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(54) Title: COATING CONTAINING PEGYLATED HYALURONIC ACID AND A PEGYLATED NON-HYALURONIC ACID POLYMER

(57) Abstract: Provided herein are a coating or a device (e.g., absorbable stent) that includes a PEGylated hyaluronic acid and a PEGylated non-hyaluronic acid biocompatible polymer and the methods of use thereof.



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COATING CONTAINING PEGYLATED HYALURONIC ACID AND A PEGYLATED NON-HYALURONIC ACID POLYMER

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BACKGROUND OF THE INVENTION

Field of the Invention

This invention generally relates to a coating or a medical device such as stent
10 formed of a PEGylated hyaluronic acid (HA) and a PEGylated non-HA polymer.

Description of the Background

A current paradigm in the art of stenting is to use biomaterials to modulate
biological responses to the implant surface. One of the biomaterials is hyaluronic acid
(HA). Due to HA's hydrophilicity, it is often modified for the ease of manufacture
15 process. One of the modification methods is to modify HA with PEG and/or adding
positive charge tridodecyl methyl ammonium chloride (TDMAC) to neutralize the
negative charges of HA to make the HA dissolvable in an organic solvent. However, a
coating formed of such derivatized HA often lacks the mechanical properties required of
the coating for an implantable device (e.g., a stent).

20 The present invention provides embodiments as follows to address the above-
identified needs and problems.

SUMMARY OF THE INVENTION

The present invention provides for a polymer blend that includes a PEGylated HA
and a PEGylated non-HA polymer. The polymer defined herein can be used alone or in
25 combination with another biocompatible polymer and/or a biobeneficial material to form
coatings on implantable medical devices or to form the implantable medical devices
themselves. The polymers or polymer blends described herein can also be used to form

the implantable device itself. The implantable device can optionally include a bioactive agent. Some exemplary bioactive agents are paclitaxel, docetaxel, estradiol, nitric oxide donors, super oxide dismutases, super oxide dismutases mimics, 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl (4-amino-TEMPO), biolimus, tacrolimus, dexamethasone, rapamycin, rapamycin derivatives, 40-*O*-(2-hydroxy)ethyl-rapamycin (everolimus), 40-*O*-(3-hydroxy)propyl-rapamycin, 40-*O*-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, and 40-*O*-tetrazole-rapamycin, ABT-578, clobetasol, prodrugs thereof, co-drugs thereof, and combinations thereof. The implantable device can be implanted in a patient to treat or prevent a disorder such as atherosclerosis, thrombosis, restenosis, hemorrhage, vascular dissection or perforation, vascular aneurysm, vulnerable plaque, chronic total occlusion, claudication anastomotic proliferation for vein and artificial grafts, bile duct obstruction, ureter obstruction, tumor obstruction, or combinations thereof.

DETAILED DESCRIPTION

The present invention provides for a polymer blend that includes a PEGylated HA and a PEGylated non-HA polymer. The polymer defined herein can be used alone or in combination with another biocompatible polymer and/or a biobeneficial material to form coatings on implantable medical devices or to form the implantable medical devices themselves. The coating or device can optionally include one or more other biocompatible polymers. The coating or device can optionally include one or more biobeneficial materials. Further, the coating or device can optionally include one or more bioactive agents.

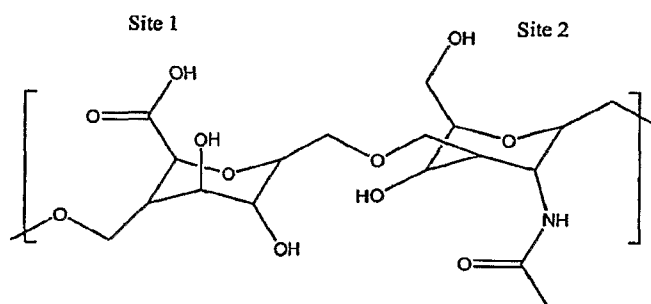
The PEGylated HA and the PEGylated non-HA polymer can be used in the ratio (PEGylated HA/PEGylated non-HA) of between about 0.01:0.99 and about 0.99:0.01, between about 0.1:0.9 and about 0.9:0.1, between about 0.2:0.8 and about 0.8:0.2, between about 0.3:0.7 and about 0.7:0.3, or between about 0.4:0.6 and about 0.6:0.4 or of

about 0.5:0.5.

A device having a coating described herein can be used to treat, prevent, or ameliorate disorder such as atherosclerosis, thrombosis, restenosis, hemorrhage, vascular dissection or perforation, vascular aneurysm, vulnerable plaque, chronic total occlusion, claudicationanastomotic proliferation for vein and artificial grafts, bile duct obstruction, ureter obstruction, tumor obstruction, or combinations thereof.

PEGylated HA

The term hyaluronic acid (HA) includes HA molecules, fragments, and derivatives thereof. In particular, the term HA and HA fragments as used herein refers to any molecules that have a unit or repeating units as shown in Formula I:



Formula I

Depending on the number of the units of Formula I present, the HA can have a weight-average molecule weight (M_w) in the range from about 250 Daltons to about 10,000,000 Daltons, e.g., about 500 Daltons to about 1,000,000 Daltons, about 1000 Daltons to about 500,000 Daltons, about 2,000 Daltons to about 400,000 Daltons, about 5,000 Daltons to about 300,000 Daltons, about 10,000 Daltons to about 200,000 Daltons, about 10,000 Daltons to about 100,000 Daltons, about 10,000 Daltons to about 75,000 Daltons, or about 10,000 Daltons to about 50,000 Daltons. Some embodiments specifically exclude one or more HA or HA fragments having the molecular weight ranges described herein.

As used herein, the term PEGylated refers to being modified with poly(ethylene

glycol) (PEG) or a molecule of the similar nature via a covalent bond or non-covalent force such as ionic interaction or hydrogen bonding. Molecules similar to PEG in nature include, but are not limited to, poly(olefin glycol) such as polypropylene glycol, poly(olefin oxide) such as poly(ethylene oxide or poly(propylene oxide), or a copolymer
5 having a PEG block, a poly(olefin glycol) block, and/or a poly(olefin oxide) block such as PLURONICTM surfactants (polypropylene oxide-co-polyethylene glycol) or poly(tetramethylene glycol).

The PEG molecules as used herein have a weight average molecular weight (M_w) preferably below about 50,000 Daltons, e.g., in the range from about 100 Daltons to about
10 50,000 Daltons, about 150 Daltons to about 45,000 Daltons, about 300 Daltons to about 45,000 Daltons, about 500 Daltons to about 45,000 Daltons, about 750 Daltons to about 45,000 Daltons, about 1,000 Daltons to about 45,000 Daltons, about 1,500 Daltons to about 45,000 Daltons, about 3,000 Daltons to about 45,000 Daltons, about 5,000 Daltons to about 45,000 Daltons, about 7,500 Daltons to about 45,000 Daltons, about 10,000
15 Daltons to about 45,000 Daltons, about 15,000 Daltons to about 45,000 Daltons, about 20,000 Daltons to about 45,000 Daltons, about 25,000 Daltons to about 45,000 Daltons, about 30,000 Daltons to about 45,000 Daltons, about 35,000 Daltons to about 45,000 Daltons, about 40,000 Daltons to about 45,000 Daltons. Some embodiments specifically exclude one or more PEG molecules having the molecular weight ranges described herein.

20 In some embodiments, the PEGylated HA described herein can have a weight average molecular weight (M_w) in the range from about 250 Daltons to about 10,000,000 Daltons, e.g., about 500 Daltons to about 1,000,000 Daltons, about 1000 Daltons to about 500,000 Daltons, about 2,000 Daltons to about 400,000 Daltons, about 5,000 Daltons to about 300,000 Daltons, about 10,000 Daltons to about 200,000 Daltons, about 10,000
25 Daltons to about 100,000 Daltons, about 10,000 Daltons to about 75,000 Daltons, or about

10,000 Daltons to about 50,000 Daltons. In some embodiments, the PEGylated HA can have a molecular weight in the range from about ,000 Daltons about 320,000 Daltons. Some embodiments specifically exclude one or more PEGylated HA or HA fragments having the molecular weight ranges described herein.

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PEGylated non-HA Polymer

The term PEGylated non-HA polymer, as used herein, refers to any biocompatible polymer modified with a PEG molecule. The modification by PEG molecule of the biocompatible polymer can be in any form known in the art. For example, the PEGylated non-HA polymer can have PEG molecule in the backbone in the form of a block
 10 copolymer or random copolymer. Alternatively, the PEGylated non-HA polymer can have PEG molecules as pendant groups.

The non-HA polymer can be any biocompatible polymer commonly used in the art of medical or biomedical coating. Some examples of the non-HA polymer for forming the PEGylated non-HA polymer include, but are not limited to, poly(ester amide), polyacids,
 15 polyesters, polyhydroxyalkanoates (PHA), polycaprolactone, poly(lactide-co-caprolactone), poly(glycolide-co-caprolactone), poly(dioxanone), poly(ortho esters), poly(anhydrides), poly(tyrosine carbonates), poly(tyrosine arylates) and derivatives thereof, poly(tyrosine ester) and derivatives thereof, poly(imino carbonates), poly(glycolic acid-co-trimethylene carbonate), polyphosphoester, polyphosphoester urethane,
 20 poly(amino acids), polycyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), polyurethanes, polyphosphazenes, silicones, polyolefins, polyisobutylene and ethylene-alphaolefin copolymers, acrylic polymers and copolymers, vinyl halide polymers and copolymers, such as polyvinyl chloride, polyvinyl ethers, such as polyvinyl methyl ether, polyvinylidene halides, such as polyvinylidene chloride,
 25 polyacrylonitrile, polyvinyl ketones, polyvinyl aromatics, such as polystyrene, polyvinyl

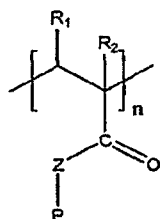
esters, such as polyvinyl acetate, copolymers of vinyl monomers with each other and olefins, such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers, polyamides, such as Nylon 66 and polycaprolactam, alkyd resins, polycarbonates, polyoxymethylenes, polyimides, polyethers, poly(glyceryl sebacate), poly(propylene fumarate), poly(*n*-butyl methacrylate), poly(*sec*-butyl methacrylate), poly(isobutyl methacrylate), poly(*tert*-butyl methacrylate), poly(*n*-propyl methacrylate), poly(isopropyl methacrylate), poly(ethyl methacrylate), poly(methyl methacrylate), epoxy resins, polyurethanes, rayon, rayon-triacetate, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ethers, carboxymethyl cellulose, polyethers, poly(ether ester), polyalkylene oxalates, polyphosphazenes, phosphoryl choline, choline, poly(aspirin), polymers and co-polymers of hydroxyl bearing monomers such as HEMA, hydroxypropyl methacrylate (HPMA), hydroxypropylmethacrylamide, PEG acrylate (PEGA), PEG methacrylate, 2-methacryloyloxyethylphosphorylcholine (MPC) and *n*-vinyl pyrrolidone (VP), carboxylic acid bearing monomers such as methacrylic acid (MA), acrylic acid (AA), alkoxymethacrylate, alkoxyacrylate, and 3-trimethylsilylpropyl methacrylate (TMSPPMA), copoly(ether-esters), hydroxy functional poly(vinyl pyrrolidone), biomolecules such as collagen, chitosan, alginate, fibrin, fibrinogen, cellulose, starch, collagen, dextran, dextrin, fragments and derivatives of hyaluronic acid, heparin, fragments and derivatives of heparin, glycosamino glycan (GAG), GAG derivatives, polysaccharide, elastin, chitosan, alginate, or combinations thereof. In some embodiments, the copolymer described herein can exclude any one of the aforementioned polymers.

The term PHA as used herein includes, but is not limited to, poly(2-hydroxyacids), poly(3-hydroxyacids), poly(4-hydroxyacids), and copolymers that include any of 2-

hydroxyacids, 3-hydroxyacids, and/or 4-hydroxyacids. 2-hydroxyacids include, but are not limited to, lactic acid, glycolic acid and other hydroxyacids having a substituent on the second carbon position of the 2-hydroxyacid molecule. 3-Hydroxyacids include, but are not limited to, 3-hydroxypropanoic acid, 3-hydroxybutyric acid, 3-hydroxyvaleric acid, 3-hydroxypentanoic acid, 3-hydroxyhexanoic acid, or 3-hydroxyhepanoic acid and other hydroxyacids having a substituent on the third carbon position of the 3-hydroxyacid molecule. 4-Hydroxyacids include, but are not limited to, 4-hydroxybutyric acid, 4-hydroxyvaleric acid, 4-hydroxypentanoic acid, 4-hydroxyhexanoic acid, 4-hydroxyhepanoic acid, or 4-hydroxyoctanoic acid and other hydroxyacids having a substituent on the fourth carbon position of the 4-hydroxyacid molecule. can be found in , Ed, Marcel Dekker, 2001; and , Eds. Academic Press, New York, 1996.

The hydroxyacids provided above, other than glycolic acid, are optically active and can include the L-enantiomer, the D-enantiomer, a blend of L-enantiomer and D-enantiomer, and a racemic mixture of the L-enantiomer and the D-enantiomer thereof. For example, the term PLA includes, but are not limited to, poly(D,L-lactide), poly(L-lactide), poly(L-lactide-co-D,L-lactide), poly(D,L-lactide-co-glycolide), or poly(L-lactide-co-glycolide).

Some examples of these PEGylated non-HA polymers include acrylate or methacrylate based polymers having a general formula of



where R_1 and R_2 are independently H, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, or phenyl, where Z is O, S, or NR_3 where R_3 is H, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, or phenyl, where P is a PEG molecule, and where n is a

positive integer ranging from 1 to 100,000.

Other examples of PEGylated non-HA polymers include PEGylated bioactive agents. Such bioactive agents or drugs can be a peptide, protein, antibody, or a drug. Examples of PEGylated proteins and peptides are PEGylated RGD peptide, PEGylated ANP peptide, PEGylated CNP peptide, and PEGylated osteopontin or combinations thereof. In some embodiments, such PEGylated bioactive agents include PEGylated Examples of PEGylated drugs include PEGylated anti-proliferatives, PEGylated inflammatories, and combinations thereof.

Other examples PEGylated non-HA polymer include, but are not limited to, e.g. poly(ethylene oxide)/poly(lactic acid) (PEO/PLA), poly(styrene-isoprene-styrene)-PEG (SIS-PEG), polystyrene-PEG, polyisobutylene-PEG, polycaprolactone-PEG (PCL-PEG), poly(lactic acid-co-PEG) (PLA-PEG), poly(methyl methacrylate)-PEG (PMMA-PEG), polydimethylsiloxane-co-PEG (PDMS-PEG), and poly(vinylidene fluoride)-PEG (PVDF-PEG).

In a preferred embodiment, the PEGylated non-HA polymer is PEGylated PLA or contains a PEGylated PLA block or moiety.

Non-HA polymers

In some embodiments, the coating or absorbable device (e.g., absorbable stent) can optionally include one or more Non-HA polymers. The combination can be mixed, blended, or coated in separate layers. The additional biocompatible polymer can be biodegradable (both bioerodable or bioabsorbable) or nondegradable, and can be hydrophilic or hydrophobic.

Representative biocompatible polymers include, but are not limited to, poly(ester amide), polyhydroxyalkanoates (PHA), poly(3-hydroxyalkanoates) such as poly(3-hydroxypropanoate), poly(3-hydroxybutyrate), poly(3-hydroxyvalerate), poly(3-

hydroxyhexanoate), poly(3-hydroxyheptanoate) and poly(3-hydroxyoctanoate), poly(4-hydroxyalkanoate) such as poly(4-hydroxybutyrate), poly(4-hydroxyvalerate), poly(4-hydroxyhexanoate), poly(4-hydroxyheptanoate), poly(4-hydroxyoctanoate) and copolymers including any of the 3-hydroxyalkanoate or 4-hydroxyalkanoate monomers described
5 herein or blends thereof, poly(D,L-lactide), poly(L-lactide), polyglycolide, poly(D,L-lactide-co-glycolide), poly(L-lactide-co-glycolide), polycaprolactone, poly(lactide-co-caprolactone), poly(glycolide-co-caprolactone), poly(dioxanone), poly(ortho esters), poly(anhydrides), poly(tyrosine carbonates) and derivatives thereof, poly(tyrosine ester) and derivatives thereof, poly(imino carbonates), poly(glycolic acid-co-trimethylene
10 carbonate), polyphosphoester, polyphosphoester urethane, poly(amino acids), polycyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), polyurethanes, polyphosphazenes, silicones, polyesters, polyolefins, polyisobutylene and ethylene-alphaolefin copolymers, acrylic polymers and copolymers, vinyl halide polymers and copolymers, such as polyvinyl chloride, polyvinyl ethers, such as polyvinyl methyl ether,
15 polyvinylidene halides, such as polyvinylidene chloride, polyacrylonitrile, polyvinyl ketones, polyvinyl aromatics, such as polystyrene, polyvinyl esters, such as polyvinyl acetate, copolymers of vinyl monomers with each other and olefins, such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers, polyamides, such as Nylon 66 and polycaprolactam,
20 alkyd resins, polycarbonates, polyoxymethylenes, polyimides, polyethers, poly(glyceryl sebacate), poly(propylene fumarate), poly(n-butyl methacrylate), poly(sec-butyl methacrylate), poly(isobutyl methacrylate), poly(tert-butyl methacrylate), poly(n-propyl methacrylate), poly(isopropyl methacrylate), poly(ethyl methacrylate), poly(methyl methacrylate), epoxy resins, polyurethanes, rayon, rayon-triacetate, cellulose acetate,
25 cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose

propionate, cellulose ethers, carboxymethyl cellulose, polyethers such as poly(ethylene glycol) (PEG), copoly(ether-esters) (e.g. PEO/PLA), polyalkylene oxides such as poly(ethylene oxide), poly(propylene oxide), poly(ether ester), polyalkylene oxalates, polyphosphazenes, phosphoryl choline, choline, poly(aspirin), polymers and co-polymers of hydroxyl bearing monomers such as HEMA, hydroxypropyl methacrylate (HPMA), hydroxypropylmethacrylamide, PEG acrylate (PEGA), PEG methacrylate, 2-methacryloyloxyethylphosphorylcholine (MPC) and *n*-vinyl pyrrolidone (VP), carboxylic acid bearing monomers such as methacrylic acid (MA), acrylic acid (AA), alkoxymethacrylate, alkoxyacrylate, and 3-trimethylsilylpropyl methacrylate (TMSPMA), poly(styrene-isoprene-styrene)-PEG (SIS-PEG), polystyrene-PEG, polyisobutylene-PEG, polycaprolactone-PEG (PCL-PEG), PLA-PEG, poly(methyl methacrylate)-PEG (PMMA-PEG), polydimethylsiloxane-co-PEG (PDMS-PEG), poly(vinylidene fluoride)-PEG (PVDF-PEG), PLURONIC™ surfactants (polypropylene oxide-co-polyethylene glycol), poly(tetramethylene glycol), hydroxy functional poly(vinyl pyrrolidone), biomolecules such as collagen, chitosan, alginate, fibrin, fibrinogen, cellulose, starch, collagen, dextran, dextrin, fragments and derivatives of hyaluronic acid, heparin, fragments and derivatives of heparin, glycosamino glycan (GAG), GAG derivatives, polysaccharide, elastin, chitosan, alginate, or combinations thereof. In some embodiments, the copolymer described herein can exclude any one of the aforementioned polymers.

As used herein, the terms poly(D,L-lactide), poly(L-lactide), poly(D,L-lactide-co-glycolide), and poly(L-lactide-co-glycolide) can be used interchangeably with the terms poly(D,L-lactic acid), poly(L-lactic acid), poly(D,L-lactic acid-co-glycolic acid), or poly(L-lactic acid-co-glycolic acid), respectively.

Biobeneficial Material

In some embodiments, a coating having the features described above can include a

biobeneficial material. The biobeneficial material can be a polymeric material or non-polymeric material. The biobeneficial material is preferably non-toxic, non-antigenic and non-immunogenic. A biobeneficial material is one which enhances the biocompatibility of the coating or device by being non-fouling, hemocompatible, actively non-thrombogenic, or anti-inflammatory, all without depending on the release of a pharmaceutically active agent.

Representative biobeneficial materials include, but are not limited to, polyethers such as poly(ethylene glycol), copoly(ether-esters) (e.g. PEO/PLA), polyalkylene oxides such as poly(ethylene oxide), poly(propylene oxide), poly(ether ester), polyalkylene oxalates, polyphosphazenes, phosphoryl choline, choline, poly(aspirin), polymers and copolymers of hydroxyl bearing monomers such as hydroxyethyl methacrylate (HEMA), hydroxypropyl methacrylate (HPMA), hydroxypropylmethacrylamide, poly(ethylene glycol) acrylate (PEGA), PEG methacrylate, 2-methacryloyloxyethylphosphorylcholine (MPC) and *n*-vinyl pyrrolidone (VP), carboxylic acid bearing monomers such as methacrylic acid (MA), acrylic acid (AA), alkoxymethacrylate, alkoxyacrylate, and 3-trimethylsilylpropyl methacrylate (TMSPMA), poly(styrene-isoprene-styrene)-PEG (SIS-PEG), polystyrene-PEG, polyisobutylene-PEG, polycaprolactone-PEG (PCL-PEG), PLA-PEG, poly(methyl methacrylate)-PEG (PMMA-PEG), polydimethylsiloxane-co-PEG (PDMS-PEG), poly(vinylidene fluoride)-PEG (PVDF-PEG), PluronicTM surfactants (polypropylene oxide-co-polyethylene glycol), poly(tetramethylene glycol), hydroxy functional poly(vinyl pyrrolidone), biomolecules such as fibrin, fibrinogen, cellulose, starch, collagen, dextran, dextrin, heparin, fragments and derivatives of heparin, glycosamino glycan (GAG), GAG derivatives, polysaccharide, elastin, chitosan, alginate, silicones, PolyActiveTM, and combinations thereof. In some embodiments, the coatings can exclude any one of the aforementioned polymers.

The term PolyActive™ refers to a block copolymer having flexible poly(ethylene glycol) and poly(butylene terephthalate) blocks (PEGT/PBT). PolyActive™ is intended to include AB, ABA, BAB copolymers having such segments of PEG and PBT (e.g., poly(ethylene glycol)-block-poly(butylene terephthalate)-block poly(ethylene glycol) (PEG-PBT-PEG).

Bioactive Agents

A coating described above can include any bioactive agent. The bioactive agent can be any bioactive agent, which is a therapeutic, prophylactic, or diagnostic agent. These agents can have anti-proliferative or anti-inflammatory properties or can have other properties such as antineoplastic, antiplatelet, anti-coagulant, anti-fibrin, antithrombotic, antimitotic, antibiotic, antiallergic, and antioxidant. The agents can be cytostatic agents, agents that promote the healing of the endothelium such as NO releasing or generating agents, agents that attract endothelial progenitor cells, or agents that promote the attachment, migration and proliferation of endothelial cells (e.g., natriuretic peptide such as CNP, ANP or BNP peptide or an RGD or cRGD peptide), while quenching smooth muscle cell proliferation. Examples of suitable therapeutic and prophylactic agents include synthetic inorganic and organic compounds, proteins and peptides, polysaccharides and other sugars, lipids, and DNA and RNA nucleic acid sequences having therapeutic, prophylactic or diagnostic activities. Some other examples of the bioactive agent include antibodies, receptor ligands, enzymes, adhesion peptides, blood clotting factors, inhibitors or clot dissolving agents such as streptokinase and tissue plasminogen activator, antigens for immunization, hormones and growth factors, oligonucleotides such as antisense oligonucleotides and ribozymes and retroviral vectors for use in gene therapy. Examples of anti-proliferative agents include rapamycin and its functional or structural derivatives, 40-O-(2-hydroxy)ethyl-rapamycin (everolimus), and

its functional or structural derivatives, paclitaxel and its functional and structural derivatives. Examples of rapamycin derivatives include 40-epi-(N1-tetrazolyl)-rapamycin (ABT-578), 40-*O*-(3-hydroxy)propyl-rapamycin, 40-*O*-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, and 40-*O*-tetrazole-rapamycin. Examples of paclitaxel derivatives include docetaxel. Examples of antineoplastics and/or antimitotics include methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin hydrochloride (e.g. Adriamycin[®] from Pharmacia & Upjohn, Peapack N.J.), and mitomycin (e.g. Mutamycin[®] from Bristol-Myers Squibb Co., Stamford, Conn.). Examples of such antiplatelets, anticoagulants, antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, thrombin inhibitors such as Angiomax (Biogen, Inc., Cambridge, Mass.), calcium channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonists, lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug, brand name Mevacor[®] from Merck & Co., Inc., Whitehouse Station, NJ), monoclonal antibodies (such as those specific for Platelet-Derived Growth Factor (PDGF) receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), nitric oxide or nitric oxide donors, super oxide dismutases, super oxide dismutase mimetic, 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl (4-amino-TEMPO), estradiol, anticancer agents, dietary supplements such as various vitamins, and a combination thereof. Examples of anti-inflammatory agents including steroidal and non-steroidal anti-inflammatory agents include tacrolimus, dexamethasone, clobetasol, or combinations thereof. Examples of

cytostatic substances include angiopeptin, angiotensin converting enzyme inhibitors such as captopril (e.g. Capoten[®] and Capozide[®] from Bristol-Myers Squibb Co., Stamford, Conn.), cilazapril or lisinopril (e.g. Prinivil[®] and Prinzide[®] from Merck & Co., Inc., Whitehouse Station, NJ). An example of an antiallergic agent is permirolast potassium.

- 5 Other therapeutic substances or agents which may be appropriate include alpha-interferon, pimecrolimus, imatinib mesylate, midostaurin, bioactive RGD, and genetically engineered endothelial cells. The foregoing substances can also be used in the form of prodrugs or co-drugs thereof. The foregoing substances also include metabolites thereof and/or prodrugs of the metabolites. The foregoing substances are listed by way of example and
- 10 are not meant to be limiting. Other active agents which are currently available or that may be developed in the future are equally applicable.

The dosage or concentration of the bioactive agent required to produce a favorable therapeutic effect should be less than the level at which the bioactive agent produces toxic effects and greater than the level at which non-therapeutic results are obtained. The

15 dosage or concentration of the bioactive agent can depend upon factors such as the particular circumstances of the patient, the nature of the trauma, the nature of the therapy desired, the time over which the ingredient administered resides at the vascular site, and if other active agents are employed, the nature and type of the substance or combination of substances. Therapeutic effective dosages can be determined empirically, for example by

20 infusing vessels from suitable animal model systems and using immunohistochemical, fluorescent or electron microscopy methods to detect the agent and its effects, or by conducting suitable in vitro studies. Standard pharmacological test procedures to determine dosages are understood by one of ordinary skill in the art.

Examples of Implantable Device

25 As used herein, an implantable device may be any suitable medical substrate that

can be implanted in a human or veterinary patient. Examples of such implantable devices include self-expandable stents, balloon-expandable stents, stent-grafts, grafts (e.g., aortic grafts), heart valve prostheses, cerebrospinal fluid shunts, pacemaker electrodes, catheters, endocardial leads (e.g., FINELINE and ENDOTAK, available from Guidant Corporation, Santa Clara, CA), anastomotic devices (e.g., CABG anastomotic clips) and connectors, orthopedic implants such as screws, spinal implants, and electro-stimulatory devices. The underlying structure of the device can be of virtually any design. The device can be made of a metallic material or an alloy such as, but not limited to, cobalt chromium alloy (ELGILOY), stainless steel (316L), high nitrogen stainless steel, e.g., BIODUR 108, cobalt chrome alloy L-605, "MP35N," "MP20N," ELASTINITE (Nitinol), tantalum, nickel-titanium alloy, platinum-iridium alloy, gold, magnesium, or combinations thereof. "MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from Standard Press Steel Co., Jenkintown, PA. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum. Devices made from bioabsorbable or biostable polymers could also be used with the embodiments of the present invention. In some embodiments, the device is a absorbable stent.

Method of Use

In accordance with embodiments of the invention, a coating subjected to the treatment of a phase inversion process described above can be used to provided controlled release of a bioactive agent from a medical device (e.g., stent) during delivery and (in the case of a stent) expansion of the device, or thereafter, at a desired rate and for a predetermined time at the implantation site .

Preferably, the medical device is a stent. The stent described herein is useful for a variety of medical procedures, including, for example, treatment of obstructions caused by

tumors in bile ducts, esophagus, trachea/bronchi and other biological passageways. A stent having the above-described coating is particularly useful for treating diseased regions of blood vessels caused by lipid deposition, monocyte or macrophage infiltration, or dysfunctional endothelium or a combination thereof, or occluded regions of blood vessels caused by abnormal or inappropriate migration and proliferation of smooth muscle cells, thrombosis, and restenosis. Stents may be placed in a wide array of blood vessels, both arteries and veins. Representative examples of sites include the iliac, renal, carotid and coronary arteries.

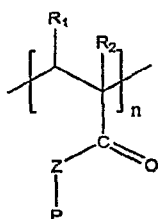
For implantation of a stent, an angiogram is first performed to determine the appropriate positioning for stent therapy. An angiogram is typically accomplished by injecting a radiopaque contrasting agent through a catheter inserted into an artery or vein as an x-ray is taken. A guidewire is then advanced through the lesion or proposed site of treatment. Over the guidewire is passed a delivery catheter that allows a stent in its collapsed configuration to be inserted into the passageway. The delivery catheter is inserted either percutaneously or by surgery into the femoral artery, brachial artery, femoral vein, or brachial vein, and advanced into the appropriate blood vessel by steering the catheter through the vascular system under fluoroscopic guidance. A stent having the above-described features may then be expanded at the desired area of treatment. A post-insertion angiogram may also be utilized to confirm appropriate positioning.

While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from this invention in its broader aspects. Therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.

CLAIMS

What is claimed is:

1. A composition comprising a PEGylated hyaluronic acid (HA) and a PEGylated non-HA polymer,
 wherein the PEGylated HA and the non-HA polymer are independently modified with poly(ethylene glycol) (PEG), PEG like molecule or a combination thereof, and
 wherein the PEGylated HA has a molecular weight in the range from about 7,000 Daltons 320,000 Daltons.
2. The composition of claim 1, wherein the PEG like molecule is selected from the group consisting of polyethers, polyglycols, polyalkylene oxides, and combinations thereof.
3. The composition of claim 1, wherein the PEGylated non-HA polymer is selected from the group consisting of polyesters, polyacrylates, PEGylated peptides, PEGylated proteins, and combinations thereof.
4. The composition of claim 1, wherein the PEGylated non-HA polymer is



- wherein R_1 and R_2 are independently H, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, or phenyl,
- wherein Z is O, S, or NR_3 where R_3 is H, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, or phenyl,
- wherein P is PEG or the PEG like molecule, and
- wherein n is a positive integer ranging from 1 to 100,000.

5. The composition of claim 1, wherein the PEGylated non-HA polymer is PEGylated poly(lactic acid) (PLA).
6. The composition of claim 1, wherein the PEG molecule has a weight average molecular weight (M_w) below about 45,000 Daltons.
7. An implantable device comprising a coating that comprises the composition of claim 1.
8. An implantable device comprising a coating that comprises the composition of claim 2.
9. An implantable device comprising a coating that comprises the composition of claim 3.
10. An implantable device comprising a coating that comprises the composition of claim 4.
11. An implantable device comprising a coating that comprises the composition of claim 5.
12. An implantable device comprising a coating that comprises the composition of claim 6.
13. An implantable device comprising a coating that comprises the composition of claim 7.
14. The implantable device of claim 8, wherein the coating further comprises a bioactive agent.
15. The implantable device of claim 14, wherein the bioactive agent is selected from the group consisting of paclitaxel, docetaxel, estradiol, nitric oxide donors, super oxide dismutases, super oxide dismutases mimics, 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl (4-amino-TEMPO), biolimus, tacrolimus, dexamethasone, rapamycin, rapamycin derivatives, 40-*O*-(2-hydroxy)ethyl-rapamycin (everolimus), 40-*O*-(3-hydroxy)propyl-

rapamycin, 40-*O*-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, and 40-*O*-tetrazole-rapamycin, 40-*epi*-(N1-tetrazolyl)-rapamycin (ABT-578), clobetasol, pimecrolimus, imatinib mesylate, midostaurin, prodrugs thereof, co-drugs thereof, and a combination thereof.

16. The implantable device of claim 15, which is a stent.

17. An absorbable stent formed of the composition of claim 1.

18. A method of treating, preventing or ameliorating a disorder in a patient comprising implanting in the patient the implantable device of claim 15,

wherein the disorder is selected from the group consisting of atherosclerosis, thrombosis, restenosis, hemorrhage, vascular dissection or perforation, vascular aneurysm, vulnerable plaque, chronic total occlusion, patent foramen ovale, claudication, anastomotic proliferation for vein and artificial grafts, bile duct obstruction, ureter obstruction, tumor obstruction, and combinations thereof.

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/004558

A. CLASSIFICATION OF SUBJECT MATTER

INV. C08L5/00 A61L31/10 C08L71/02

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)

C08L C08B A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, INSPEC, COMPENDEX, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2005/244363 A1 (HOSSAINY SYED F A [US] ET AL) 3 November 2005 (2005-11-03) claims; example 2 paragraphs [0036], [0055] - [0063]	1-18
A	US 2005/112170 A1 (HOSSAINY SYED F [US] ET AL) 26 May 2005 (2005-05-26) paragraphs [0048], [0049], [0058] claims; examples	1-18
A	WO 2004/022603 A (LG LIFE SCIENCES LTD [KR]; CHO KWANG YONG [KR]; KIM JIN HOON [KR]; LEE) 18 March 2004 (2004-03-18) claims; examples	1-18



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

24 July 2007

Date of mailing of the international search report

02/08/2007

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/004558

Box 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:
Rule 39.1(iv) PCT – Method for treatment of the human or animal body by therapy
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 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 fee, 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
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2007/004558

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