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(54) Title: COMPOSITION FOR LABELING AND VISUALIZING GRAFTS IN MAGNETIC MRI AND X-RAY FLUROSCOPY, AND USE THEREOF

(57) Abstract: The present invention concerns a composition for labeling and visualizing tissues, grafts, organs or vasculature in MRI and/or X-ray fluoroscopy, wherein said composition comprises magnetic metal oxide nanoparticles and radiopaque nanoparticles, and uses of the composition.

Composition for labeling and visualizing grafts in magnetic MRI and X-ray fluoroscopy, and use thereof

The present invention concerns compositions and methods for labeling or marking grafts such as tissues, organs, blood vessels or vasculature (veins, arteries, capillaries) and the like such that the labeled entity becomes visible in magnetic resonance imaging (MRI) and/or in X-ray fluoroscopy. The present invention further comprises the use of the nanoparticle compositions for labeling tissue grafts, organs, blood vessels, vein grafts, artery grafts, capillaries or tissues for rendering them visible in MRI and X-ray fluoroscopy.

Medical imaging techniques such as X-ray fluoroscopic imaging, computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) are among the most important and versatile methods which are used by clinicians today for diagnostic purposes. Beyond that, physicians also use medical imaging techniques in visualizing the guidance and placement of medical devices such as guidewires, catheters, stents, biopsy needles or the like within a patient's body. For example, X-ray fluoroscopy is the preferred imaging modality for cardiovascular interventional procedures because of its temporal and spatial resolution. However, X-ray fluoroscopy has some drawbacks such as the patient's exposure to ionizing radiation.

MRI is a medical imaging modality which does not use ionizing radiation and has the potential to supplant X-ray fluoroscopy. Moreover, MRI has greater soft tissue contrast than X-ray based imaging techniques. Beyond mere diagnostic purposes, interventional magnetic resonance (iMR) angiography as well as stent placements under MRI have been performed to demonstrate feasibility of MRI.

X-ray fluoroscopy is an imaging modality which utilizes ionizing X-ray radiation. Visualization and tracking of medical devices under X-ray fluoroscopy is

accomplished either by the devices inherent absorption of X-rays or by securing radiopaque markers to the medical device, intermittent injection of radiopaque material in the veins. Radiopaque material absorbes X-rays and thereby creates contrast within the image, and thus is visible.

In MRI, the detection of atomic nuclei utilizes magnetic fields and radio-frequency radiation rather than ionizing radiation. Signal intensity is determined by longitudinal relaxation time (T1), transverse relaxation time (T2), proton density and flow. MRIs provide a distribution map of protons and their properties in organs and tissues. MRI contrast agents usually shorten either the T1 relaxation time or the T2 relaxation time.

There is a medical demand in some particular cases to make an *"'in vivo"* staining of various parts of biological tissue in order to make them visible with X-ray angiography and/or magnetic resonance imaging (MRI) in case a second surgical intervention is needed. As an example the coronary artery bypass graft (CABG) is a surgical procedure used to divert blood around narrow or clogged coronary arteries. This surgical procedure is performed in order to improve the blood flow and oxygen supply to the heart. Every year approximately 800,000 CABGs are performed worldwide, and nearly 80% of those needing the operation are men over the age of 60. CABG involves taking a blood vessel from another part of the body, usually the chest or leg, and using it as a graft. The grafts replace any hardened or narrowed arteries in the heart. A surgeon will attach the new blood vessel to the coronary artery above and below the narrowed area or blockage.

CABG is often done to supply the cardiac muscle with the necessary blood flow and reduce the risk of having a myocardial infarction. CABG can be carried out more than once and repeated in the future if necessary, for example, if a bypass graft has become blocked. Due to this reason there a clear demand to label the bypass grafts and to provide them with a marking system for different medical imaging modalities, especially for X-ray fluoroscopic imaging and for magnetic resonance imaging (MRI).

It was an object of the present invention to provide a marking system for labeling tissue grafts, organs, vasculature, tissues and the like for *in-vivo* permanent visualization in X-ray fluoroscopy and MRI.

The object of the present invention is contemplated by providing magnetic MRI and X-ray responsive ink compositions and its use for tissue-graft marking applications.

According to the present invention, a MRI and X-ray responsive composition is provided, said ink composition comprises metal oxide nanoparticles and colloidal metallic nanoparticles in a pre-dispersion combined with an aqueous carrier composition, wherein the preferred metal oxide pre-dispersion contains iron oxide nanoparticles as MRI contrast agent and wherein the preferred colloidal metallic consists of colloidal gold as X-ray contrast agent. The hybrid magnetic MRI and X-ray responsive ink contains at least one adjuvant, preferably as surfactant to aid the dispersion and the stabilization of the metal oxide/metal nanoparticles. The ink composition contains at least one responsive material as nanoparticles dispersed within a carrier and at most both type of nanoparticles thus as a result a hybrid responsive ink is created.

In the broadest sense, the present invention comprises magnetic MRI and X-ray responsive ink compositions for permanent visualization and positioning of any tissue-graft or vasculature (vein, artery, capillary) using magnetic resonance imaging and X-ray fluoroscopic imaging. In a preferred embodiment, the present invention concerns an imprinting MRI and X-ray responsive ink composition containing colloidal gold as attached onto glass beads, gold nanoparticles coated iron oxide nanoparticles as dispersed within an aqueous sterile carrier.

The ink compositions of the present invention contain at least one either MRI or X-ray responsive material as nanoparticles dispersed within a carrier and at

most both type of nanoparticles and as a result a hybrid responsive ink is created. In some cases, in order to improve the stability of these systems, some dispersant compounds are needed to be added.

Various attempts have been made to address the problem of retaining the magnetic pigment or particulate matter in suspension. For example, U.S. Patent Nos. 5,026,427 and 5,656,071 each suggest the use of specific dispersants to improve the stability of the suspension.

The U.S. Patent No. 5,656,071 patent discloses an ink composition including a polymeric dispersant to maintain a metal oxide in solution and a co-solvent mixture of 1,3-propanediol or 1,4-butanediol with a second solvent selected from polyethylene glycol-type materials and polyol/polyalkylene oxide condensates.

The other patents involve the use of colloidally dispersed magnetite in conjunction with a specified dispersant component. U.S. Patent No. 5,240,626 discloses an ink including colloidally dispersed magnetite particles coated with a carboxy compound-type anti-agglomeration agent and a dispersing aid.

Another strategy of addressing the suspension stability issue is disclosed in U.S. Patent No. 4,026,713 by means the use of a combination of surfactants and glycerol to make stable magnetic inks.

The composition of the present invention for labeling grafts to render the graft visible in MRI and X-ray fluoroscopy comprises magnetic metal oxide nanoparticles and radiopaque nanoparticles. In a preferred embodiment, the metal oxide of the magnetic metal oxide nanoparticles is selected from the group consisting of gadolinium oxide, dysprosium oxide, terbium oxide, nickel oxide, iron oxide, magnesium oxide, cobalt oxide and mixtures thereof. The magnetic metal oxide of the most preferred metal oxide nanoparticles is magnetite (Fe_3O_4).

The term "magnetic" also refers to particles comprising paramagnetic material. Paramagnetic material possesses magnetism only in the presence of an externally applied magnetic field, and does not retain any magnetization in the absence of an externally applied magnetic field. However, paramagnetic materials are attracted to magnetic fields and hence have a relative magnetic permeability of greater than one, i. e. a positive magnetic susceptibility. Suitable paramagnetic iron oxides include FeO, Fe_2O_3 and Fe_3O_4.

The magnetic metal oxide nanoparticles have a diameter of at least 100 nm, preferably at least 200 nm, more preferably at least 400 nm, and most preferably at least 500 nm. The diameter of the magnetic metal oxide nanoparticles is less than 2,000 nm, preferably less than 1,000 nm and more preferably less than 800 nm.

The radiopaque nanoparticles of the composition comprise or consist of a material that is selected from the group consisting of gold, platinum, tungsten, tantalum, rhenium, bismuth, silver, iridium, and mixtures thereof. The preferred material is colloidal gold.

The radiopaque nanoparticles have a diameter of at least 5 nm, preferably at least 10 nm and more preferably at least 20 nm. The diameter of the radiopaque nanoparticles is less than 100 nm, preferably less than 50 nm, and more preferably less than 40 nm.

In a preferred embodiment, the composition of the present invention further comprises a carrier which is selected from the group comprising water and water-soluble organic solvents, wherein the preferred water-soluble organic solvents are selected from the group comprising saline solutions, glycerol, propylenglycol and polypropylenglycol.

The saline solution may contain a salt selected from the group comprising sodium chloride, sodium phosphate, sodium dihydrogen phosphate, disodium hydrogen phosphate, potassium chloride, potassium phosphate, potassium dihydrogen phosphate, dipotassium hydrogenphosphate, calcium chloride and magnesium chloride, or mixtures thereof.

In a preferred embodiment the composition of the present invention further comprises an adjuvant, preferably selected from the group comprising biodegradable polymers, ionic surfactants and non-ionic surfactants.

The biodegradable polymer may be selected from the group comprising alginates, polylactic acid, polyvinyl alcohols, poly glycolic acids, gelatin, and mixtures thereof.

The non-ionic surfactant may be selected from the group comprising monoalkyl glycerol ester, dialkyl glycerol ester, trialkyl glycerol ester, and mixtures thereof, and wherein the fatty acid residues of the preferred monoalkyl glycerol esters, dialkyl glycerol esters and trialkyl glycerol esters are selected from the group comprising lauric acid, myrisitc acid, palmitic acid, palmitoleic acid, stearic acid, oleic acid, linoleic acid, gamma-linolenic acid, arachidic acid, arachidonic acid, and mixtures thereof.

The ionic surfactant is selected from the group comprising sorbitan monolaurate (Polysorbate 20, Span® 20, Tween® 20), sorbitan monopalmitate (Polysorbate 40, Span® 40), sorbitan monostearate (Polysorbate 60, Span® 60), sorbitan monooleate (Polysorbate 80, Span® 80, Tween® 80), and mixtures thereof.

In a preferred embodiment, the magnetic nanoparticles further comprise a polymer coating, preferably a polymer coating wherein the polymer comprises or consists of polyvinylpyrrolidone.

The radiopaque nanoparticles are embedded within the shell of the magnetic nanoparticles in a preferred embodiment of the composition.

In another preferred embodiment, the magnetic nanoparticles and/or the radiopaque nanoparticles comprise antibodies, preferably antibodies against collagen, which are conjugated to the nanoparticles.

The composition of the present invention is understood as at least one suspension of nanoparticles in a carrier fluid or embedded in a film such that the composition can be applied as an "ink" or "film" into the site or tissue graft to be marked. In a preferred embodiment, the composition of the present invention consists of a single suspension comprising the magnetic metal oxide nanoparticles and the radiopaque nanoparticles. This ink composition is designated multi-functional ink, because it provides visualization in both X-ray fluoroscopy and MRI. In the multi-functional ink it is preferred that the amount of magnetic metal oxide nanoparticles is equal to or greater than tha amount of radiopaque nanoparticles.

In another preferred embodiment, the composition of the present invention comprises two suspensions, wherein the magnetic metal oxide nanoparticles are present in one suspension, and the radiopaque nanoparticles are provided in a separate suspension. Thus the composition may comprise two types of suspension. The first suspension comprises radiopaque nanoparticles but no magnetic metal oxide nanoparticles, whereas the second suspension

comprises magnetic metal oxide nanoparticles, but no radiopaque nanoparticles.

The composition of the present invention shall be sterile. It can be sterilized by methods known to the skilled artisan.

The ink composition of the present invention can be incorporated into the structure of a graft prior to transplantation or implantation, and is intended to remain in the application area for long term.

The graft may be any organ or tissue that was or is intended to be explanted from a human or animal body to be implanted into another human or animal body. The term "graft" also comprises blood vessels such as arteries, veins and capillaries. The term "graft" also refers to tissues, organs and blood vessels that were not explanted from a human or animal body, but grown in vitro only. "Grown in vitro only" refers to tissue engineering wherein cells are propagated and differentiated in culture such that a desired tissue can be obtained without the need of surgical intervention prior to implantation of the graft.

The grafts and blood vessels which are provided with the composition of the present invention can be visualized in X-ray fluoroscopy and/of MRI due to their labeling with the composition. The labeled graft can be easily tracked and visualized "in vivo" in a patient's body.

Therefore, the present invention also pertains to methods of labeling or marking grafts for their visualization in MRI and X-ray fluoroscopy. The method of labeling or marking grafts comprises application of the composition of the present invention to the site or tissue graft to be marked. Using the multi-functional ink composition, a single marking element is sufficient to render the labeled organ, tissue or graft visible in MRI and X-ray fluoroscopy. In the method wherein a composition is used which comprises two suspension, the

first suspension first suspension comprising radiopaque nanoparticles but no magnetic metal oxide nanoparticles, and the second suspension comprising magnetic metal oxide nanoparticles, but no radiopaque nanoparticles, it is necessary to provide the organ, tissue or graft to be labeled with two marking elements, a first marking element comprising radiopaque nanoparticles but no magnetic metal oxide nanoparticles, and a second marking element comprising magnetic metal oxide nanoparticles, but no radiopaque nanoparticles.

The present invention will be more easily understood with reference to the following examples, which however are intended to illustrate the invention only and are not to be construed to limit the scope of the invention, and in the examples quantities of components are expressed in parts by weight.

EXAMPLE 1

compound	%-wt.
Iron oxide (Bayferrox 318) (LANXESS Deutschland GmbH):	5.000
Glycerol 87% (aqueous solution):	25.000
Polyethylenglycol (PEG) 400:	20.000
Polyvinylpyrrolidone (PVP):	0.500
Sterile water:	49.495
Tween 20:	0.005

EXAMPLE 2

compound	%-wt.
Silica coated iron oxide (Bayferrox 318) (LANXESS Deutschland GmbH):	2.0
Colloidal gold nanoparticles (10 - 90 nm) (as synthesyzed at MagnaMedics):	4.0
Glycerol 87% (aqueous solution):	20.0
Polyethylenglycol (PEG) 400:	20.0
Polyvinylpyrrolidone (PVP):	0.5
Sterile water:	49.4
Tween 20:	0.05
Glycerol Monooleate :	0.05

EXAMPLE 3

compound	%-wt.
Colloidal gold nanoparticles (10-90 nm) embeded in porous glass (2 -10 µm; as synthesized at MagnaMedics):	7.50
Glycerol 87% (aqueous solution):	15.00
Polyethylenglycol (PEG) 400:	15.00
Polyvinylpyrrolidone (PVP):	2.50
Sterile water:	59.40
Tween 20:	0.05
Glycerol Monooleate :	0.05

Claims

1. A composition for visualizing tissues, tissue grafts, organs or vasculature in MRI and/or X-ray fluoroscopy, said composition comprising magnetic metal oxide nanoparticles and radiopaque nanoparticles.

2. The composition according to claim 1, characterized in that the magnetic metal oxide nanoparticles comprise a metal oxide selected from the group consisting of gadolinium oxide, dysprosium oxide, terbium oxide, nickel oxide, iron oxide, magnesium oxide, cobalt oxide and mixtures thereof.

3. The composition according to claim 1 or 2, characterized in that the magnetic metal oxide nanoparticles comprise magnetite (Fe_3O_4).

4. The composition according to any one of the preceding claims, characterized in that the magnetic metal oxide nanoparticles have a diameter of at least 100 nm, preferably at least 200 nm, more preferably at least 400 nm, and most preferably at least 500 nm.

5. The composition according to any one of the preceding claims, characterized in that the magnetic metal oxide nanoparticles have a diameter of less than 2,000 nm, preferably of less than 1,000 nm and more preferably of less than 800 nm.

6. The composition according to any one of the preceding claims, characterized in that the radiopaque nanoparticles comprise a material

that is selected from the group consisting of gold, platinum, tungsten, tantalum, rhenium, bismuth, silver, iridium, and mixtures thereof, preferably colloidal gold.

7. The composition according to any one of the preceding claims, characterized in that the radiopaque nanoparticles have a diameter of at least 5 nm, preferably at least 10 nm and more preferably at least 20 nm.

8. The composition according to any one of the preceding claims, characterized in that the radiopaque nanoparticles have a diameter of less than 100 nm, preferably less than 50 nm, and more preferably less than 40 nm.

9. The composition according to any one of the preceding claims, characterized in that the composition further comprises a carrier selected from the group comprising water and water-soluble organic solvents, wherein the preferred water-soluble organic solvents are selected from the group comprising saline solutions, glycerol, propylenglycol and polypropylenglycol.

10. The composition according to any one of the preceding claims, characterized in that the composition further comprises an adjuvant, preferably selected from the group comprising biodegradable polymers, surfactants and non-ionic surfactants.

11. The composition according to claim 10, characterized in that the biodegradable polymer is selected from the group comprising alginates,

polylactic acid, polyvinyl alcohols, poly glycolic acids, gelatin, and mixtures thereof.

12. The composition according to claim 10, characterized in that the surfactant is selected from the group comprising monoalkyl glycerol ester, dialkylglycerol ester, trialkylglycerol ester, and mixtures thereof, and wherein the fatty acid residues of the preferred monoalkyl glycerol esters, dialkylglycerol esters and trialkylglycerol esters are selected from the group comprising lauric acid, myrisitc acid, palmitic acid, palmitoleic acid, stearic acid, oleic acid, linoleic acid, gamma-linolenic acid, arachidic acid, arachidonic acid, and mixtures thereof.

13. The composition according to claim 10, characterized in that the non-ionic surfactant is selected from the group comprising sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate, and mixtures thereof.

14. The composition according to any one of the preceding claims, characterized in that the magnetic nanoparticles further comprise a polymer coating.

15. The composition according to claim 14, characterized in that the polymer of the polymer coating comprises polyvinylpyrrolidone.

16. The composition according to any one of the preceding claims, characterized in that the radiopaque nanoparticles are embedded within the shell of the magnetic nanoparticles.

17. The composition according to any one of the preceding claims, characterized in that the magnetic nanoparticles and/or the radiopaque nanoparticles comprise antibodies.

18. The composition according to claim 17, characterized in that the antibodies are antibodies against collagen.

19. The composition according to any one of the preceding claims, characterized in that the composition is sterile.

20. Use of a composition according to any one of the preceding claims for labeling and/or visualizing an organ, a tissue, a graft or vasculature such as a vein graft or artery graft for in vivo in MRI and X-ray fluoroscopy.

21. Use according to claim 20, wherein the organ, tissue, graft or vasculature was produced in-vitro.

22. A method of labeling and visualizing an organ, tissue, graft or vasculature in MRI and/or X-ray fluoroscopy, characterized in that the organ, tissue, graft or vasculature is provided with the composition according to any one of claims 1 to 19.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/008789

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K49/04 A61K49/18
ADD.

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)
A61K

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, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009/263331 A1 (WU AI-GUO [US] ET AL) 22 October 2009 (2009-10-22) claims 1,2,8 paragraphs [0006], [0007], [0096], [0101], [0157] - [0162], [0181] - [0186], [0238]	1-6,16, 17,19-22
X	WANG XIANXIANG ET AL: "Preparation of Fe3O4@Au nano-composites by self-assembly technique for immobilization of glucose oxidase" CHINESE SCIENCE BULLETIN, vol. 54, no. 7, April 2009 (2009-04), pages 1176-1181, XP002577889 ISSN: 1001-6538 abstract page 1178, column 1	1-3, 6-10,16

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[X] Further documents are listed in the continuation of Box C.

[X] 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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 April 2010	27/04/2010

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/008789

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FANG C -L ET AL: "Monodisperse [alpha]-Fe2O3@SiO2@Au core/shell nanocomposite spheres: Synthesis, characterization and properties" NANOTECHNOLOGY 20080326 GB LNKD- DOI:10.1088/0957-4484/19/12/125601, vol. 19, no. 12, 26 March 2008 (2008-03-26), XP002577891 abstract page 3, column 1 page 7, section "Conclusion"	1,2,4-7, 16
X	TANG D ET AL: "Magnetic nanogold microspheres-based lateral-flow immunodipstick for rapid detection of aflatoxin B2 in food" BIOSENSORS AND BIOELECTRONICS, ELSEVIER BV, NL LNKD- DOI:10.1016/J.BIOS.2009.07.030, vol. 25, no. 2, 15 October 2009 (2009-10-15), pages 514-518, XP026600460 ISSN: 0956-5663 [retrieved on 2009-08-04] abstract page 515, column 1 - column 2, paragraph 1	1,2, 6-10,14, 16,17
X	WO 2005/046733 A1 (PHILIPS INTELLECTUAL PROPERTY [DE]; KONINKL PHILIPS ELECTRONICS NV [NL) 26 May 2005 (2005-05-26) page 4, lines 15-30 page 9, line 22 - page 10, line 19 page 10, line 24 - page 12, line 23 examples 1,2	1,2,4,5, 7-10,14, 17,19-22
Y	PARK YEON-SU ET AL: "Concentrated colloids of silica-encapsulated gold nanoparticles: colloidal stability, cytotoxicity, and X-ray absorption" JOURNAL OF NANOSCIENCE AND NANOTECHNOLOGY, AMERICAN SCIENTIFIC PUBLISHERS, US LNKD- DOI:10.1166/JNN.2007.601, vol. 7, no. 8, 1 August 2007 (2007-08-01), pages 2690-2695, XP008095054 ISSN: 1533-4880 abstract	1-22

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/008789

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/008789

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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