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(54) Title: IMPLANT FOR TISSUE ENGINEERING

(57) Abstract: The present invention relates to uses of resorbable medical implants that are metallic or semi-metallic, to produce soft tissues, membranous tissues, organs or organ parts within the body by fibrosis. The present invention further relates to such uses when the implants are made of specified alloys or metals, e.g. magnesium and its alloys. The present invention further relates to such uses when the implant is surface modified. The present invention further relates to such uses when the implant is pre-implanted at another part of the body before implantation into the target site.



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## IMPLANT FOR TISSUE ENGINEERING

## CROSS-REFERENCE TO A RELATED APPLICATION

The subject application claims the benefit of U.S. Provisional Application Serial  
5 No. 61/021,709, filed January 17, 2008, which is incorporated herein by reference in its  
entirety.

## FIELD OF THE INVENTION

This invention relates generally to the use of resorbable metallic medical implants in  
10 the generation and/or regeneration of soft tissues, membranous tissues, or organs. The  
implant may be surface modified and/or pre-implanted into another part of the body  
before implantation into the target site.

## BACKGROUND OF THE INVENTION

15

Resorbable (alternatively called absorbable, degradable, bioabsorbable,  
bio-absorbable, bioresorbable, bio-resorbable, biodegradable, bio-degradable,  
biocorroddible or bio-corroddible) implants have to date been generally prepared from  
polymers. Unfortunately, the use of polymers in implants has two serious disadvantages.  
20 First, plasticizers harmful to the body can be released from the implant. Furthermore,  
the mechanical properties of the polymers are often unsatisfactory.

Since the beginning of the 20th century it has been known that implants made of  
magnesium and its alloys are easily absorbable and biocompatible. The absorbability in

the body is based on the corrosion of magnesium in saline immersions. Its essential character for the body's functions and the elimination of excess doses via the urinary tract qualify magnesium as a basic implant substance with a high level of physical and chemical biocompatibility.

5       The average distribution of magnesium in the body mass is 470 mg/kg, the recommended daily dose is 200 to 300 mg/d MgSO<sub>4</sub>. Magnesium also has an antiarrhythmic effect and lowers blood pressure and sensitivity to pain. The maximum dose for short-term infusion in a human weighing 75 kg is 57.6 mg pure magnesium. Blood plasma contains, for example, 107 mMol/l, and gastric juice contains 160 mval/l of  
10 magnesium chloride ions.

The developments in the first Mg period before World War Two (Verbrugge 1933, McBride 1938, Lambotte 1932) did not result in alloys that corrode sufficiently slowly. The developments in the second Mg period during the Cold War (Stroganov, DE-OS 1 953 241) provided alloys with greater corrosion resistance whose cadmium additive was  
15 intended to accelerate bone fusion, but whose toxicity substantially limited its use.

Other more recent magnesium alloys contain rare earth metals, preferably in addition to lithium. With these alloys, the absorption of the implant is considerably delayed, but with these materials there is still an appreciable development of hydrogen and gas pockets in the tissue. For many applications, the rate of corrosion of the alloys  
20 containing rare earth metals is still too high, since the stability losses associated with absorption occur too early in the healing or tissue formation process.

The use of surface modifications on such resorbable metallic implants has been mentioned in US2005079088, which aims to use surface modification to improve mechanical and corrosion properties.

It is difficult to culture cells onto resorbable metallic material in a physiologically relevant environment because the ions released and/or the change in pH is likely to harm cells. For example, it is known that the alkaline environment produced by corroding magnesium can kill cells.

However, even if the modification were considered successful, the application would still be limited to hard tissues. Application to soft tissues, membranous tissues, organs or organ parts would be unsuitable because of the perceived rigidity of magnesium or other metallic materials, regardless of the resorbability.

Therefore, the use of resorbable metallic materials for the application on soft tissues, membranous tissues or organs especially for the generation or regeneration of such tissues is a largely unexplored field. Such generation or regeneration of tissues with engineering technique may also be called "tissue engineering".

From experiments of our team, a tough, dense layer of soft tissue is formed on a piece of magnesium implanted subcutaneously into a mouse. According to literature (Witte F, Ulrich H et. al. (2007) J Biomed Mater Res 81A: 748-756), this layer should be cell-infiltrated collagen, produced by "foreign body response" in the form of fibrosis on biomaterials.

The principle of fibrosis induction had actually been used in the 1980s (Mendes DG, Soudry M, et. al. (1988) Clinical Orthopaedics and Related Research 234:291-295) for the regeneration of ligaments, although without much popularity, and the bio-material

used was carbon fiber. Carbon fiber is too stiff, and it does not have the required bioactivity. Either of these factors is sufficient to create the unpopularity of such prior art.

Also intravascular fibrosis-inducing agents are used by some investigators to generate biological tissues by fibrosis for the purpose to facilitate cell anchoring.

5

#### BRIEF SUMMARY OF THE INVENTION

The subject invention provides an innovative use of metallic and semi-metallic implants for the generation and/or regeneration of soft tissues and/or membranous tissues and/or organs. In accordance with the subject invention, the effect of self-induced collagen formation (on a piece of metallic or semi-metallic implant that can be absorbed  
10 by the body) by fibrosis is used to induce the natural self-production of such tissue in the body.

The tissues to which the materials and methods of the subject invention can be applied include, but are not limited to, ligament, tendon, periodontal fiber, skin, internal  
15 organs, muscles and vessels, but excluding bone and cartilage.

In one aspect, the present invention pertains to the use of metallic or semi-metal materials in resorbable medical implants, for an application of soft tissues such as ligaments, tendons and periodontal fibers.

In another aspect, the present invention pertains to the use of metallic or  
20 semi-metallic materials in resorbable medical implants, for the generation and/or regeneration of organs and membranous tissues, but excluding bone.

In a specific embodiment, the present invention pertains to the use of metallic or semi-metallic materials in resorbable metallic implants, for the generation and/or regeneration of soft tissue for hernia correction.

One or more of the following features may be used to further characterize the subject invention: the implant is, or comprises, magnesium; the implant is, or comprises a magnesium alloy; the implant is, or comprises tungsten; the implant is, or comprises a tungsten alloy; the implant is, or comprises zinc; the implant is, or comprises a zinc alloy; the implant is, or comprises aluminum; the implant is, or comprises an aluminum alloy; the implant is, or comprises iron; the implant is, or comprises an iron alloy; the implant is, or comprises steel; the implant is, or comprises manganese; the implant is, or comprises a manganese alloy; the implant is, or comprises calcium; the implant is, or comprises a calcium alloy; the implant is, or comprises zirconium; the implant is, or comprises a zirconium alloy; the implant is, or comprises silicon; the implant is, or comprises a silicon alloy.

In a further aspect, the implant may comprise a non-metallic solid. The non-metallic solid may be in one or more of the following forms: powder, fiber, film, crystal, nanocrystal, nanoparticle, nano-film or nano-fiber. More than one chemical composition of non-metallic solid can be present. The non-metallic solid can be one or more of the following elements or compounds: carbon, carbonate compound, phosphate compound, non-metallic compound of metallic element, non-metallic compound of semimetallic element, polymer, anticoagulant, or their combinations.

The implant can be surface modified in accordance with one or more of the following processes: oxidation, nitriding, solution immersion, anodization, deposition,

electrolytic deposition, precipitation, immersion into molten metal, immersion into molten alloy, immersion into molten semi-metal, immersion into collagen, immersion into organic material, plasma immersion, plasma deposition, plasma spraying, flame spraying, chemical vapour deposition, physical vapour deposition, powder deposition, powder immersion, plasma immersion, plasma immersion ion implantation, electric arc deposition, painting, coating, heat treatment, cold treatment, thermomechanical processing, polishing, diffusion alloying, melt alloying, incubation in cell culture condition rapid prototyping, selective laser sintering, solution spraying, particulate leaching, etching, evaporation, sublimation, or sterilization; and the surface modification may cover the whole surface or only a portion of it.

In a further aspect, the solution immersion is further characterized in that it comprises one or more of the following: alkali treatment, hot alkali treatment, phosphate buffered saline immersion, cell culture medium immersion, body fluid immersion, simulated body fluid immersion, serum immersion, phosphate solution immersion, acid treatment, immersion into collagen solution, immersion into organic material solution, immersion into growth factor solution, immersion into solution containing antibiotics, immersion into synthetic growth factor solution, immersion into solution containing synthetic antibiotics, immersion into extracellular matrix solution, immersion into simulated extracellular matrix solution, immersion into growth factor solution with mammal cells, immersion into solution containing antibiotics and mammal cells, immersion into synthetic growth factor solution with mammal cells, immersion into solution containing synthetic antibiotics and cells, immersion into extracellular matrix solution with cells, immersion into simulated extracellular matrix solution with cells.

In a further aspect of the current invention, the implant may be implanted into a part of the body other than the ultimate target site before being retrieved and put at the target site of generation/regeneration.

5

#### BRIEF DESCRIPTION OF THE DRAWINGS

**Figure 1A-C:** Well-structured, tough, dense layer of soft tissue formed by fibrosis after subcutaneous implantation of an AM60B rod into a mouse; retrieved 1 month post-implantation. (slightly scratched; electron microscope photo taken under Stereoscan 440 SEM). Scale: 100x, 200x, 500x.

10

**Figure 2:** Giemsa-Eosin stained section of tissue around an AM50A implant of 2mm diameter, 3 months post-operation. Objective: 20x.

**Figure 3:** Photo illustrating the surface property of AM50A implants at 6-months post-operation with surrounding membranous tissue (note the gas bubbles).

**Figure 4:** Photo illustrating the surface property of 99.95% magnesium implants at 15 6-months post-operation with surrounding membranous tissue (note the gas bubbles).

**Figure 5:** Photo illustrating the surface property of AZ91D implants at 6-months post-operation with surrounding membranous tissue (note the gas bubble).

**Figure 6:** Fibrous tissue on AZ91D after 6-months post-op. Note the large gas bubble, and micron-sized tiny bubbles created due to the vacuum environment inside 20 Stereoscan 440 SEM. Glutaraldehyde treated, sputter-coated.

**Figure 7:** Subcutaneous pre-implantation before moving the implant to the target site of generation or regeneration.

**Figure 8:** Example of application for hernia correction.

**Figure 9:** Examples of specific shapes of implants according to the current

invention.

#### DETAILED DESCRIPTION OF THE INVENTION

In accordance with the subject invention, tissues produced by the process of fibrosis  
5 can be utilized to generate and/or regenerate soft tissues, membranous tissue, or organs  
within the body. Advantageously, the subject invention provides materials and methods  
for generating or regenerating such tissues with a biomaterial that has very high  
bioactivity and low toxicity, combined with good mechanical strength and favorable  
degradability profile.

10 The materials and methods of the subject invention can be used for tissue  
regeneration for various tissues including, but not limited to, ligaments and tendons,  
which are currently relying on costly and unreliable cell-based therapy, or the  
transplantation of such tissues removed from another part of the body.

The current invention exploits the phenomenon of fibrosis to generate or regenerate  
15 soft tissues, membranous tissues, organs or organ parts within the body. However, two  
applications, namely the generation and regeneration of cartilage and bones, are  
intentionally dedicated to the public.

"Fibrosis", "scarring", or "fibrotic response" refers to the formation of fibrous tissue  
or any excess production, accumulation or deposition of extracellular matrix components  
20 (including collagen and other biomolecules) with or without cell infiltration, in response  
to injury or medical intervention which includes biomaterial implantation, and is referred  
to as "fibrosis" hereafter. Therapeutic agents that promote fibrosis, which may be called  
"fibrosis-inducing agents," "scarring agents," "adhesion-inducing agent," "fibrosing

agent”, and the like, promote fibrosis through one or more mechanisms including: inducing or promoting angiogenesis, stimulating migration or proliferation of soft tissue or connective tissue cells (such as fibroblasts, smooth muscle cells, and vascular smooth muscle cells), inducing ECM production, and/or promoting tissue remodeling.

5 Other terms, as used herein, are defined as follows:

“Foreign body response” is defined as a reaction of biological tissue to any foreign material in the tissue. “Fibrosis” is one kind of foreign body response. “Foreign body response” in the form of fibrosis is traditionally considered an undesirable “side effect” because it is triggered by an inflammatory response. As a result, past researchers have  
10 failed to appreciate any positive aspects of cell-infiltrated collagen formation by fibrosis.

“Soft tissue” refers to tissues that connect, support, or surround other structures and organs of the body. Soft tissue includes muscles, tendons (bands of fiber that connect muscles to bones), fibrous tissues, fat, blood vessels, nerves, stroma, ligaments and  
15 synovial tissues other than ligament. Specifically, as used herein, it does not include cartilage or skin.

“Implant” as a noun is used herein at a broad sense, to include any material placed inside the body by any method other than ingestion or inhalation, or placed on the surface of an open wound. “Implant” as a verb refers herein to the process of putting the material  
20 inside the body by any method other than ingestion or inhalation.

“Membranous tissue” is used herein to mean any tissue of an animal that forms a sheet or sheath; membranous tissue commonly encloses or delimits a tissue, or divides an organ into separate compartments.

"Cardiovascular tissue" refers to any tissue of the cardiovascular system, and is exemplified to include blood vessels, capillaries, heart, blood vessel valves, and any membranous or non-membranous tissue of the cardiovascular system.

"Growth factor" refers to a substance that is effective to promote the growth of cells and which, unless added to the culture medium as a supplement, is not otherwise a component of the basal medium. Put another way, a growth factor is a molecule that is not secreted by cells being cultured (including any feeder cells, if present) or, if secreted by cells in the culture medium, is not secreted in an amount sufficient to achieve the result obtained by adding the growth factor exogenously. Growth factors include, but are not limited to, basic fibroblast growth factor (bFGF), acidic fibroblast growth factor (aFGF), epidermal growth factor (EGF), insulin-like growth factor-I (IGF-T), insulin-like growth factor-II (IGF-II), platelet-derived growth factor-AB (PDGF), vascular endothelial cell growth factor (VEGF), activin-A, bone morphogenic proteins (BMPs), insulin, cytokines, chemokines, morphogens, neutralizing antibodies, other proteins, and small molecules.

"Tissue or organ" is used herein to refer to any natural or engineered biological tissue or organ, including, but not limited to, vascularized tissues and avascular tissues, including musculoskeletal tissue, such as cartilage, menisci, muscles, ligaments and tendons, skin, cardiovascular tissue, such as heart valves and myocardium, neuronal tissue, periodontal tissue, glandular tissue, organ tissue, islets of Langerhans, cornea, ureter, urethra, breast tissue, and organs, such as pancreas, bladder, kidney, breast, liver, intestine, heart and sections or pieces thereof.

"Internal organ" herein refers to any organ as defined above, but excluding skin.

The term "resorbable" refers to the ability of materials to be broken down and/or absorbed by normal chemical, biochemical and/or physical processes such as erosion, dissolution, corrosion, degradation, hydrolysis, abrasion, fatigue etc, and their combinations.

5       The term "collagen" as used herein refers to all forms of collagen, including natural collagen and pro-collagen, or those that have been recombinantly produced, extracted, processed, or otherwise modified. Preferred collagens may be immunogenic or non-immunogenic, soluble or insoluble, and may be in the fibrillar or non-fibrillar form.

10       In one aspect, the present invention pertains to the use of a metallic or semi-metallic material as a resorbable medical implant, for an application of soft tissues such as ligaments, tendons and periodontal fibers. An application to ligament or tendon regeneration is specifically exemplified herein.

15       In another aspect, the present invention pertains to the use of a metallic or semi-metallic material as a resorbable medical implant, for generation and/or regeneration of organs and membranous tissues (but excluding cartilage, bone and skin). An application to organ wall and membranous tissues is specifically exemplified herein.

20       A "hernia" is a protrusion of an organ or part (as the intestine) through connective tissue or through a wall of the cavity (as of the abdomen) in which it is normally enclosed (Merriam-Webster Dictionary). In another aspect, the present invention pertains to the use of a metallic or semi-metallic material as a resorbable metallic implant, for generation and regeneration of soft tissue for hernia correction. An application to abdominal hernia is specifically exemplified herein.

In another aspect, the present invention pertains to the use of a metallic or

semi-metallic material as a resorbable medical material applied on the surface, for generation and/or regeneration of skin.

One or more of the following features may further define the invention: the implant is, or comprises, magnesium; the implant is, or comprises a magnesium alloy; the implant is, or comprises tungsten; the implant is, or comprises a tungsten alloy; the implant is, or comprises zinc; the implant is, or comprises a zinc alloy; the implant is, or comprises aluminum; the implant is, or comprises an aluminum alloy; the implant is, or comprises iron; the implant is, or comprises an iron alloy; the implant is, or comprises steel; the implant is, or comprises manganese; the implant is, or comprises a manganese alloy; the implant is, or comprises calcium; the implant is, or comprises a calcium alloy; the implant is, or comprises zirconium; the implant is, or comprises a zirconium alloy; the implant is, or comprises silicon; the implant is, or comprises a silicon alloy.

Preferred embodiments include pure magnesium of purity 99.95% to 99.9999%, or magnesium alloys with aluminum 0-16 wt. %, calcium 0-5 wt. %, rare earth metals 0-8 wt. %, lithium 0-5 wt. %, and manganese 0-5 wt. %. Preferably, the implants of the subject invention are not in particle or powder form.

In certain specific embodiments, the metal, semi-metal or alloy part of the implant is manufactured by die casting, investment casting, solvent casting, injection moulding, compression moulding, blow moulding, extrusion, intrusion, laminating, sintering, forging, stamping, welding, lathing, tooling, machining, or a combination thereof.

The raw material for manufacturing the metal, semi-metal or alloy part of the implant can be a metal. The raw material for manufacturing the metal, semi-metal or alloy part of the implant can also be a non-metallic compound of the metal, semi-metal or

alloy.

In certain embodiments, the metal or semi-metal part of the implant contains not more than 40% of non-metallic solid, or not more than 10% of non-metallic solid, or not more than 3% of non-metallic solid.

5 The non-metallic solid in the metal, semi-metal or alloy part of the implant can be in the form of powder, fiber, crystal, nanocrystal, nanoparticle or nano-fiber, or a combination thereof. More than one chemical composition of non-metallic solid can be present.

The non-metallic solid can be one or more of the following elements or compounds:  
10 carbon, carbonate compound, phosphate compound, non-metallic compound of metallic element, non-metallic compound of semimetallic element, polymer, anticoagulant, or their combinations. For a preferred embodiment, the mass of the non-metallic solid is less than 20% of the total mass of the implant.

The implant can be surface modified utilizing, for example, one or more of the  
15 following processes: oxidation, nitriding, solution immersion, anodization, deposition, electrolytic deposition, precipitation, immersion into molten metal, immersion into molten alloy, immersion into molten semi-metal, immersion into collagen, immersion into organic material, plasma immersion, plasma deposition, plasma spraying, flame  
20 spraying, chemical vapour deposition, physical vapour deposition, powder deposition, powder immersion, plasma immersion, plasma immersion ion implantation, electric arc deposition, painting, coating, heat treatment, cold treatment, thermomechanical processing, polishing, diffusion alloying, melt alloying, incubation in cell culture condition, rapid prototyping, selective laser sintering, solution spraying, particulate

leaching, etching, evaporation, sublimation, or sterilization.

In a further aspect, the solution immersion is further characterized in that it comprises one or more of the following: alkali treatment, hot alkali treatment, phosphate buffered saline immersion, cell culture medium immersion, body fluid immersion, 5 simulated body fluid immersion, serum immersion, phosphate solution immersion, acid treatment, immersion into collagen solution, immersion into organic material solution, immersion into growth factor solution, immersion into solution containing antibiotics, immersion into synthetic growth factor solution, immersion into solution containing synthetic antibiotics, immersion into extracellular matrix solution, immersion into 10 simulated extracellular matrix solution, immersion into growth factor solution with mammal cells, immersion into solution containing antibiotics and mammal cells, immersion into synthetic growth factor solution with mammal cells, immersion into solution containing synthetic antibiotics and cells, immersion into extracellular matrix solution with cells, immersion into simulated extracellular matrix solution with cells.

15 The implant can be in the form of a wire, a rod, a bent wire, a spring, a thread, a string, a cylinder, a cuboid, a rope, a mesh, a scaffold, a coil, a screw, a spiral, a helix, a double helix, a multiple helix, a plate, the shape of a part or a whole of the target tissue to be generated or regenerated, an irregular shape, a portion of the a single or a multiple of the aforementioned shapes, a modification of a single or a multiple of the aforementioned 20 shapes, a single or a multiple of the aforementioned shapes with single or multiple holes, a single or a multiple of the aforementioned shapes with single or multiple rings, a single or a multiple of the aforementioned shapes with single or multiple hooks, or a combination thereof.

In one embodiment, part of the implant is bent inside the body at the time of implantation.

In a further aspect of the current invention, the implant may be implanted into a part of the body other than the ultimate target site before being retrieved and put at the target site of generation/regeneration. For example, the material may be pre-implanted subcutaneously to generate an initial layer of fibrous tissue, before implantation into the target site such as ligament. The time period between the initial implantation at a non-target site to the time of retrieval and re-implantation at a target site may be, for example, from 3 minutes to 3 years, or preferably 15 minutes to 1 year, 1 hour to 6 months, or 1 day to 2 months.

In a further aspect, the surface modification may act on the whole surface of the implant, or only a portion of the implant surface.

Aspects and/or embodiments of the subject invention may have one or more of the following advantages. The induction of fibrosis allows the recruitment of cells and collagen formation without, or with less artificially added cells, which greatly reduces the time and cost for the generation or regeneration of soft tissue. The surface modification and/or inclusion of non-metallic solid improves the corrosion properties by increasing or decreasing the corrosion resistance, depending on the specific application. The surface modification and/or inclusion of non-metallic solid increases or decreases the rate of gas production due to implant corrosion, and/or increases or decreases the rate of resorption of the gas, depending on the specific application. The implant shape facilitates the implantation process and/or improves the mechanical properties of the implant, and/or improves the corrosion properties of the implant, depending on the specific application.

Currently, replacement of soft tissues are either achieved by synthetic material with or without cells or growth factors, replacement with allografts, or replacement with autografts. As compared with the current standard synthetic materials (i.e. polymers with or without cells or growth factors) and allografts for the regeneration of soft tissues, the materials used according to the current invention provide better mechanical properties, lower cost, lower chance of infection, shorter preparation time, and the supply is virtually unlimited. As compared to autograft, the supply is virtually unlimited, and does not cause donor-site morbidity, or a decrease in range-of-motion and weakness.

The principle of this invention is simple, yet unconventional. It is a unique combination of two disparate principles (resorbable metallic implant, and the use of a foreign body response to regenerate soft tissue).

Advantageously, it has been determined that the corrosion and resorption of small amounts of Mg and Mg alloys in mice did not lead to significant systemic toxicological effects. Also, toxicological effects are not anticipated in humans. See, Advance Materials Research Vols. 47-50 (2008) pp 604-607, which is incorporated herein, in its entirety, by reference.

Following are examples which illustrate procedures for practicing the invention. These examples should not be construed as limiting. All percentages are by weight and all solvent mixture proportions are by volume unless otherwise noted. AM60B and AM50A are standard magnesium alloy compositions as specified by ASTM Standard B94 (2007) as specified by ASTM International.

#### EXAMPLE 1

Lathed AM60B magnesium alloy wire, diameter 0.5mm and length 30mm, polished and immersed into 12M sodium hydroxide solution for 10 minutes, is further immersed into sterile DMEM for 1 hour. The material is then implanted subcutaneously for 30 days, retrieved, and implanted into a ligament defect site to replace or reinforce a broken  
5 ligament.

#### EXAMPLE 2

10 Extruded AM50A magnesium alloy wire, diameter 0.3mm and length 100mm, folded at the mid-point and then folded again at the new mid-point resulting in a new length of 50mm, polished and immersed into 12M sodium hydroxide solution for 10 minutes, is further immersed into sterile DMEM for 1 hour. The material is then implanted subcutaneously for 30 days, retrieved, and implanted into a ligament defect site  
15 to replace or reinforce a broken ligament.

#### EXAMPLE 3

99.99% pure magnesium mesh, size 80mm by 80mm, immersed into 12M sodium hydroxide solution for 1 minute, is further immersed into sterile phosphate-buffered  
20 saline for 1 hour. The material is then implanted into the body to seal the body wall defect which causes organ protrusion at the abdomen.

#### EXAMPLE 4

AZ31hp magnesium alloy plate, thickness 0.3mm, width 3mm, length 20mm, with rounded corners, with drill holes of 0.7mm diameter and centred at 2mm and 5mm from the terminals, is polished and immersed into 12M potassium hydroxide for 5 minutes. The material is then washed under running sterile distilled water for 5 minutes. The material is then implanted subcutaneously for 60 days. The material is then retrieved and implanted again into a small ligament defect site to replace a broken ligament, using four AZ31hp screws for anchorage onto the adjacent bones.

It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application.

All patents, patent applications, provisional applications, and publications referred to or cited herein are incorporated by reference in their entirety, including all figures and tables, to the extent they are not inconsistent with the explicit teachings of this specification.

## CLAIMS

We claim:

1. Use of a metal, semi-metal, or alloy thereof for preparing a bioresorbable implant for generating or regenerating soft tissue, membranous tissue or an organ, in whole or in part, within a patient, wherein said implant induces fibrosis within the patient, and wherein the fibrosis contributes to the generation or regeneration of the soft tissue, membrane tissue, or internal organ, in whole or in part.
2. The use according to claim 1, wherein the said implant is initially placed at a location in the patient other than the target site of generation or regeneration before implantation in the target site, the implant is then retrieved and re-implanted at the target site.
3. The use according to claim 1, wherein the patient is a human.
4. The use according to claim 1, wherein the implant is bent during the implantation process.
5. A bioresorbable medical implant made of metal, semi-metal or alloy, adapted for use in the body of a mammal, such that the bioresorbable medical implant itself induces fibrosis within the body, and the fibrosis induced by the implant is utilized to

generate or regenerate soft tissue, membranous tissue or an organ, in whole or in part, within the mammal, in whole or in part.

6. The medical implant according to claim 5, wherein said implant is adapted to be utilized to generate or regenerate soft tissues for hernia correction.

7. The medical implant according to claim 5, wherein said implant comprises magnesium, a magnesium alloy, tungsten, a tungsten alloy, zinc, a zinc alloy, aluminum, an aluminum alloy, iron, an iron alloy, steel, manganese, a manganese alloy, calcium, a calcium alloy, zirconium, a zirconium alloy, silicon or a silicon alloy.

8. The medical implant according to claim 5, wherein said implant is surface modified with a metallic material, a semi-metallic material, a non-metallic material, a metallic element in non-metallic or semi-metallic form, a non-metallic element in metallic or semi-metallic form, a semi-metallic element in non-metallic or metallic form, no additional material, or a combination thereof.

9. The medical implant according to claim 8, further characterized in that the surface modification comprises one or more of the following: oxidation, nitriding, solution immersion, anodization, deposition, electrolytic deposition, precipitation, immersion into molten metal, immersion into molten alloy, immersion into molten semi-metal, immersion into collagen, immersion into organic material, plasma immersion, plasma deposition, plasma spraying, flame spraying, chemical vapour deposition, physical

vapour deposition, powder deposition, powder immersion, plasma immersion, plasma immersion ion implantation, electric arc deposition, painting, coating, heat treatment, cold treatment, thermomechanical processing, polishing, diffusion alloying, melt alloying, incubation in cell culture condition, or sterilization.

10. The medical implant according to claim 9, further characterized in that the solution immersion comprises one or more of the following: alkali treatment, hot alkali treatment, phosphate buffered saline immersion, cell culture medium immersion, body fluid immersion, simulated body fluid immersion, serum immersion, phosphate solution immersion, acid treatment, immersion into collagen solution, immersion into organic material solution, immersion into growth factor solution, immersion into solution containing antibiotics, immersion into synthetic growth factor solution, immersion into solution containing synthetic antibiotics, immersion into extracellular matrix solution, immersion into simulated extracellular matrix solution, immersion into growth factor solution with mammal cells, immersion into solution containing antibiotics and mammal cells, immersion into synthetic growth factor solution with mammal cells, immersion into solution containing synthetic antibiotics and cells, immersion into extracellular matrix solution with cells, immersion into simulated extracellular matrix solution with cells.

11. The medical implant according to claim 5, wherein the implant is in the form of a wire, a rod, a bent wire, a spring, a thread, a string, a cylinder, a cuboid, a rope, a mesh, a scaffold, a coil, a screw, a spiral, a helix, a double helix, a multiple helix, a plate, the shape of a part or a whole of the target tissue to be generated or regenerated, an

irregular shape, a portion of the a single or a multiple of the aforementioned shapes, a modification of a single or a multiple of the aforementioned shapes, a single or a multiple of the aforementioned shapes with single or multiple holes, a single or a multiple of the aforementioned shapes with single or multiple rings, a single or a multiple of the aforementioned shapes with single or multiple hooks, or a combination thereof.

12. The medical implant according to claim 5, adapted for use in generating or regenerating an internal organ, in whole or in part.

13. The medical implant according to claim 5, wherein the soft tissue or membranous tissue is not cardiovascular tissue or an internal organ.

14. The medical implant according to claim 13, adapted for use in hernia repair.

15. The medical implant according to claim 5, adapted for use in generating or regenerating cardiovascular tissue.

16. The medical implant according to claim 5, adapted for use in generating or regenerating skin.

17. The medical implant according to claim 5, adapted for use in generating or regenerating a ligament, tendon, or periodontal fiber.

18. The medical implant according to claim 5, wherein the implant is manufactured by die casting, investment casting, solvent casting, injection moulding, compression moulding, blow moulding, extrusion, intrusion, laminating, sintering, forging, stamping, welding, lathing, tooling, machining, and a combination thereof.

19. The medical implant according to claim 5, wherein the implant comprises a non-metallic solid.

20. The medical implant according to claim 19, wherein the non-metallic solid is carbon, carbonate compound, phosphate compound, non-metallic compound of metallic element, non-metallic compound of semimetallic element, polymer, anticoagulant, or a combination thereof.

21. The medical implant according to claim 19, wherein the non-metallic solid is in the form of powder, fiber, film, crystal, nanocrystal, nanoparticle, nano-film or nano-fiber.

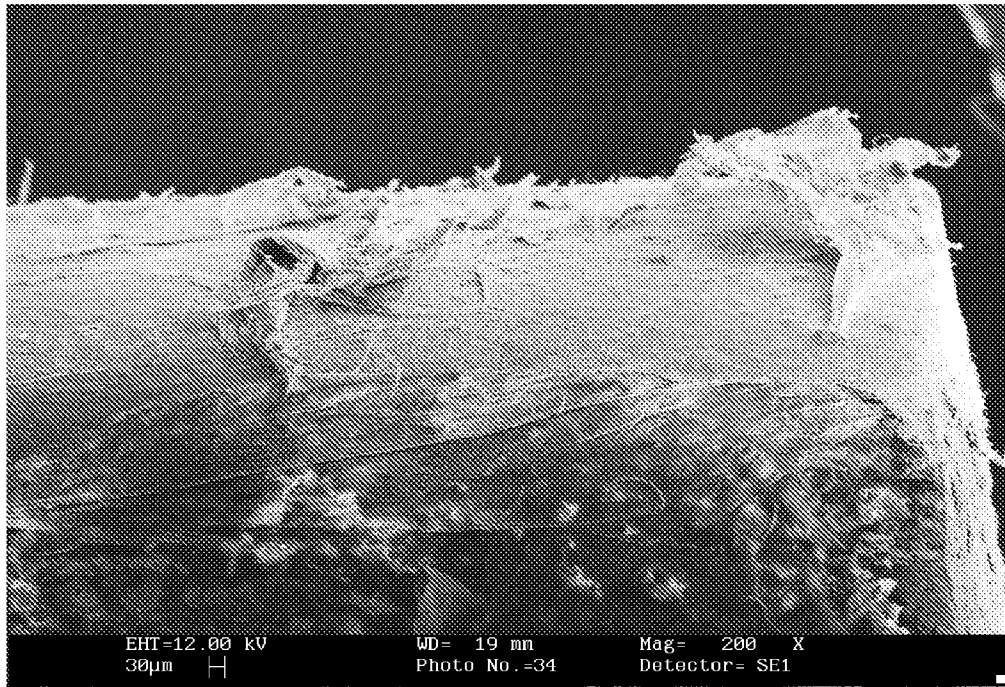


FIG. 1A

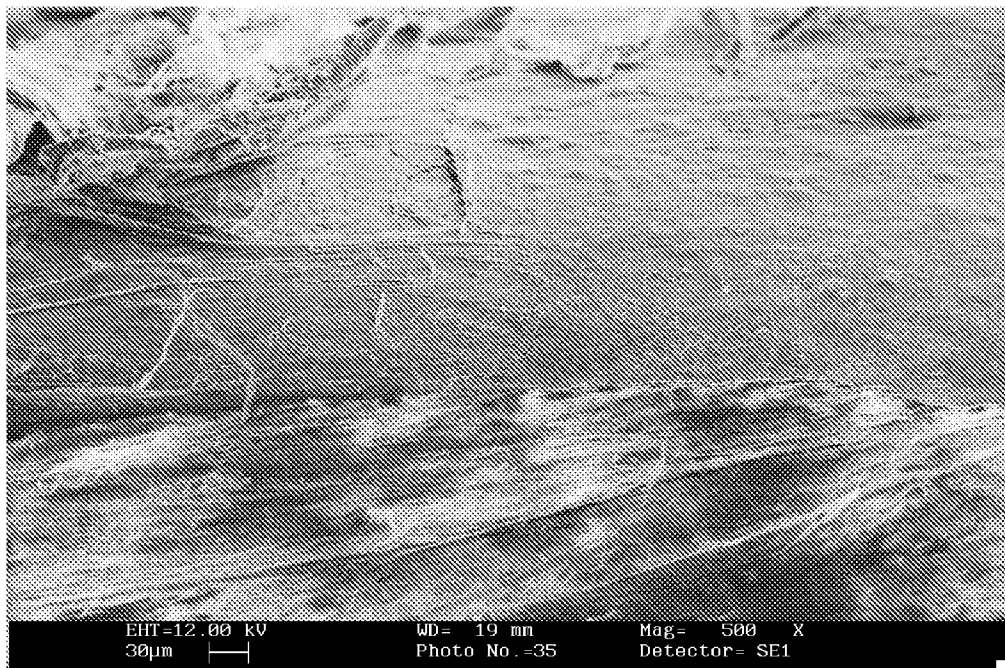


FIG. 1B

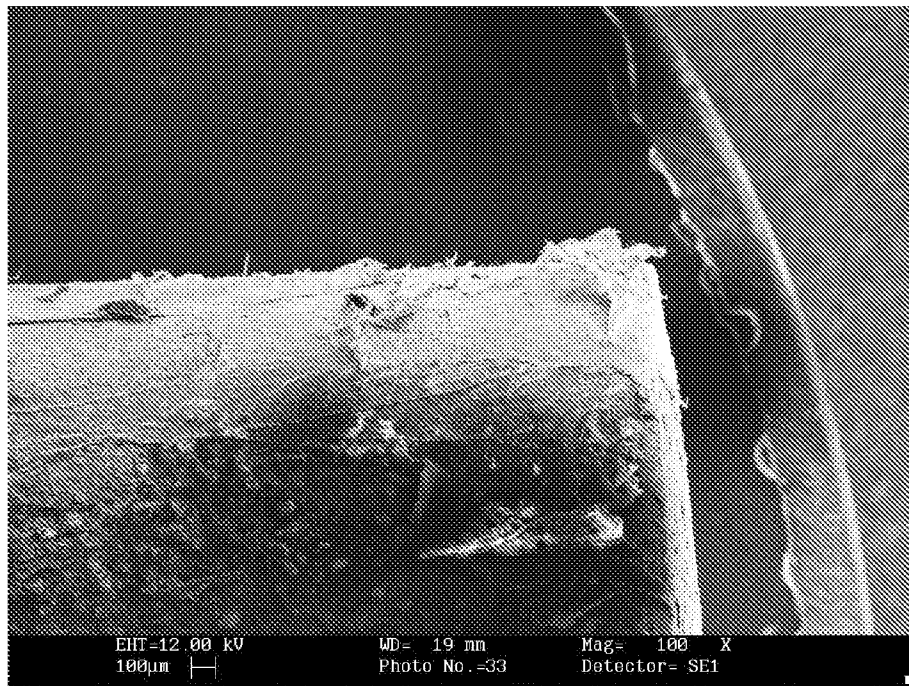


FIG. 1C

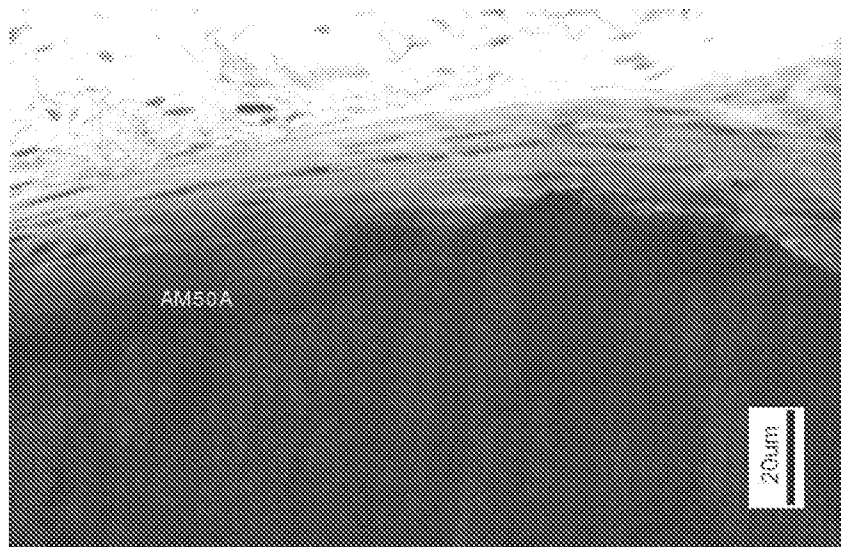


FIG. 2

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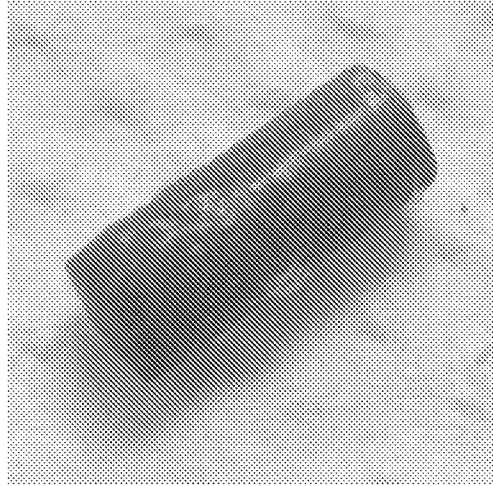


FIG. 3

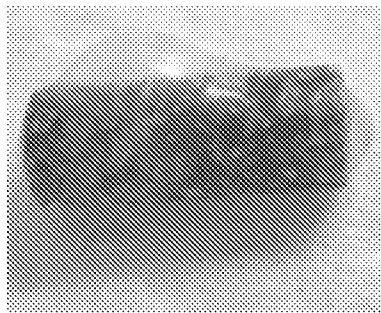


FIG. 4

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FIG. 5

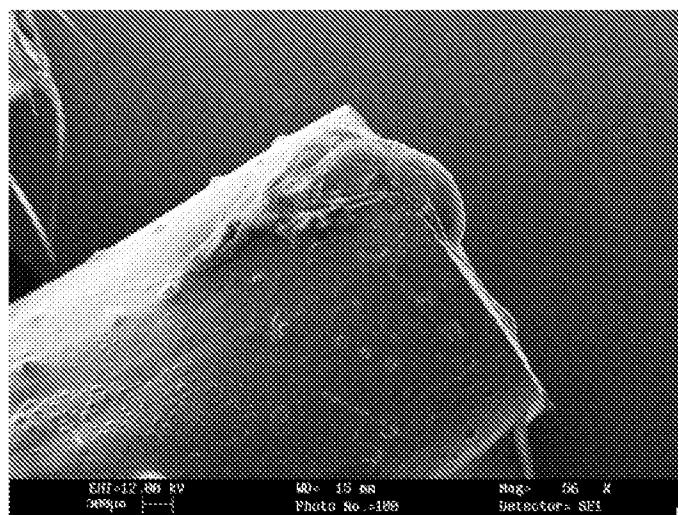


FIG. 6

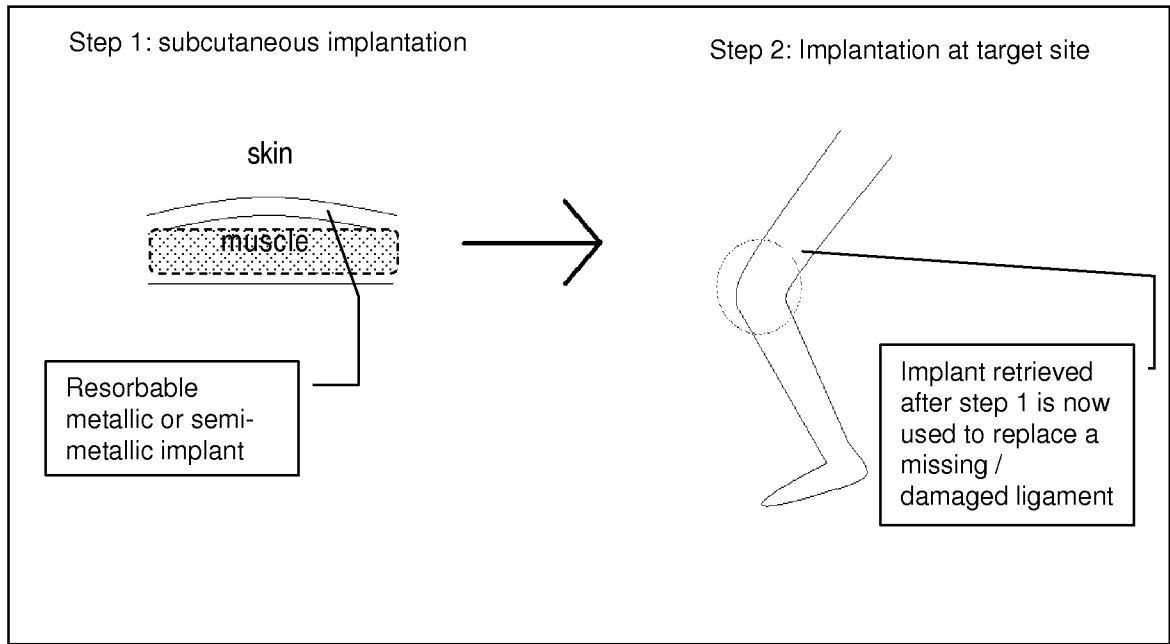


FIG. 7

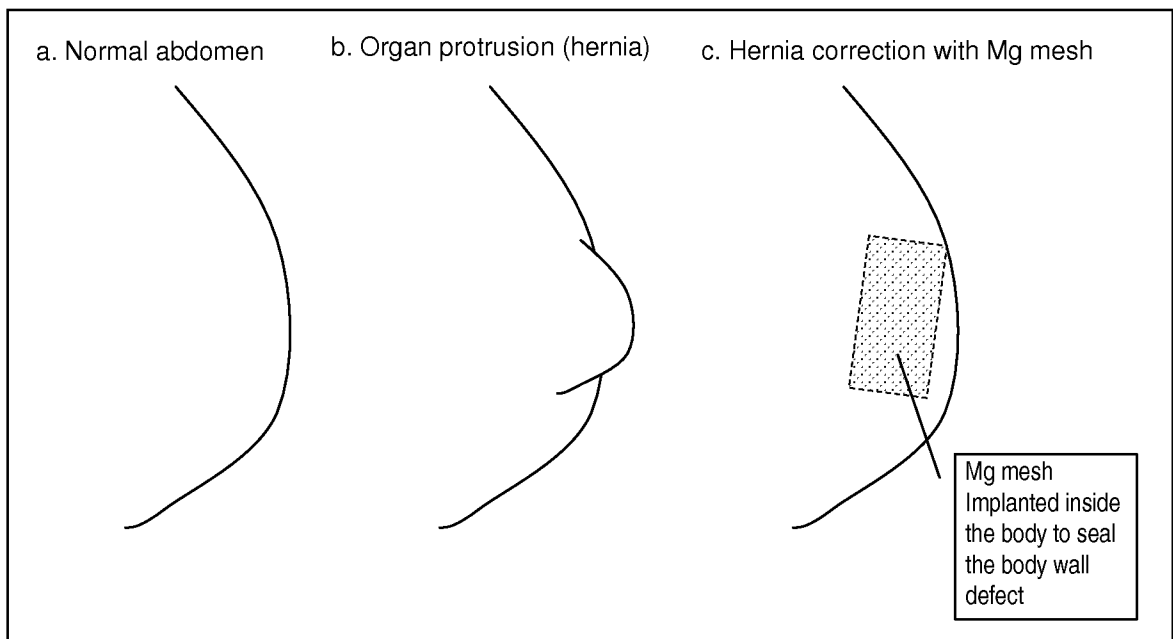


FIG. 8

Rod/wire	Bent wire	Spring	Interweaving into a thread, string, etc (for one or more than one compositions)	2D or 3D mesh (for one or more than one compositions)	Application of more than one piece of the specified biomaterial (for one or more than one compositions)
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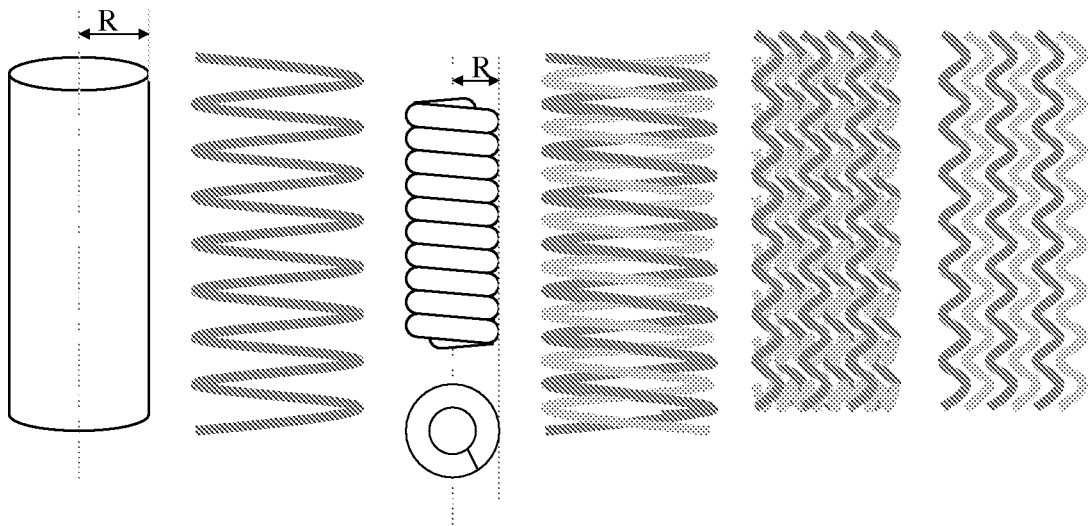


FIG. 9

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2009/000068

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>  <p style="text-align: center;">See extra sheet</p> <p>According to International Patent Classification (IPC) or to both national classification and IPC</p>		
<b>B. FIELDS SEARCHED</b>  <p>Minimum documentation searched (classification system followed by classification symbols)</p> <p style="text-align: center;">IPC: A61L27/-, A61L29/-, A61L31/-, A61F2/04 – 2/48</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched</p> <p>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)</p> <p style="text-align: center;">WPI, EPODOC, PAJ, CNPAT: implant, bioresorbable, fibrosis, compatible, regeneration, metal, semimetal, hernia</p>		
<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	CN101032632A (CHINESE ACAD SCI METAL RES INS) 12 Sep. 2007(12.09.2007)	5, 7-10, 12, 13, 18-21
Y	See page 1, line 6-page 3, line 31 of description	6, 11, 14-17
Y	CN101005812A (ADVANCED BIO PROSTHETIC SURFACES LTD) 25 Jul. 2007(25.07.2007) See page 1, line 3-page 7, line 12, figures 1-5	6, 11, 14-17
A	CN101065156A (HI-LEX CORP) 31 Oct. 2007(31.10.2007) See the whole document	5-21
A	US5607463A (Schwartz et al.) 04 Mar. 1997(04.03.1997) See the whole document	5-21
<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:	“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	
“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		
Date of the actual completion of the international search 25 Mar. 2009(25.03.2009)	Date of mailing of the international search report <b>16 Apr. 2009 (16.04.2009)</b>	
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer  <b>YU, Hanzheng</b> Telephone No. (86-10)62412920	

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2009/000068

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US20040057978A1 (Mattes et al.) 25 Mar. 2004(25.03.2004) See the whole document	5-21
A	US20030023305A1 (McKay) 30 Jan. 2003(30.01.2003) See the whole document	5-21

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2009/000068

### 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.: 1-4

because they relate to subject matter not required to be searched by this Authority, namely:

The subject matter of claims 1-4 relates to a method of surgery, and does not meet the criteria set out in PCT Rule 39.1(iv).

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:

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 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.:

**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**  
Information on patent family members

International application No.  
PCT/CN2009/000068

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
CN101032632A	12.09.2007	None	
CN101005812A	25.07.2007	WO2004100827A2	25.11.2004
		US2005033418A1	10.02.2005
		EP1620047A2	01.02.2006
		AU2004238270A1	25.11.2004
		MXPA05011852A	01.02.2006
		JP2007503279T	22.02.2007
CN101065156A	31.10.2007	WO2006033435A1	30.03.2006
		EP1800699A1	27.06.2007
		JP2006536437T	15.05.2008
		US2008124766A1	29.05.2008
US5607463A	04.03.1997	None	
US20040057978A1	25.03.2004	WO2004026360A2	01.04.2004
		US7025982B	11.04.2006
US20030023305A1	30.01.2003	WO0168004A2	20.09.2001
		AU4554101A	24.09.2001
		EP1263353A2	21.12.2002
		JP2003526457T	09.09.2003
		US2006025861A1	02.02.2006
		AU2001245541B	06.07.2006

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2009/000068

Continuation of: A: CLASSIFICATION OF SUBJECT MATTER

A61L27/02 (2006.01)i

A61F 2/00 (2006.01)i

A61L29/00(2006.01)i