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

**ETHICON ENDO-SURGERY, INC** [US/US]; 4545  
Creek Road, Cincinnati, Ohio 45242 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **VOEGELE, James  
W.** [US/US]; 11486 Kemperknoll Road, Cincinnati, Ohio

45245 (US). **TRUSTY, Robert M.** [US/US]; 12126 Coyote Court, Cincinnati, Ohio 45241 (US). **GILL, Robert M.** [US/US]; 9122 Nottingham Way, Mason, Ohio 45040 (US). **DLUGOS, Daniel F.** [US/US]; 8072 Lois Lane, Middletown, Ohio 45044 (US). **MURRAY, Michael A.** [US/US]; 24 Harrison Avenue, Bellevue, Kentucky 41073 (US). **HESS, Christopher J.** [US/US]; 1704 East McMillian Street, Cincinnati, Ohio 45206 (US).

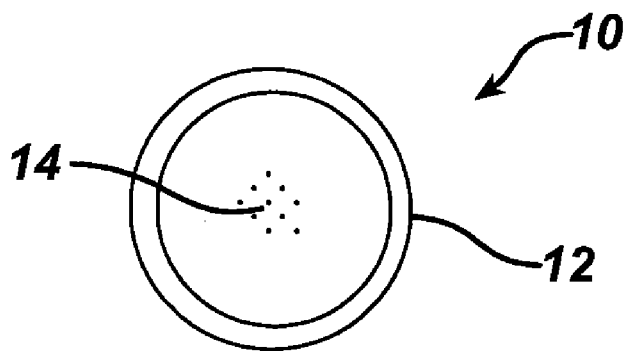
(74) Agents: **JOHNSON, Philip S.** et al.; One Johnson & Johnson Plaza, New Brunswick, New Jersey 08933 (US).

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[Continued on next page]

(54) Title: FLUORESCENT NANOPARTICLE COMPOSITIONS, METHODS AND DEVICES



**FIG. 1**

(57) Abstract: Various compositions, methods, and devices are provided that use fluorescent nanoparticles, which can function as markers, indicators, and light sources. The fluorescent nanoparticles can be formed from a fluorophore core surrounded by a biocompatible shell, such as a silica shell. In one embodiment, the fluorescent nanoparticles can be delivered to tissue to mark the tissue, enable identification and location of the tissue, and/or illuminate an area surrounding the tissue. In another embodiment, the fluorescent nanoparticles can be used on a device or implant to locate the device or implant in the body, indicate an orientation of the device or implant, and/or illuminate an area surrounding the device or implant. The fluorescent nanoparticles can also be used to provide a therapeutic effect.



WO 2008/128051 A3



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).

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<b>A. CLASSIFICATION OF SUBJECT MATTER</b> INV. A61K49/00      A61K41/00      A61B1/05      A61B1/313      A61B5/00 ADD.			
According to International Patent Classification (IPC) or to both national classification and IPC			
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) A61K A61B G02B A61L A61M			
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, WPI Data, INSPEC			
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>			
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	
X	WO 2004/108902 A2 (VISEN MEDICAL INC [US]; POSS KIRTLAND G [US]; MADDEN KAREN N [US]; GRO) 16 December 2004 (2004-12-16)  page 5, paragraph 3 page 22, paragraph 2 - page 23, paragraph 3 page 24, last paragraph - page 25, paragraph 1 page 26, last paragraph - page 27, paragraph 4 page 29, paragraphs 2,3 page 31, paragraph 2 - page 32, paragraph 1 examples	1-10,25, 30, 54-72, 74-80, 82-87, 113	
<input checked="" type="checkbox"/>	Further documents are listed in the continuation of Box C.	<input checked="" type="checkbox"/>	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  <p align="center">30 August 2010</p>		Date of mailing of the international search report  <p align="center">14/09/2010</p>	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer  <p align="center">Chen, Amy</p>	

## INTERNATIONAL SEARCH REPORT

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X	----- US 2007/016075 A1 (TAKEDA MOTOHIRO [JP] ET AL) 18 January 2007 (2007-01-18)  paragraphs [0040] - [0046], [0051] - [0054] example 1	1-3,9, 10,25, 26,30, 54,55, 57,61, 62,69, 71,74, 76-78, 113-115
X	----- YEZHELIEV M V ET AL: "Emerging use of nanoparticles in diagnosis and treatment of breast cancer" LANCET ONCOLOGY, LANCET PUBLISHING GROUP, LONDON, GB, vol. 7, no. 8, 1 August 2006 (2006-08-01), pages 657-667, XP025228942 ISSN: 1470-2045 [retrieved on 2006-08-01] page 662, column 2, paragraph 2 - page 263, column 1, paragraph 1 ----- -/--	1,2,9, 10,25, 30,54, 55,57, 61,69, 71,72, 74, 76-78, 113

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International application No

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X	<p>EDWARD G SOLTESZ ET AL: "Sentinel Lymph Node Mapping of the Gastrointestinal Tract by Using Invisible Light" ANNALS OF SURGICAL ONCOLOGY, SPRINGER-VERLAG, NE, vol. 13, no. 3, 1 March 2006 (2006-03-01), pages 386-396, XP019369785 ISSN: 1534-4681</p> <p>* abstract page 387, section "NIR Fluorescent Lymphatic Tracer and Imaging System" page 394, column 2, paragraph 3 - page 395, column 1, paragraph 1 figures 1-4</p> <p>-----</p>	<p>1-3,9, 10,25, 27,30, 54,55, 57, 59-61, 69, 71-74, 76-87, 89,113, 118-128</p>
X	<p>WO 2007/022196 A2 (UNIV TEXAS [US]; RICHARDS-KORTUM REBECCA [US]; SOKOLOV KOSTIA [US]; DW) 22 February 2007 (2007-02-22)</p> <p>page 8, lines 1-26 page 12, lines 8-10 page 13, lines 3-6,29-30 page 20, lines 18-19 page 20, line 24 - page 21, line 6 page 21, lines 11-19 claims 18-24,26,27,35</p> <p>-----</p>	<p>1,2,10, 25, 54-57, 59,61, 71,72, 82,83, 85,86, 113</p>
X	<p>SZENTKUTI L: "Light microscopical observations on luminally administered dyes, dextrans, nanospheres and microspheres in the pre-epithelial mucus gel layer of the rat distal colon" JOURNAL OF CONTROLLED RELEASE, ELSEVIER, AMSTERDAM, NL, vol. 46, no. 3, 2 June 1997 (1997-06-02), pages 233-242, XP004092169 ISSN: 0168-3659 page 234, column 2, last paragraph - page 235, column 1, paragraph 2 figure 1 page 239; table 3</p> <p>-----</p> <p style="text-align: center;">-/--</p>	<p>1,2,5,6, 9,10,25, 54,55, 57,58, 60,61, 64-66, 69-71, 113</p>

## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2008/060045

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>US 2006/245971 A1 (BURNS ANDREW A [US] ET AL) 2 November 2006 (2006-11-02) cited in the application</p> <p>paragraphs [0023], [0027], [0032], [0033], [0034], [0049] example 1 claims 33-38</p> <p>-----</p>	<p>1,2,25, 26,54, 55,57, 61, 113-116</p>
X	<p>WANG LIN ET AL: "Dual-luminophore-doped silica nanoparticles for multiplexed signaling." NANO LETTERS JAN 2005, vol. 5, no. 1, January 2005 (2005-01), pages 37-43, XP002553200 ISSN: 1530-6984 * abstract figure 1 page 38, column 2 page 39, column 1, paragraph 2 - column 2, paragraph 1 page 42, column 2, paragraph 2</p> <p>-----</p>	<p>25,26, 113-116</p>
X	<p>US 2003/060718 A1 (ALAM ABU [US] ET AL) 27 March 2003 (2003-03-27)</p> <p>paragraphs [0048] - [0051] example 4 claims 52-55,66-69</p> <p>-----</p>	<p>1-3,7-9, 25, 54-57, 59-62, 67-69, 113</p>
E	<p>WO 2008/127880 A1 (ETHICON ENDO SURGERY INC [US]; DUNKI-JACOBS ROBERT J [US]; YOUSEPH YAZ) 23 October 2008 (2008-10-23)</p> <p>paragraphs [0025] - [0029], [0032], [0050], [0055], [0057], [0058] claims</p> <p>-----</p>	<p>1-10,25, 30, 54-72, 74-80, 82-87, 113,116</p>
E	<p>US 2008/319307 A1 (VOEGELE JAMES W [US] ET AL) 25 December 2008 (2008-12-25)</p> <p>paragraphs [0003], [0025], [0027], [0028]; claims</p> <p>-----</p> <p style="text-align: center;">-/--</p>	<p>1-3, 54-57, 61,62</p>

## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2008/060045

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 2006/110733 A2 (ETHICON ENDO SURGERY INC [US]; VOEGELE JAMES W [US]; GILL ROBERT P [US] 19 October 2006 (2006-10-19)</p> <p>paragraphs [0206], [0211], [0214], [0228], [0230] claims 43,58-60</p> <p>-----</p>	<p>1-10, 25-27, 30, 74-87, 89, 113-116, 118-128</p>
A	<p>EP 1 310 206 A2 (ETHICON ENDO SURGERY INC [US]) 14 May 2003 (2003-05-14)</p> <p>paragraph [0046]</p> <p>-----</p>	<p>1-10, 25-27, 30, 74-87, 89, 113-116, 118-128</p>
A	<p>EP 1 759 628 A1 (OLYMPUS CORP [JP]; OLYMPUS MEDICAL SYSTEMS CORP [JP]) 7 March 2007 (2007-03-07)</p> <p>paragraph [0039]</p> <p>-----</p>	<p>1-10, 25-27, 30, 74-87, 89, 113-116, 118-128</p>
X	<p>US 2004/101822 A1 (WIESNER ULRICH [US] ET AL) 27 May 2004 (2004-05-27) cited in the application</p> <p>paragraphs [0036], [0041], [0043], [0068], [0070] claims 38,39,41,42,50,54 examples 1,2</p> <p>-----</p>	<p>28,29, 88,117, 129-132, 134-146</p>
X	<p>YI D K ET AL: "Silica-coated nanocomposites of magnetic nanoparticles and quantum dots" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY 20050413 US, vol. 127, no. 14, 13 April 2005 (2005-04-13), pages 4990-4991, XP002563780 ISSN: 0002-7863 page 4990, column 1, lines 1-13 Scheme 1 figure 2</p> <p>-----</p> <p style="text-align: center;">-/--</p>	<p>28,117, 129-132, 134,135</p>

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2008/060045

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>LU CHEN-WEN ET AL: "Bifunctional magnetic silica nanoparticles for highly efficient human stem cell labeling." NANO LETTERS JAN 2007, vol. 7, no. 1, January 2007 (2007-01), pages 149-154, XP002563781 ISSN: 1530-6984 * abstract</p>	28,117, 129-132, 134,135
X	<p>WO 2006/102307 A2 (UNIV LOUISVILLE RES FOUND [US]; KANG KYUNG AIH [US]; SHI DONGLU [US]) 28 September 2006 (2006-09-28) page 5, lines 14-25 page 7, lines 13-14 page 11, lines 21-23 page 12, line 1 - page 13, line 10 figure 1 claims</p>	28,29, 88,117, 129-146
X	<p>US 2002/186921 A1 (SCHUMACHER LYNN C [CA] ET AL) 12 December 2002 (2002-12-12)</p> <p>paragraph [0002] - paragraph [0004] paragraph [0012] - paragraph [0022] paragraph [0032] - paragraph [0051] figures 1-4</p>	1,12, 14-16, 90,91, 93-103
X	<p>WO 2006/086578 A1 (ALFRED E MANN INST BIOMED ENG [US]; LOEB GERALD E [US]; GEORGE THOMAS) 17 August 2006 (2006-08-17)</p> <p>paragraph [0019] - paragraph [0028] paragraph [0038] - paragraph [0039] figures 1-3</p>	11,14, 15,90, 94-96, 98-100, 102
A	<p>US 2002/115922 A1 (WANER MILTON [US] ET AL) 22 August 2002 (2002-08-22)</p> <p>paragraph [0035] - paragraph [0041] figures 1,9</p>	12,13, 91,92, 103,104
A	<p>DE 10 2005 041271 A1 (ZEISS CARL MEDITEC AG [DE]; ZEISS CARL JENA GMBH [DE]) 1 March 2007 (2007-03-01) paragraph [0132] - paragraph [0133] figure 2</p>	12,13, 91,92, 103,104
A	<p>US 2005/096509 A1 (OLSON GREG [US]) 5 May 2005 (2005-05-05) paragraph [0002] paragraph [0014] - paragraph [0017] paragraph [0026]</p>	15,94, 98-100



## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

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Continuation of Box II.1

Claims Nos.: 17-24, 32, 50-53, 105-112(completely); 1-10, 27, 29, 30, 54-89, 118-128, 136-146(partially)

Remark concerning claims 1-10, 27, 29, 30, 54-89, 118-128, 136-146 related to inventions 1 and 3. Claims 27, 72, 118-128 relates to methods of surgery. Claims 1-10, 29, 30, 54-71, 73-89, comprise a step of administration which might be considered as being of surgical nature. Claims 29, 136-146 relates to methods of treatment by therapy. Claims 82-89 relates to a diagnostic method performed on the human/animal body. For the assessment of said claims on the question whether they are patentable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a product, in particular substances or compositions for use in a first or further medical treatment. The examination of the patentability of present claims 1-10, 27, 29, 30, 54-89, 118-128, 136-146 has been made assuming that they would be reformulated according to EPO practice when entering into the regional phase. Excluded subject-matter related to invention 2. Claims 17-24 a surgical method. Claims 32 and 50-53 method for viewing nanoparticles in a body lumen comprising a surgical step of inserting the distal end of an endoscope into a body lumen. Claim 105 a surgical method. It is pointed out that no unified criteria exist within the PCT contracting states as to what subject-matter is considered to fall under the provisions of Rules 39.1(iv) and 67.1(i) PCT, in particular what subject-matter may be considered as industrially applicable or not. In the present case, the claimed subject-matter of method claims 17-24 and 105 may, during prosecution in the regional and national phase, be considered to be surgical, and therefore, not acceptable under the applicable law.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2008/060045

## 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:  
see FURTHER INFORMATION sheet PCT/ISA/210
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:

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 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.:

### 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.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

## 1. claims: 1-10, 25-27, 30, 54-87, 89, 113-116, 118-128

A method for locating, marking or illuminating tissue with the means of fluorescent nanoparticles as mentioned in claims 1 or 54;

A medical composition comprising a fluorescent nanoparticle having a core containing at least one dye adapted to emit at a first frequency, and at least one dye adapted to emit light at a second frequency that differs from the first frequency, and a biocompatible shell surrounding the core;

A surgical method comprising delivering at least one fluorescent nanoparticle to tissue, delivering visible light to the tissue to cause a first dye contained within the at least one fluorescent nanoparticle to emit visible light, and delivering invisible light to the tissue to cause a second dye contained within the at least one fluorescent nanoparticle to emit invisible light;

A method for identifying tumour passage into the sentinel lymph node according to claims 30 or 74;

A method for identifying the spread of cancerous cells according to claim 82.

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## 2. claims: 11-24, 90-112

A medical device according to claim 11;

A surgical method for positioning a medical device containing at least one fluorescent nanoparticle;

An endoscopic adaptor for viewing fluorescent nanoparticles according to claim 31;

A method for viewing fluorescent nanoparticles according to claim 32.

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## 3. claims: 28, 29, 88, 117, 129-146

A medical composition comprising a fluorescent nanoparticle having a core containing at least one fluorescent dye, a biocompatible shell surrounding the core, and a magnetic material located in at least one of the core and the shell;

A method for treating tissue, comprising:

delivering at least one fluorescent nanoparticle to tissue, and

delivering energy to tissue to locate at least one fluorescent nanoparticle to cause a magnetic material in the at least one fluorescent nanoparticle to deliver heat to tissue.

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## 4. claims: 31, 33-49

Endoscope adaptor for attaching a filter to the eyepiece of

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

an endoscope and method of viewing fluorescent  
nanoparticles.

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## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2008/060045

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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Information on patent family members

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