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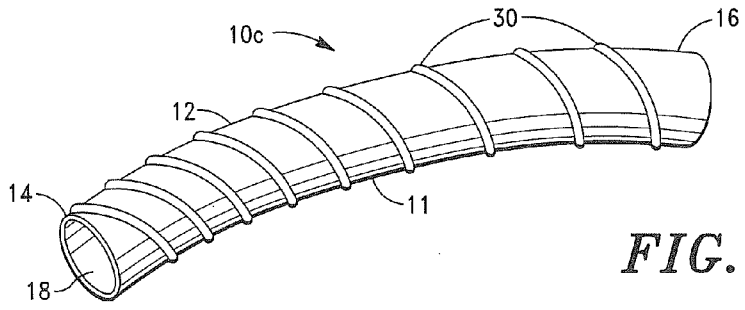

FIG. 3A

(57) Abstract: Vascular grafts for treating, reconstructing and replacing damaged or diseased cardiovascular vessels that are formed from decellularized extracellular matrix (ECM). The vascular grafts include structural reinforcement means, such as a strand of wound biodegradable polymeric material disposed proximate the outer surface of the graft.

REINFORCED VASCULAR PROSTHESES

FIELD OF THE INVENTION

[0001] The present invention relates to methods and apparatus for treating damaged or diseased cardiovascular vessels. More particularly, the present invention relates to reinforced vascular grafts or prostheses for treating and/or reconstructing damaged or diseased cardiovascular vessels.

BACKGROUND OF THE INVENTION

[0002] As is well known in the art, various vascular grafts or prostheses are often employed to treat and reconstruct damaged or diseased cardiovascular vessels.

[0003] Currently, the vascular grafts often employed to reconstruct (or replace) damaged or diseased cardiovascular vessels are autologous arteries and veins, e.g., internal mammary artery or saphenous vein; particularly, in situations where small diameter (i.e. 3-4 mm) vessels are required, such as below the knee and coronary artery bypass grafting.

[0004] Autologous arteries and veins are, however, often unavailable, due to prior harvest, or unsuitable, due to arterial disease.

[0005] When autologous arteries and veins are unavailable or unsuitable, synthetic polytatrafluoroethylene (PTFE) or Dacron® grafts are often employed to reconstruct or replace damaged or diseased cardiovascular vessels; particularly, in situations where large diameter (i.e. $\geq$ 6 mm) vessels are required.

[0006] There are, however, numerous drawbacks and disadvantages associated with synthetic grafts. A major drawback is the poor median patency exhibited by synthetic grafts, due to stenosis, thromboembolization, calcium deposition and infection. Indeed, it has been found that patency is > 25% @ 3 years using synthetic and cryopreserved grafts in peripheral and coronary bypass surgeries, compared to > 70% for autologous vascular grafts. See Chard, et al., *Aorta-Coronary Bypass Grafting with Polytetrafluoroehtylene Conduits: Early and Late Outcome in Eight Patients*, j Thorac Cardiovasc Surg, vol. 94, pp. 312-134 (1987).

[0007] Decellularized bovine internal jugular xenografts and human allograft vessels from cadavers have also employed to reconstruct or replace damaged or diseased cardiovascular vessels. Such grafts are, however, prone to calcification and thrombosis and, thus, have not gained significant clinical acceptance.

[0008] Vascular prostheses constructed of various biodegradable materials, such as poly (trimethylene carbonate), have also been developed to reconstruct damaged or diseased cardiovascular vessels. There are, however, several drawbacks and disadvantages associated with such prostheses.

[0009] One major disadvantage is that the biodegradable materials and, hence, prostheses formed therefrom, often break down at a faster rate than is desirable for the application. A further disadvantage is that the materials can, and in many instances will, break down into large, rigid fragments that can cause obstructions in the interior of the vessel.

[00010] More recently, vascular grafts comprising various remodelable materials, such as extracellular matrix sheets, have been developed to treat and reconstruct damaged or diseased cardiovascular vessels. Illustrative are the vascular grafts disclosed in Applicant's Co-Pending App. No. 13/573,226.

[00011] Although such grafts have garnered overwhelming success and, hence, gained significant clinical acceptance, there are a few drawbacks associated with such grafts. Among the drawbacks are the construction and, hence, configuration of the noted vascular grafts.

[00012] As discussed in detail in Co-Pending App. No. 13/573,226, such grafts typically comprise one or more sheets of ECM tissue, e.g., small intestine submucosa, which is secured at one edge to form a tubular structure. The secured edge or seam can, and in many instances will, disrupt blood flow through the graft. A poorly secured edge also poses a significant risk of thrombosis.

[00013] Further, in some instances, wherein the ECM graft comprises two or more sheets, i.e. a multi-sheet laminate, such as disclosed in Co-pending Application No. 14/031,423, the laminate structure is prone to delamination.

[00014] Thus, readily available, versatile vascular grafts that are not prone to calcification, thrombosis and intimal hyperplasia would fill a substantial and growing clinical need.

[00015] It is therefore an object of the present invention to provide vascular grafts (including "endografts") that substantially reduce or eliminate (i) the risk of thrombosis, (ii) intimal hyperplasia after intervention in a vessel, (iii) the harsh biological responses associated with conventional polymeric and metal prostheses, and (iv) the formation of biofilm, inflammation and infection.

[00016] It is another object of the present invention to provide vascular grafts that can effectively replace or improve biological functions or promote the growth of new tissue in a subject.

[00017] It is another object of the present invention to provide vascular grafts that induce host tissue proliferation, bioremodeling and regeneration of new tissue and tissue structures with site-specific structural and functional properties.

[00018] It is another object of the present invention to provide vascular grafts that are capable of administering a pharmacological agent to host tissue and, thereby produce a desired biological and/or therapeutic effect.

SUMMARY OF THE INVENTION

[00019] The present invention is directed to reinforced vascular grafts or prostheses for treating, reconstructing or replacing damaged or diseased cardiovascular vessels.

[00020] As discussed in detail herein, the vascular grafts comprise tubular members having first (or proximal) and second (or distal) ends.

[00021] In a preferred embodiment of the invention, the tubular members comprise a decellularized ECM material from a mammalian tissue source, i.e. tubular ECM members.

[00022] According to the invention, the ECM material can be derived from a variety of mammalian tissue sources, including, without limitation, small intestine submucosa (SIS), urinary bladder submucosa (UBS), stomach submucosa (SS), central nervous system tissue, epithelium of mesodermal origin, i.e. mesothelial tissue, dermal extracellular matrix, subcutaneous extracellular matrix, gastrointestinal extracellular matrix, i.e. large and small intestines, tissue surrounding growing bone, placental extracellular matrix, ornamentum extracellular matrix, cardiac extracellular matrix, e.g., pericardium and/or myocardium, kidney extracellular matrix, pancreas extracellular matrix, lung extracellular matrix, and combinations thereof. The ECM material can also comprise collagen from mammalian sources.

[00023] In a preferred embodiment, the mammalian tissue source comprises an adolescent mammalian tissue source.

[00024] In some embodiments of the invention, the tubular ECM members and, hence, vascular grafts formed therefrom, further comprise at least one additional biologically active

agent or composition, i.e. an agent that induces or modulates a physiological or biological process, or cellular activity, e.g., induces proliferation, and/or growth and/or regeneration of tissue.

[00025] In some embodiments, the biologically active agent comprises a cell, such as a human embryonic stem cell, fetal cardiomyocyte, myofibroblast, mesenchymal stem cell, etc.

[00026] In some embodiments, the biologically active agent comprises a growth factor, such as a transforming growth factor-alpha (TGF-α), transforming growth factor-beta (TGF-β), fibroblast growth factor-2 (FGF-2), basic fibroblast growth factor (bFGF), and vascular epithelial growth factor (VEGF).

[00027] In some embodiments, the tubular ECM members and, hence, vascular grafts formed therefrom, further comprise at least one pharmacological agent or composition (or drug), i.e. an agent or composition that is capable of producing a desired biological effect *in vivo*, e.g., stimulation or suppression of apoptosis, stimulation or suppression of an immune response, etc.

[00028] Suitable pharmacological agents and compositions include any of the aforementioned agents, including, without limitation, antibiotics, anti-viral agents, analgesics, steroidal anti-inflammatories, non-steroidal anti-inflammatories, anti-neoplastics, anti-spasmodics, modulators of cell-extracellular matrix interactions, proteins, hormones, enzymes and enzyme inhibitors, anticoagulants and/or antithrombic agents, DNA, RNA, modified DNA and RNA, NSAIDs, inhibitors of DNA, RNA or protein synthesis, polypeptides, oligonucleotides, polynucleotides, nucleoproteins, compounds modulating cell migration, compounds modulating proliferation and growth of tissue, and vasodilating agents.

[00029] In some embodiments of the invention, the pharmacological agent comprises a statin, i.e. a HMG-CoA reductase inhibitor, such as cerivastatin.

[00030] In a preferred embodiment of the invention, the tubular ECM members and, hence, vascular grafts formed therefrom, further comprise reinforcement means, i.e. reinforced vascular prostheses.

[00031] In some embodiments, the reinforcement means comprises a thin strand or thread of reinforcing material that is wound around the tubular member.

[00032] In some embodiments, the reinforcing strand comprises a biocompatible and biodegradable polymeric material.

[00033] In some embodiments, the reinforcing strand comprises an ECM strand or thread.

[00034] In some embodiments, the reinforcing strand comprises a biocompatible metal, such as stainless steel or Nitinol®, or a biocompatible and biodegradable metal, such as magnesium.

[00035] In some embodiments, the reinforcement means comprises a braided or mesh configuration.

[00036] In some embodiments of the invention, the tubular ECM members and, hence, vascular grafts formed therefrom, further comprise at least one anchoring mechanism.

BRIEF DESCRIPTION OF THE DRAWINGS

[00037] Further features and advantages will become apparent from the following and more particular description of the preferred embodiments of the invention, as illustrated in the accompanying drawings, and in which like referenced characters generally refer to the same parts or elements throughout the views, and in which:

[00038] FIGURE 1A is a perspective view of one embodiment of a tubular ECM vascular graft, in accordance with the invention;

[00039] FIGURE 1B is a side or edge plan view of the tubular ECM vascular graft shown in FIGURE 1A, in accordance with the invention;

[00040] FIGURE 2A is a perspective view of one embodiment of a coated ECM vascular graft, in accordance with the invention;

[00041] FIGURE 2B is a side or edge plan view of the coated ECM vascular graft shown in FIGURE 2A, in accordance with the invention;

[00042] FIGURE 3A is a perspective view of one embodiment of a reinforced ECM vascular graft, in accordance with the invention;

[00043] FIGURE 3B is a side or edge plan view of the reinforced ECM vascular egraft shown in FIGURE 3A, in accordance with the invention;

[00044] FIGURE 4A is a perspective view of another embodiment of a reinforced ECM vascular graft, in accordance with the invention; and

[00045] FIGURE 4B is a side or edge plan view of the reinforced ECM vascular graft shown in FIGURE 4A, in accordance with the invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[00046] Before describing the present invention in detail, it is to be understood that this invention is not limited to particularly exemplified apparatus, systems, structures or methods as such may, of course, vary. Thus, although a number of apparatus, systems and methods similar or equivalent to those described herein can be used in the practice of the present invention, the preferred apparatus, systems, structures and methods are described herein.

[00047] It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments of the invention only and is not intended to be limiting.

[00048] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one having ordinary skill in the art to which the invention pertains.

[00049] Further, all publications, patents and patent applications cited herein, whether *supra* or *infra*, are hereby incorporated by reference in their entirety.

[00050] As used in this specification and the appended claims, the singular forms “a, “an” and “the” include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to “a pharmacological agent” includes two or more such agents and the like.

[00051] Further, ranges can be expressed herein as from "about" or “approximately” one particular value, and/or to "about" or “approximately” another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about" or “approximately”, it will be understood that the particular value forms another embodiment. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint.

[00052] It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as "about" or “approximately” that particular value in addition to the value itself. For example, if the value "10" is disclosed, then "approximately 10" is also disclosed. It is also understood that when a value is disclosed that "less than or

equal to" the value, "greater than or equal to the value" and possible ranges between values are also disclosed, as appropriately understood by the skilled artisan. For example, if the value "10" is disclosed then "less than or equal to 10" as well as "greater than or equal to 10" is also disclosed.

Definitions

[00053] The terms "graft" and "endograft" are used interchangeably herein, and mean and include a structure that is configured for implantation in a cardiovascular structure, e.g., a cardiovascular vessel.

[00054] The terms "extracellular matrix", "ECM" and "ECM material" are used interchangeably herein, and mean and include a collagen-rich substance that is found in between cells in mammalian tissue, and any material processed therefrom, e.g. decellularized ECM. According to the invention, the ECM material can be derived from a variety of mammalian tissue sources, including, without limitation, small intestine submucosa (SIS), urinary bladder submucosa (UBS), stomach submucosa (SS), central nervous system tissue, epithelium of mesodermal origin, i.e. mesothelial tissue, dermal extracellular matrix, subcutaneous extracellular matrix, gastrointestinal extracellular matrix, i.e. large and small intestines, tissue surrounding growing bone, placental extracellular matrix, ornamentum extracellular matrix, cardiac extracellular matrix, e.g., pericardium and/or myocardium, kidney extracellular matrix, pancreas extracellular matrix, lung extracellular matrix, and combinations thereof. The ECM material can also comprise collagen from mammalian sources.

[00055] The terms "urinary bladder submucosa (UBS)", "small intestine submucosa (SIS)" and "stomach submucosa (SS)" also mean and include any UBS and/or SIS and/or SS material that includes the tunica mucosa (which includes the transitional epithelial layer and the tunica propria), submucosal layer, one or more layers of muscularis, and adventitia (a loose connective tissue layer) associated therewith.

[00056] The ECM material can also be derived from basement membrane of mammalian tissue/organs, including, without limitation, urinary basement membrane (UBM), liver basement membrane (LBM), and amnion, chorion, allograft pericardium, allograft acellular dermis, amniotic membrane, Wharton's jelly, and combinations thereof.

[00057] Additional sources of mammalian basement membrane include, without limitation, spleen, lymph nodes, salivary glands, prostate, pancreas and other secreting glands.

[00058] The ECM material can also be derived from other sources, including, without limitation, collagen from plant sources and synthesized extracellular matrices, i.e. cell cultures.

[00059] The term "angiogenesis", as used herein, means a physiologic process involving the growth of new blood vessels from pre-existing blood vessels.

[00060] The term "neovascularization", as used herein, means and includes the formation of functional vascular networks that can be perfused by blood or blood components. Neovascularization includes angiogenesis, budding angiogenesis, intussuceptive angiogenesis, sprouting angiogenesis, therapeutic angiogenesis and vasculogenesis.

[00061] The term "Artelon", as used herein, means a poly(urethane urea) material distributed by Artimplant AB in Goteborg, Sweden.

[00062] The terms "biologically active agent" and "biologically active composition" are used interchangeably herein, and mean and include agent that induces or modulates a physiological or biological process, or cellular activity, e.g., induces proliferation, and/or growth and/or regeneration of tissue.

[00063] The terms "biologically active agent" and "biologically active composition" thus mean and include, without limitation, the following growth factors: platelet derived growth factor (PDGF), epidermal growth factor (EGF), transforming growth factor alpha (TGF-alpha), transforming growth factor beta (TGF-beta), fibroblast growth factor – 2 (FGF-2), basic fibroblast growth factor (bFGF), vascular epithelial growth factor (VEGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), nerve growth factor (NGF), platlet derived growth factor (PDGF), tumor necrosis factor alpha (TNA-alpha), and placental growth factor (PLGF).

[00064] The terms "biologically active agent" and "biologically active composition" also mean and include, without limitation, human embryonic stem cells, fetal cardiomyocytes, myofibroblasts, mesenchymal stem cells, autotransplated expanded cardiomyocytes, adipocytes, totipotent cells, pluripotent cells, blood stem cells, myoblasts, adult stem cells, bone marrow cells, mesenchymal cells, embryonic stem cells, parenchymal cells, epithelial

cells, endothelial cells, mesothelial cells, fibroblasts, osteoblasts, chondrocytes, exogenous cells, endogenous cells, stem cells, hematopoietic stem cells, bone-marrow derived progenitor cells, myocardial cells, skeletal cells, fetal cells, undifferentiated cells, multi-potent progenitor cells, unipotent progenitor cells, monocytes, cardiac myoblasts, skeletal myoblasts, macrophages, capillary endothelial cells, xenogenic cells, allogenic cells, and post-natal stem cells.

[00065] The terms "biologically active agent" and "biologically active composition" also mean and include, without limitation, the following biologically active agents (referred to interchangeably herein as a "protein", "peptide" and "polypeptide"): collagen (types I-V), proteoglycans, glycosaminoglycans (GAGs), glycoproteins, growth factors, cytokines, cell-surface associated proteins, cell adhesion molecules (CAM), angiogenic growth factors, endothelial ligands, matrikines, cadherins, immuoglobins, fibril collagens, non-fibrallar collagens, basement membrane collagens, multiplexins, small-leucine rich proteoglycans, decorins, biglycans, fibromodulins, keratocans, lumicans, epiphycans, heparin sulfate proteoglycans, perlecans, agrins, testicans, syndecans, glypicans, serglycins, selectins, lecticans, aggrecans, versicans, neurocans, brevicans, cytoplasmic domain-44 (CD-44), macrophage stimulating factors, amyloid precursor proteins, heparins, chondroitin sulfate B (dermatan sulfate), chondroitin sulfate A, heparin sulfates, hyaluronic acids, fibronectins, tenascins, elastins, fibrillins, laminins, nidogen/enactins, fibulin I, finulin II, integrins, transmembrane molecules, thrombospondins, ostepontins, and angiotensin converting enzymes (ACE).

[00066] The terms "pharmacological agent", "active agent", "drug" and "active agent formulation" are used interchangeably herein, and mean and include an agent, drug, compound, composition of matter or mixture thereof, including its formulation, which provides some therapeutic, often beneficial, effect. This includes any physiologically or pharmacologically active substance that produces a localized or systemic effect or effects in animals, including warm blooded mammals, humans and primates; avians; domestic household or farm animals, such as cats, dogs, sheep, goats, cattle, horses and pigs; laboratory animals, such as mice, rats and guinea pigs; fish; reptiles; zoo and wild animals; and the like.

[00067] The terms "pharmacological agent", "active agent", "drug" and "active agent formulation" thus mean and include, without limitation, antibiotics, anti-arrhythmic agents, anti-viral agents, analgesics, steroidal anti-inflammatories, non-steroidal anti-inflammatories, anti-neoplastics, anti-spasmodics, modulators of cell-extracellular matrix interactions, proteins, hormones, growth factors, matrix metalloproteinases (MMPS), enzymes and enzyme inhibitors, anticoagulants and/or antithrombic agents, DNA, RNA, modified DNA and RNA, NSAIDs, inhibitors of DNA, RNA or protein synthesis, polypeptides, oligonucleotides, polynucleotides, nucleoproteins, compounds modulating cell migration, compounds modulating proliferation and growth of tissue, and vasodilating agents.

[00068] The terms "pharmacological agent", "active agent", "drug" and "active agent formulation" thus include, without limitation, atropine, tropicamide, dexamethasone, dexamethasone phosphate, betamethasone, betamethasone phosphate, prednisolone, triamcinolone, triamcinolone acetonide, fluocinolone acetonide, anecortave acetate, budesonide, cyclosporine, FK-506, rapamycin, ruboxistaurin, midostaurin, flurbiprofen, suprofen, ketoprofen, diclofenac, ketorolac, nepafenac, lidocaine, neomycin, polymyxin b, bacitracin, gramicidin, gentamicin, oyxtetracycline, ciprofloxacin, ofloxacin, tobramycin, amikacin, vancomycin, cefazolin, ticarcillin, chloramphenicol, miconazole, itraconazole, trifluridine, vidarabine, ganciclovir, acyclovir, cidofovir, ara-amp, foscarnet, idoxuridine, adefovir dipivoxil, methotrexate, carboplatin, phenylephrine, epinephrine, dipivefrin, timolol, 6-hydroxydopamine, betaxolol, pilocarpine, carbachol, physostigmine, demecarium, dorzolamide, brinzolamide, latanoprost, sodium hyaluronate, insulin, verteporfin, pegaptanib, ranibizumab, and other antibodies, antineoplastics, anti VGEFs, ciliary neurotrophic factor, brain-derived neurotrophic factor, bFGF, Caspase-1 inhibitors, Caspase-3 inhibitors, α-Adrenoceptors agonists, NMDA antagonists, Glial cell line-derived neurotrophic factors (GDNF), pigment epithelium-derived factor (PEDF), and NT-3, NT-4, NGF, IGF-2.

[00069] The terms "pharmacological agent", "active agent", "drug" and "active agent formulation" further mean and include the following Class I – Class V antiarrhythmic agents: (Class Ia) quinidine, procainamide and disopyramide; (Class Ib) lidocaine, phenytoin and mexiletine; (Class Ic) flecainide, propafenone and moricizine; (Class II) propranolol, esmolol,

timolol, metoprolol and atenolol; (Class III) amiodarone, sotalol, ibutilide and dofetilide; (Class IV) verapamil and diltiazem) and (Class V) adenosine and digoxin.

[00070] The terms "pharmacological agent", "active agent", "drug" and "active agent formulation" further mean and include, without limitation, the following antiobiotics: aminoglycosides, cephalosporins, chloramphenicol, clindamycin, erythromycins, fluoroquinolones, macrolides, azolides, metronidazole, penicillins, tetracyclines, trimethoprim-sulfamethoxazole and vancomycin.

[00071] The terms "pharmacological agent", "active agent", "drug" and "active agent formulation" further include, without limitation, the following steroids: andranes (e.g., testosterone), cholestanes, cholic acids, corticosteroids (e.g., dexamethasone), estraenes (e.g., estradiol) and pregnanes (e.g., progesterone).

[00072] The terms "pharmacological agent", "active agent", "drug" and "active agent formulation" can further include one or more classes of narcotic analgesics, including, without limitation, morphine, codeine, heroin, hydromorphone, levorphanol, meperidine, methadone, oxycodone, propoxyphene, fentanyl, methadone, naloxone, buprenorphine, butorphanol, nalbuphine and pentazocine.

[00073] The terms "pharmacological agent", "active agent", "drug" and "active agent formulation" can further include one or more classes of topical or local anesthetics, including, without limitation, esters, such as benzocaine, chloroprocaine, cocaine, cyclomethycaine, dimethocaine/larocaine, piperocaine, propoxycaine, procaine/novacaine, proparacaine, and tetracaine/amethocaine. Local anesthetics can also include, without limitation, amides, such as articaine, bupivacaine, cinchocaine/dibucaine, etidocaine, levobupivacaine, lidocaine/lignocaine, mepivacaine, prilocaine, ropivacaine, and trimecaine. Local anesthetics can further include combinations of the above from either amides or esters.

[00074] The terms "anti-inflammatory" and "anti-inflammatory agent" are also used interchangeably herein, and mean and include a "pharmacological agent" and/or "active agent formulation", which, when a therapeutically effective amount is administered to a subject, prevents or treats bodily tissue inflammation i.e. the protective tissue response to

injury or destruction of tissues, which serves to destroy, dilute, or wall off both the injurious agent and the injured tissues.

[00075] Anti-inflammatory agents thus include, without limitation, alclofenac, alclometasone dipropionate, algestone acetonide, alpha amylase, amcinafal, amcinafide, amfenac sodium, amiprilose hydrochloride, anakinra, anirolac, anitrazafen, apazone, balsalazide disodium, bendazac, benoxaprofen, benzydamine hydrochloride, bromelains, broperamole, budesonide, carprofen, cicloprofen, cintazone, cliprofen, clobetasol propionate, clobetasone butyrate, clopirac, cloticasone propionate, cormethasone acetate, cortodoxone, decanoate, deflazacort, delatestryl, depo-testosterone, desonide, desoximetasone, dexamethasone dipropionate, diclofenac potassium, diclofenac sodium, diflorasone diacetate, diflumidone sodium, diflunisal, difluprednate, diftalone, dimethyl sulfoxide, drocinonide, endrysone, enlimomab, enolicam sodium, epirizole, etodolac, etofenamate, felbinac, fenamole, fenbufen, fenclofenac, fenclorac, fendosal, fenpipalone, fentiazac, flazalone, fluazacort, flufenamic acid, flumizole, flunisolide acetate, flunixin, flunixin meglumine, fluocortin butyl, fluorometholone acetate, fluquazone, flurbiprofen, fluretofen, fluticasone propionate, furaprofen, furobufen, halcinonide, halobetasol propionate, halopredone acetate, ibufenac, ibuprofen, ibuprofen aluminum, ibuprofen piconol, ilonidap, indomethacin, indomethacin sodium, indoprofen, indoxole, intrazole, isoflupredone acetate, isoxepac, isoxicam, ketoprofen, lofemizole hydrochloride, lomoxicam, loteprednol etabonate, meclofenamate sodium, meclofenamic acid, meclorisone dibutyrate, mefenamic acid, mesalamine, meseclazone, mesterolone, methandrostenolone, methenolone, methenolone acetate, methylprednisolone suleptanate, momiflumate, nabumetone, nandrolone, naproxen, naproxen sodium, naproxol, nimazone, olsalazine sodium, orgotein, orpanoxin, oxandrolane, oxaprozin, oxyphenbutazone, oxymetholone, paranyline hydrochloride, pentosan polysulfate sodium, phenbutazone sodium glycerate, pirfenidone, piroxicam, piroxicam cinnamate, piroxicam olamine, pirprofen, prednazate, prifelone, prodolic acid, proquazone, proxazole, proxazole citrate, rimexolone, romazarit, salcolex, salnacedin, salsalate, sanguinarium chloride, seclazone, sermetacin, stanozolol, sudoxicam, sulindac, suprofen, talmetacin, talniflumate, talosalate, tebufelone, tenidap, tenidap sodium, tenoxicam, tesicam, tesimide, testosterone, testosterone blends,

tetrydamine, tiopinac, tixocortol pivalate, tolmetin, tolmetin sodium, triclonide, triflumidate, zidometacin, and zomepirac sodium.

[00076] The term "pharmacological composition", as used herein, means and includes a composition comprising a "pharmacological agent" and/or a "biologically active agent" and/or any additional agent or component identified herein.

[00077] The term "therapeutically effective", as used herein, means that the amount of the "pharmacological agent" and/or "biologically active agent" and/or "pharmacological composition" administered is of sufficient quantity to ameliorate one or more causes, symptoms, or sequelae of a disease or disorder. Such amelioration only requires a reduction or alteration, not necessarily elimination, of the cause, symptom, or sequelae of a disease or disorder.

[00078] The term "adolescent", as used herein, means and includes a mammal that is preferably less than three (3) years of age.

[00079] The terms "patient" and "subject" are used interchangeably herein, and mean and include warm blooded mammals, humans and primates; avians; domestic household or farm animals, such as cats, dogs, sheep, goats, cattle, horses and pigs; laboratory animals, such as mice, rats and guinea pigs; fish; reptiles; zoo and wild animals; and the like.

[00080] The term "comprise" and variations of the term, such as "comprising" and "comprises," means "including, but not limited to" and is not intended to exclude, for example, other additives, components, integers or steps.

[00081] The following disclosure is provided to further explain in an enabling fashion the best modes of performing one or more embodiments of the present invention. The disclosure is further offered to enhance an understanding and appreciation for the inventive principles and advantages thereof, rather than to limit in any manner the invention. The invention is defined solely by the appended claims including any amendments made during the pendency of this application and all equivalents of those claims as issued.

[00082] As stated above, the present invention is directed to vascular grafts or prostheses for treating, reconstructing or replacing damaged or diseased cardiovascular vessels.

[00083] In a preferred embodiment of the invention, the tubular members comprise a decellularized ECM material from a mammalian tissue source. As stated above, according to

the invention, the ECM material can be derived from a variety of mammalian tissue sources, including, without limitation, small intestine submucosa (SIS), urinary bladder submucosa (UBS), stomach submucosa (SS), central nervous system tissue, epithelium of mesodermal origin, i.e. mesothelial tissue, dermal extracellular matrix, subcutaneous extracellular matrix, gastrointestinal extracellular matrix, i.e. large and small intestines, tissue surrounding growing bone, placental extracellular matrix, ornamentum extracellular matrix, cardiac extracellular matrix, e.g., pericardium and/or myocardium, kidney extracellular matrix, pancreas extracellular matrix, lung extracellular matrix, and combinations thereof. The ECM material can also comprise collagen from mammalian sources.

[00084] In a preferred embodiment, the mammalian tissue source comprises an adolescent mammalian tissue source, i.e. an adolescent mammal, such as a piglet, which is preferably less than three (3) years of age.

[00085] In a preferred embodiment, the ECM material is decellularized and, hence, remodelable. According to the invention, the ECM material can be decellularized by various conventional means. In a preferred embodiment, the ECM material is decellularized via one of the unique Novasterilis processes disclosed in U.S. Pat. No. 7,108,832 and U.S. Pat. App. No. 13/480,204; which are incorporated by reference herein in their entirety.

[00086] According to the invention, upon implanting a vascular graft of the invention in a cardiovascular system of a subject, the vascular graft induces host tissue proliferation, bioremodeling, including neovascularization, e.g., vasculogenesis, angiogenesis, and intussusception, and regeneration of tissue structures with site-specific structural and functional properties. The graft also provides a vessel having a smooth, non-thrombogenic interior surface.

[00087] As stated above, in some embodiments of the invention, the vascular grafts further comprise at least one additional biologically active agent or composition, i.e. an agent that induces or modulates a physiological or biological process, or cellular activity, e.g., induces proliferation, and/or growth and/or regeneration of tissue.

[00088] In a preferred embodiment of the invention, the biologically active agent is similarly derived from an adolescent mammal, i.e. a mammal less than three (3) years of age.

[00089] Suitable biologically active agents include any of the aforementioned biologically active agents, including, without limitation, the aforementioned cells and proteins.

[00090] In some embodiments of the invention, the biologically active agent comprises a growth factor selected from the group comprising transforming growth factor-alpha (TGF-α), transforming growth factor-beta (TGF-β), fibroblast growth factor-2 (FGF-2), basic fibroblast growth factor (bFGF) and vascular epithelial growth factor (VEGF).

[00091] According to the invention, upon implanting a vascular graft of the invention in a cardiovascular system of a subject, the growth factors link to and interact with at least one molecule in the vascular graft and further induce and/or control host tissue proliferation, bioremodeling, and regeneration of new tissue structures.

[00092] In some embodiments of the invention, the biologically active agent comprises a protein selected from the group comprising proteoglycans, glycosaminoglycans (GAGs), glycoproteins, heparins, chondroitin sulfate B (dermatan sulfate), chondroitin sulfate A, heparin sulfates, and hyaluronic acids.

[00093] In some embodiments of the invention, the protein comprises a cytokine selected from the group comprising a stem cell factor (SCF), stromal cell-derived factor-1 (SDF-1), granulocyte macrophage colony-stimulating factor (GM-CSF), interferon gamma (IFN-gamma), interleukin-3, interleukin-4, interleukin-10, interleukin-13, leukemia inhibitory factor (LIF), amphiregulin, thrombospondin 1, thrombospondin 2, thrombospondin 3, thrombospondin 4, thrombospondin 5, and angiotensin converting enzyme (ACE).

[00094] According to the invention, upon implanting a vascular graft of the invention in a cardiovascular system of a subject, the proteins similarly link to and interact with at least one molecule in the graft and further induce and/or control host tissue proliferation, bioremodeling, and regeneration of new tissue structures.

[00095] In some embodiments, the vascular grafts further comprise at least one pharmacological agent or composition (or drug), i.e. an agent or composition that is capable of producing a desired biological effect *in vivo*, e.g., stimulation or suppression of apoptosis, stimulation or suppression of an immune response, etc.

[00096] Suitable pharmacological agents and compositions include any of the aforementioned agents, including, without limitation, antibiotics, anti-viral agents, analgesics,

steroidal anti-inflammatories, non-steroidal anti-inflammatories, anti-neoplastics, anti-spasmodics, modulators of cell-extracellular matrix interactions, proteins, hormones, enzymes and enzyme inhibitors, anticoagulants and/or antithrombic agents, DNA, RNA, modified DNA and RNA, NSAIDs, inhibitors of DNA, RNA or protein synthesis, polypeptides, oligonucleotides, polynucleotides, nucleoproteins, compounds modulating cell migration, compounds modulating proliferation and growth of tissue, and vasodilating agents.

[00097] In some embodiments of the invention, the pharmacological agent comprises one of the aforementioned anti-inflammatories.

[00098] In some embodiments of the invention, the pharmacological agent comprises a statin, i.e. a HMG-CoA reductase inhibitor. According to the invention, suitable statins include, without limitation, atorvastatin (Lipitor®), cerivastatin, fluvastatin (Lescol®), lovastatin (Mevacor®, Altocor®, Altoprev®), mevastatin, pitavastatin (Livalo ®, Pitava®), pravastatin (Pravachol®, Selektine®, Lipostat®), rosuvastatin (Crestor®), and simvastatin (Zocor®, Lipex®). Several actives comprising a combination of a statin and another agent, such as ezetimbe/simvastatin (Vytorin®), are also suitable.

[00099] Applicant has found that the noted statins exhibit numerous beneficial properties that provide several beneficial biochemical actions or activities. The properties and beneficial actions are set forth in Applicant's Co-Pending Application Nos. 13/373,569, filed on September 24, 2012 and 13/782,024, filed on March 1, 2013; which are incorporated by reference herein in their entirety.

[000100] In some embodiments of the invention, the vascular grafts further comprise at least one outer coating. In some embodiments, the outer coating comprises a pharmacological composition.

[000101] In some embodiments of the invention, the vascular grafts further comprise reinforcement means, i.e. reinforced vascular grafts.

[000102] As discussed in detail below, in some embodiments, the reinforcement means comprises a thin strand or thread of reinforcing material that is wound around the tubular graft. According to the invention, the reinforcing strand can comprise various biocompatible materials.

[000103] In a preferred embodiment, the reinforcing strand comprises a biocompatible and biodegradable polymeric material. According to the invention, suitable biodegradable polymeric materials similarly include, without limitation, polyhydroxyalkonates (PHAs), polylactides (PLLA) and polyglycolides (PLGA) and their copolymers, polyanhydrides, and like polymers.

[000104] A further suitable polymeric material comprises "Artelon", i.e. a poly(urethane urea) material distributed by Artimplant AB in Goteborg, Sweden.

[000105] According to the invention, the reinforcing strand can also comprise an ECM strand or thread, such as a small intestine or urinary bladder submucosa suture.

[000106] According to the invention, the reinforcing strand can be disposed on the outer surface of the graft manually or via an electro-spin procedure.

[000107] According to the invention, the reinforcing strand can also comprise a biocompatible metal, such as stainless steel or Nitinol®, or a biocompatible and biodegradable metal, such as magnesium.

[000108] In some embodiments, the reinforcement means comprises a braided or mesh configuration or other conventional stent structure.

[000109] In some embodiments of the invention, the vascular grafts further comprise at least one anchoring mechanism, such as disclosed in Co-pending Application Nos. 13/782,024 and 13/686,131; which are incorporated by reference herein in their entirety.

[000110] Referring now to Figs. 1A and 1B, there is shown one embodiment of a vascular graft of the invention. As illustrated in Fig. 1A, the graft 10a comprises a continuous tubular member 12 having proximal 14 and distal 16 ends, and a lumen 18 that extends therethrough.

[000111] As indicated above, in a preferred embodiment of the invention, the tubular member 12 comprises a decellularized ECM material. As also indicated above, preferably, the ECM material is derived from an adolescent mammal, i.e. a mammal less than three (3) years of age.

[000112] According to the invention, the tubular member 12, and, hence vascular graft 10a (and grafts 10b-10d, discussed below) formed therefrom, can have various diameters, e.g. 3.0 mm, 10.0 mm, etc.

[000113] In some embodiments of the invention, the vascular graft 10a further comprises at least one additional biologically active agent or composition, i.e. an agent that induces or modulates a physiological or biological process, or cellular activity, e.g., induces proliferation, and/or growth and/or regeneration of tissue.

[000114] Suitable biologically active agents include any of the aforementioned biologically active agents, including, without limitation, the aforementioned cells, growth factors and proteins.

[000115] In some embodiments, the vascular graft 10a further comprises at least one pharmacological agent or composition (or drug), i.e. an agent or composition that is capable of producing a desired biological effect *in vivo*, e.g., stimulation or suppression of apoptosis, stimulation or suppression of an immune response, etc.

[000116] Suitable pharmacological agents and compositions include any of the aforementioned agents, including, without limitation, antibiotics, anti-viral agents, analgesics, steroidal anti-inflammatories, non-steroidal anti-inflammatories, anti-neoplastics, anti-spasmodics, modulators of cell-extracellular matrix interactions, proteins, hormones, enzymes and enzyme inhibitors, anticoagulants and/or antithrombic agents, DNA, RNA, modified DNA and RNA, NSAIDs, inhibitors of DNA, RNA or protein synthesis, polypeptides, oligonucleotides, polynucleotides, nucleoproteins, compounds modulating cell migration, compounds modulating proliferation and growth of tissue, and vasodilating agents.

[000117] In some embodiments of the invention, the pharmacological agent comprises a statin, i.e. a HMG-CoA reductase inhibitor.

[000118] Referring now to Figs. 2A and 2B, there is shown another embodiment of a vascular graft of the invention. As illustrated in Fig. 2A, the endograft 10b similarly comprises a continuous tubular member 12 having proximal 14 and distal 16 ends, and a lumen 18 that extends therethrough.

[000119] However, in this embodiment, the vascular endograft 10b further comprises at least one outer coating 20. In some embodiments, the outer coating 20 comprises a pharmacological composition.

[000120] As indicated above, in some embodiments of the invention, the vascular grafts of the invention further comprise reinforcement means, i.e. reinforced vascular grafts.

[000121] Referring now to Figs. 3A and 3B there is shown one embodiment of a reinforced vascular graft of the invention. As illustrated in Fig. 3A, the graft 10c similarly comprises a continuous tubular member 12 having proximal 14 and distal 16 ends, and a lumen 18 that extends therethrough.

[000122] The graft 10c further comprises reinforcement means, which, in the illustrated embodiment, comprises a thin strand or thread of reinforcing material 30, which is wound around the tubular endograft 10c, and, hence, disposed proximate the outer surface 11 thereof. According to the invention, the reinforcing strand 30 can comprise various biocompatible materials.

[000123] As indicated above, in a preferred embodiment, the reinforcing strand 30 comprises a biocompatible and biodegradable polymeric material. Suitable biodegradable polymeric materials similarly include, without limitation, polyhydroxyalkonates (PHAs), polylactides (PLLA) and polyglycolides (PLGA) and their copolymers, polyanhydrides, and like polymers.

[000124] In some embodiments, the reinforcing strand 30 can alternatively comprise an ECM strand or thread, such as a small intestine or urinary bladder submucosa suture. In a preferred embodiment, the ECM strand comprises a cross-linked ECM material.

[000125] According to the invention, the reinforcing strand 30 can also comprise a biocompatible metal, such as stainless steel or Nitinol®, or a biocompatible and biodegradable metal, such as magnesium.

[000126] As indicated above, in some embodiments, the reinforcement means comprises a braided or mesh configuration.

[000127] Referring now to Figs. 4A and 4B there is shown another embodiment of a reinforced vascular graft of the invention (denoted "10d"), wherein the graft 10d includes a braided reinforcing structure 32.

[000128] According to the invention, the braided structure 32 can comprise various configurations and can be formed by various conventional means. The braided structure 32 can also comprise any of the aforementioned biocompatible and biodegradable materials.

[000129] In a preferred embodiment, the braided structure 32 comprises one of the aforementioned biodegradable polymeric materials.

[000130] In some embodiments of the invention, the vascular grafts 10a-10d further comprise at least one anchoring mechanism, such as disclosed in Co-pending Application Nos. 13/782,024 and 13/686,131, which are incorporated by reference herein in their entirety.

[000131] As will readily be appreciated by one having ordinary skill in the art, the present invention provides numerous advantages compared to prior art prosthetic valves. Among the advantages are the following:

- The provision of reinforced vascular grafts that substantially reduce or eliminate (i) the risk of thrombosis, (ii) intimal hyperplasia after intervention in a vessel, (iii) the harsh biological responses associated with conventional polymeric and metal prostheses, and (iv) the formation of biofilm, inflammation and infection.
- The provision of reinforced vascular grafts, which can be effectively employed to treat, reconstruct, replace and improve biological functions or promote the growth of new cardiovascular tissue in a cardiovascular structure.
- The provision of reinforced vascular grafts that induce host tissue proliferation, bioremodeling and regeneration of new tissue and tissue structures with site-specific structural and functional properties.
- The provision of reinforced vascular grafts, which are capable of administering a pharmacological agent to host tissue and, thereby produce a desired biological and/or therapeutic effect.

[000132] Without departing from the spirit and scope of this invention, one of ordinary skill can make various changes and modifications to the invention to adapt it to various usages and conditions. As such, these changes and modifications are properly, equitably, and intended to be, within the full range of equivalence of the following claims.

CLAIMS

What is claimed is:

1. A vascular graft for reconstructing damaged cardiovascular vessels, comprising:

a tubular member comprising decellularized extracellular matrix (ECM) material from a mammalian tissue source, said tubular member having proximal and distal ends, an outer surface and a lumen that extends therethrough

said tubular member further comprising reinforcement means, said reinforcement means comprising a linear strand of first polymeric material that is wound around and disposed proximate said tubular member outer surface.

2. The vascular graft of Claim 1, wherein said reinforcement means extends from said tubular member proximal end to said tubular member distal end.

3. The vascular graft of Claim 1, wherein said mammalian tissue source is selected from the group consisting of small intestine submucosa (SIS), urinary bladder submucosa (UBS), urinary basement membrane (UBM), liver basement membrane (LBM), stomach submucosa (SS), mesothelial tissue, subcutaneous extracellular matrix, large intestine extracellular matrix, placental extracellular matrix, ornamentum extracellular matrix, heart extracellular matrix and lung extracellular matrix.

4. The vascular graft of Claim 1, wherein said mammalian tissue source comprises an adolescent mammalian tissue source.

5. The vascular graft of Claim 1, wherein said first polymeric material comprises a biodegradable polymeric material selected from the group consisting of polyhydroxy-alkonates (PHAs), polylactides (PLLA) and polyglycolides (PLGA) and their copolymers, and polyanhydrides.

6. The vascular graft of Claim 1, wherein said first polymeric material comprises poly(urethane urea) (Artelon^{TM}).

7. The vascular graft of Claim 1, wherein said tubular member further comprises at least one additional biologically active agent.

8. The vascular graft of Claim 7, wherein said biologically active agent comprises a cell selected from the group consisting of a human embryonic stem cell, fetal cardiomyocyte, myofibroblast, and mesenchymal stem cell.

9. The vascular graft of Claim 7, wherein said biologically active agent comprises a growth factor selected from the group consisting of a transforming growth factor-alpha (TGF-α), transforming growth factor-beta (TGF-β), fibroblast growth factor-2 (FGF-2), basic fibroblast growth factor (bFGF), and vascular epithelial growth factor (VEGF).

10. The vascular graft of Claim 1, wherein said tubular member further comprises at least one pharmacological agent.

11. The vascular graft of Claim 10, wherein said pharmacological agent comprises a statin selected from the group consisting of atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin.

12. The vascular graft of Claim 10, wherein said pharmacological agent comprises an anti-arrhythmic agent selected from the group comprising quinidine, procainamide, , disopyramide, lidocaine, phenytoin, mexiletine, flecainide, propafenone, moricizine, propranolol, esmolol, timolol, metoprolol, atenolol, amiodarone, sotalol, ibutilide, dofetilide, verapamil, diltiazem, adenosine and digoxin.

13. The vascular graft of Claim 10, wherein said pharmacological agent comprises an anti-inflammatory.

14. A vascular graft for reconstructing damaged cardiovascular vessels, comprising:

a tubular member comprising decellularized first extracellular matrix (ECM) material from a first mammalian tissue source, said tubular member having proximal and distal ends, an outer surface and a lumen that extends therethrough

said tubular member further comprising reinforcement means, said reinforcement means comprising a linear strand of second ECM material from a second mammalian tissue source, said linear strand of second ECM material being wound around and disposed proximate said tubular member outer surface.

15. The vascular graft of Claim 14, wherein said reinforcement means extends from said tubular member proximal end to said tubular member distal end.

16. The vascular graft of Claim 14, wherein said first mammalian tissue source is selected from the group consisting of small intestine submucosa (SIS), urinary bladder submucosa (UBS), urinary basement membrane (UBM), liver basement membrane (LBM), stomach submucosa (SS), mesothelial tissue, subcutaneous extracellular matrix, large intestine extracellular matrix, placental extracellular matrix, ornamentum extracellular matrix, heart extracellular matrix and lung extracellular matrix.

17. The vascular graft of Claim 14, wherein said second mammalian tissue source is selected from the group consisting of small intestine submucosa (SIS), urinary bladder submucosa (UBS), urinary basement membrane (UBM), liver basement membrane (LBM), stomach submucosa (SS), mesothelial tissue, subcutaneous extracellular matrix, large intestine extracellular matrix, placental extracellular matrix, ornamentum extracellular matrix, heart extracellular matrix and lung extracellular matrix.

18. The vascular graft of Claim 14, wherein said first mammalian tissue source comprises an adolescent mammalian tissue source.

19. The vascular graft of Claim 14, wherein said tubular member further comprises at least one additional biologically active agent.

20. The vascular graft of Claim 19, wherein said biologically active agent comprises a cell selected from the group consisting of a human embryonic stem cell, fetal cardiomyocyte, myofibroblast, and mesenchymal stem cell.

21. The vascular graft of Claim 19, wherein said biologically active agent comprises a growth factor selected from the group consisting of a transforming growth factor-alpha (TGF-α), transforming growth factor-beta (TGF-β), fibroblast growth factor-2 (FGF-2), basic fibroblast growth factor (bFGF), and vascular epithelial growth factor (VEGF).

22. The vascular graft of Claim 14, wherein said tubular member further comprises at least one pharmacological agent.

23. The vascular graft of Claim 22, wherein said pharmacological agent comprises a statin selected from the group consisting of atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin.

24. The vascular graft of Claim 22, wherein said pharmacological agent comprises an anti-arrhythmic agent selected from the group comprising quinidine, procainamide, , disopyramide, lidocaine, phenytoin, mexiletine, flecainide, propafenone, moricizine, propranolol, esmolol, timolol, metoprolol, atenolol, amiodarone, sotalol, ibutilide, dofetilide, verapamil, diltiazem, adenosine and digoxin.

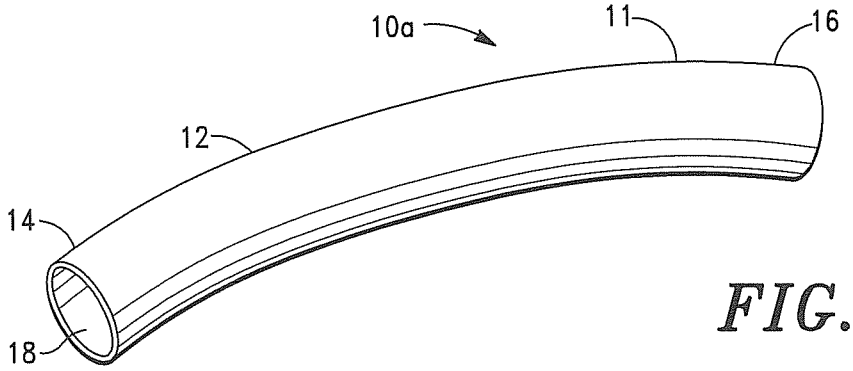

FIG. 1A

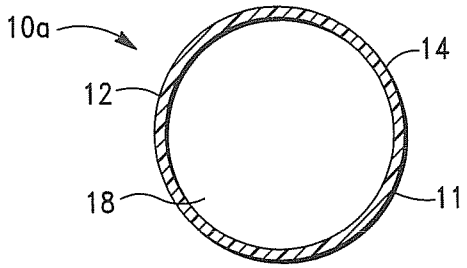

FIG. 1B

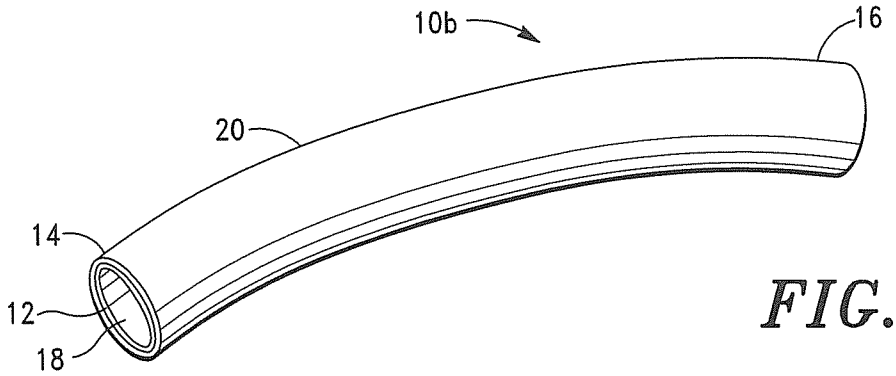

FIG. 2A

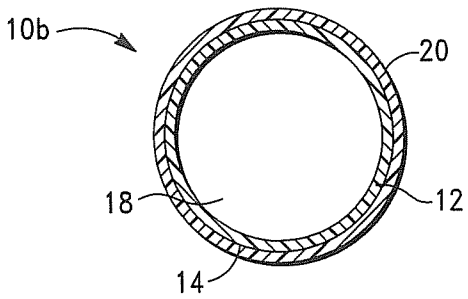

FIG. 2B

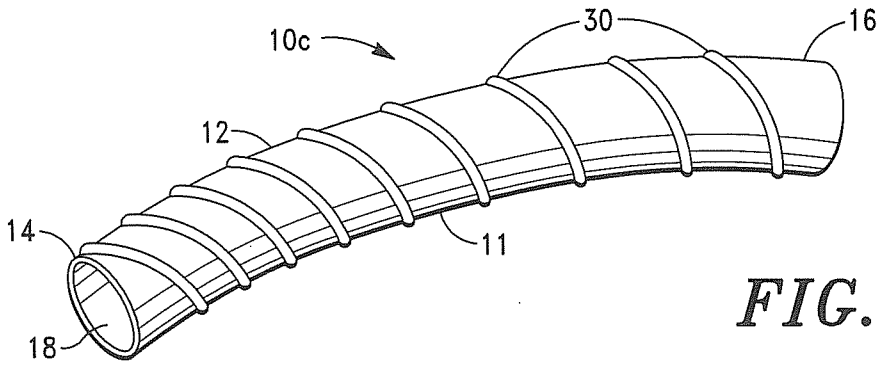

FIG. 3A

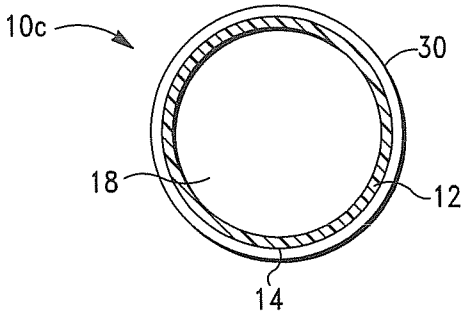

FIG. 3B

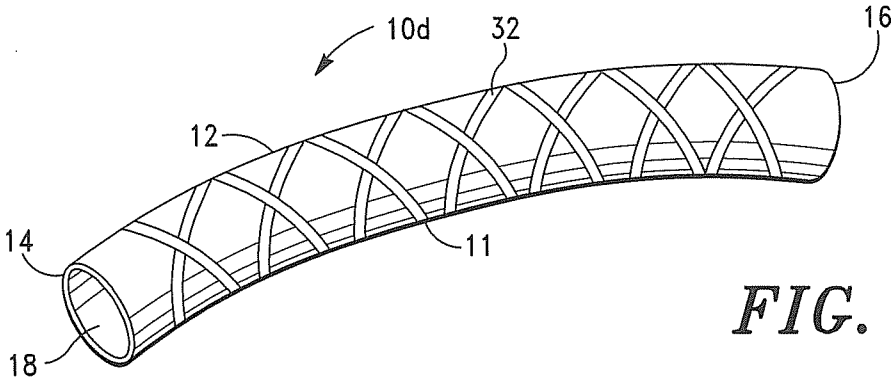

FIG. 4A

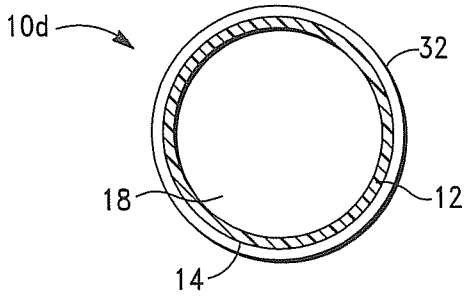

FIG. 4B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/39868

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61F 2/06 (2015.01)
CPC - A61F 02/062
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)
IPC(8): A61F 2/06 (2015.01)
CPC: A61F 02/062

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 623/1.1, 1.32, 1.38, 1.41, 1.42, 1.44, 1.46, 1.49, 1.54
CPC: A61F 02/062, A61F 2/06

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase(Full-text: AU BE BR CA CH CN DE DK EP ES FI FR GB IN JP KR SE TH TW US WO); Google Scholar (Articles and Patents); Search Terms Used: arterial vascular prosthesis graft ECM extracellular* reinforce wrap* wind* wound* spin* spun fiber* strap* strand* string* filament*

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2005/0187604 A1 (Eells et al.) 25 August 2005 (25.08.2005) entire document, especially fig. 1E and para [0040]	1-3, 7, 9, 10 ---------- 4-6, 8, 11-24
Y	US 2014/0100648 A1 (Matheny) 10 April 2014 (10.04.2014) entire document, especially fig. 3 and para [0123]	8, 11-24
Y	US 2012/0059487 A1 (Cunanan et al.) 08 March 2012 (08.03.2012) para [0011]-[0012]	4, 18
Y	US 5,628,782 A (Myers et al.) 13 May 1997 (13.05.1997) fig. 1 and column 7, lines 18-28	5
Y	US 2002/0169499 A1 (Zilla et al.) 14 November 2002 (14.11.2002) fig. 1 and para [0022]	6

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01 December 2015 (01.12.2015)	29 DEC 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/39868

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
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 continuation sheet)

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/39868

Continuation of Box III. (Lack of Unity):

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-13, directed to a vascular graft having reinforcement means comprising a linear strand of polymeric material

Group II: Claims 14-24, directed to a vascular graft having reinforcement means comprising a linear strand of ECM material

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Group I includes a linear strand of first polymeric material, which is not present in Group II.

Group II includes a linear strand of second ECM material, which is not present in Group I.

Groups I and II share the technical features of:
a vascular graft for reconstructing damaged cardiovascular vessels, comprising:
a tubular member comprising decellularized extracellular matrix (ECM) material from a mammalian tissue source, said tubular member having proximal and distal ends, an outer surface and a lumen that extends therethrough;
said tubular member further comprising reinforcement means, said reinforcement means comprising a linear strand that is wound around and disposed proximate said tubular member outer surface.

However, all of the above shared technical features do not represent a contribution over the prior art as shown as being anticipated by US 2005/0187604 A1to Eells et al.:
a vascular graft for reconstructing damaged cardiovascular vessels (see para [0002]), comprising:
a tubular member (tubular construct 33 formed of bioremodleable substance 14 cast onto form 10, see figs. 1-1B and para [0022]-[0024]) comprising decellularized extracellular matrix (ECM) material from a mammalian tissue source (bioremodelable substance comprising extracellular collagen matrix from disinfected porcine small intestine submucosa (SIS), see figs. 1-2 and para [0026]) said tubular member having proximal and distal ends, an outer surface and a lumen that extends therethrough;
said tubular member further comprising reinforcement means (straps 28, see figs. 1E and para [0040]), said reinforcement means comprising a linear strand that is wound around and disposed proximate said tubular member outer surface (straps 28 are wound around the outside of the graft, see figs. 1E and para [0040]).

Therefore, Groups I-II lack unity under PCT Rule 13.