19 May 2005 (19.05.2005), abstract, para [0002], [0106], [0111], [0220], [0241], [0242] and [0909].	8-10
Y	US 2007/0190106 A1 (BERSTEIN et al.) 16 August 2007 (16.08.2007), abstract, para [0023], [0056], [0058], [0075]-[0081], [0138]-[0141], [0145], [0152], [0159]-[0162], [0177]-[0179], [0191], [0198], [0202] and [0213]-[0215].	30-36
A	US 2005/0191491 A1 (WANG et al.) 01 September 2005 (01.09.2005), entire document.	1-12 and 30-36
A	US 2004/0101822 A1 (WEISNER et al.) 27 May 2004 (27.05.2004), entire document.	1-12 and 30-36
A	US 2007/0166385 A1 (GOLOMB et al.) 19 July 2007 (19.07.2007), entire document.	1-12 and 30-36
A	US 2006/0240092 A1 (BREITENKAMP et al.) 26 October 2006 (26.10.2006), entire document.	1-12 and 30-36

☐ 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
01 May 2009 (01.05.2009)	12 MAY 2009
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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/13336

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.: 101-105
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:
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 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.:
1-12 and 30-36

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/US 08/13336

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 1-12 and 30-36, drawn to a polymer matrix comprising nanoparticles loaded with one or more bioactive agents and kits thereof.
Group II: claims 13-19, drawn to a method of making the product of Group I.
Group III: claims 20-22, drawn to a method of using the product of Group I.
Group IV: claims 23-27, drawn to a method of making a polymer matrix comprising nanoparticles.
Group V: claims 28-29, drawn to a method of using an polymer matrix
Group VI: claims 37-46, drawn to a composition comprising a hydrogel and a bioactive agent.
Group VII: claims 47-52, drawn to a method of making the composition of Group VI
Group VIII: claims 53-100, drawn to methods of use for the composition of Group VI.

The technical feature shared among the inventions of Groups I-V is the polymer matrix. This shared technical feature fails to provide a contribution over the prior art. Wang et al. (Wang et al. Polymer coating/encapsulation of nanoparticles using a supercritical anti-solvent process. The Journal of Supercritical Fluids. January 2004, Vol. 28, No. 1, 85-99.) teaches a polymer matrix comprising nanoparticles. Wang et al. also suggests the addition of bioactive agents. In the absence of a contribution over the prior art, the shared technical feature is not a shared special technical feature. Without a shared special technical feature, the inventions lack unity with one another.

The special technical feature of the inventions listed as Groups II-V is the specific design for carrying out of each of the listed method/process. The specific design of each of the listed inventions differ from one another. Therefore, the inventions lack a shared special technical feature. Without a shared special technical feature, the inventions lack unity with one another.

The technical feature shared among the inventions of Groups VI-VIII is the composition of Group VI. This shared technical feature fails to provide a contribution over the prior art. Ottoboni et al. (U.S. Patent No. 5,731,005) teaches a composition comprising a hydrogel and a bioactive agent. In the absence of a contribution over the prior art, the shared technical feature is not a shared special technical feature. Without a shared special technical feature, the inventions lack unity with one another.

The special technical feature of the inventions listed as Groups VII-VIII is the specific design for carrying out of each of the listed method/process. The specific design of each of the listed inventions differ from one another. Therefore, the inventions lack a shared special technical feature. Without a shared special technical feature, the inventions lack unity with one another.