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(54) Title: POLYMERS OF FLUORINATED MONOMERS AND HYDROCARBON MONOMERS

(57) Abstract: A polymer of fluorinated monomers and hydrocarbon monomers is provided. It is also provided a polymer blend that contains a polymer formed of fluorinated monomers and hydrocarbon monomers and another biocompatible polymer. The polymer or polymer blend described herein and optionally a bioactive agent can form an implantable device such as a stent or a coating on an implantable device such as a drug-delivery stent, which can be used for treating or preventing 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.



WO 2006/069010 A2

POLYMERS OF FLUORINATED MONOMERS AND HYDROCARBON  
MONOMERS

5

Stephen D. Pacetti

BACKGROUND OF THE INVENTION

Field of the Invention

This invention generally relates to a polymeric material useful for coating  
10 an implantable device, such as a stent.

Description of the Background

Although stents work well mechanically, the chronic issues of restenosis  
and, to a lesser extent, stent thrombosis remain. Pharmacological therapy in the  
form of a drug-delivery stent appears a feasible means to tackle these biologically  
15 derived issues. Polymeric coatings placed onto the stent serve to act both as the  
drug reservoir, and to control the release of the drug. One of the commercially  
available polymer coated products is a stent manufactured by Boston Scientific.  
For example, U.S. Patent Nos. 5,869,127; 6,099,563; 6,179,817; and 6,197,051,  
assigned to Boston Scientific Corporation, describe various compositions for  
20 coating medical devices. These compositions provide to stents described therein  
an enhanced biocompatibility and may optionally include a bioactive agent. U.S.  
Patent No. 6,231,590 to Scimed Life Systems, Inc., describes a coating  
composition, which includes a bioactive agent, a collagenous material, or a  
collagenous coating optionally containing or coated with other bioactive agents.

The nature of the coating polymers plays an important role in defining the surface properties of a coating. For example, a very low  $T_g$ , amorphous coating material induces unacceptable rheological behavior upon mechanical perturbation such as crimping, balloon expansion, etc. On the other hand, a high  $T_g$ , or highly  
5 crystalline coating material introduces brittle fracture in the high strain areas of the stent pattern. Furthermore, a very low  $T_g$ , amorphous coating material can have a high drug permeability leading to an unacceptably high drug release rate. While a high  $T_g$ , or highly crystalline coating material can have a very low polymer permeability, which lead to an unacceptably low drug release rate. These are  
10 general principles which must also be combined with the properties of the drug such as the drug solubility in the polymer and in the tissue.

Some of the currently used polymeric materials have some undesirable properties such as lack of sufficient elongation to use on a stent or low permeability to drugs. One such polymer is poly(vinylidene fluoride) (PVDF).  
15 Therefore, there is a need for new polymeric materials suitable for use as coating materials on implantable devices.

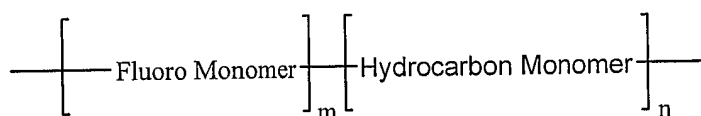
The present invention addresses such problems by providing a polymeric material for coating implantable devices.

## 20 SUMMARY OF THE INVENTION

Provided herein is a polymer containing fluorinated monomers and hydrocarbon monomers useful for coating an implantable device such as a stent.

The fluorinated monomers can provide mechanical strength for the polymer. The hydrocarbon monomers described herein impart flexibility to the polymer.

In one embodiment, the polymer can be a random or block polymer having a general formula as shown below (Formula I):



Formula I

where m and n can be positive integers ranging from 1 to 100,000.

The fluoro monomers are generally fluorinated alkylene monomers and can be unsubstituted or substituted fluorinated ethylene. In one embodiment, the fluoro monomer is a substituted fluorinated ethylene bearing a substituent (R) such as -

CF<sub>2</sub>-CRF-, -CHF-CRF-, -CH<sub>2</sub>-CRF-, -CF<sub>2</sub>-CRH-, and -CFH-CRH-. R can be hydrogen, Cl, Br, I, methyl, ethyl, n-propyl, isopropyl, short chain alkyl groups, phenyl, substituted phenyl, cyclic alkyl, heterocyclic, heteroaryl, fluorinated short chain alkyl groups, fluorinated phenyl, fluorinated cyclic alkyl, fluorinated heterocyclic, or combinations thereof. Some exemplary fluorinated alkylene monomers include tetrafluoroethylene, trifluoroethylene, vinylidene fluoride, chlorotrifluoroethylene, pentafluoropropene, hexafluoropropene, vinyl fluoride, and -CHF-CHF-.

The hydrocarbon monomers can be any hydrocarbon vinyl monomers or substituted hydrocarbon vinyl monomers capable of forming biocompatible polymers. The hydrocarbon vinyl monomers generally have the formulae CHR=CH<sub>2</sub> or CR<sub>2</sub>=CH<sub>2</sub> in which R can be hydrogen, methyl, ethyl, n-propyl,

isopropyl, short chain alkyl groups, phenyl, substituted phenyl, cyclic alkyl, heterocyclic, heteroaryl, or combinations thereof. Representative hydrocarbon vinyl monomers include isobutylene, styrene, methyl styrene, and alkyl substituted styrene. Other hydrocarbon monomers that will yield biocompatible polymers  
5 include, but are not limited to, ethylene, propylene, and butylene.

In another embodiment, the hydrocarbon monomer can be a non vinyl monomer. Useful non vinyl monomers include  $\text{CHR}=\text{CHR}$  or  $\text{CR}_2=\text{CHR}$  in which R can be methyl, ethyl, n-propyl, isopropyl, short chain alkyl groups, phenyl, substituted phenyl, cyclic alkyl, heterocyclic, heteroaryl, or combinations thereof.  
10 Representative non vinyl monomers include, but are not limited to, 2-butylene, 2-pentene, 2-hexene, and 3-hexene.

In the polymer of Formula I, the fluoro monomers generally account for about 25.01 mole% to about 99.99 mole%, or more narrowly, 50.01 mole% to about 94.99% of the total monomers forming the polymer, and the hydrocarbon  
15 monomers generally account for about 0.01 mole% to about 74.99 mole% mole%, or more narrowly 5.01 mole% to about 49.99 mole% of the total monomers forming the polymer. By varying the mole percentages of the two components of the polymer, one can fine-tune physical properties of the polymer. The polymer described herein can be a random or block copolymer.

20 In another embodiment, it is provided a polymer blend that includes a polymer that has fluorinated monomers and at least one other biocompatible polymer. In one embodiment, the polymer that has fluorinated monomers has a structure of Formula I as defined above.

The polymer or polymer blends described herein, optionally with a bioactive agent, can be used to form an implantable device such as a stent or coating(s) on an implantable device such as a stent. Some exemplary bioactive agents are paclitaxel, docetaxel, estradiol, nitric oxide donors, super oxide

5   dismutases, super oxide dismutases mimics, 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl (4-amino-TEMPO), 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,

10   clobetasol, prodrugs thereof, co-drugs thereof, and combinations thereof. The implantable device can be implanted in a patient to treat, prevent or ameliorate 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

15   duct obstruction, ureter obstruction, tumor obstruction, or combinations thereof.

#### DETAILED DESCRIPTION

Provided herein is a polymer containing fluorinated monomers and hydrocarbon monomers. The fluorinated monomers can provide mechanical

20   strength for the polymer. The hydrocarbon monomers impart flexibility to the polymer. The polymer or polymer blends described herein, optionally with a bioactive agent, can be used to form an implantable device such as a stent or coating(s) on an implantable device such as a stent. 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), tacrolimus, dexamethasone, rapamycin, rapamycin derivatives, 40-*O*-(2-hydroxy)ethyl-rapamycin

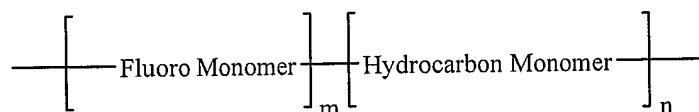
5 (everolimus), 40-*O*-(3-hydroxy)propyl-rapamycin, 40-*O*-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, and 40-*O*-tetrazole-rapamycin, ABT-578, clobetasol, prodrugs thereof, co-drugs thereof, and combinations thereof. The implantable device can be implanted in a patient to treat, prevent or ameliorate a disorder such as atherosclerosis, thrombosis, restenosis, hemorrhage, vascular

10 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.

#### Polymers of fluorinated monomers and hydrophilic monomers

In one embodiment, the polymer can be a random or block polymer having

15 a general formula as shown below (Formula I):



Formula I

where m and n can be positive integers ranging from, e.g., 1 to 100,000.

The fluoro monomers are generally fluorinated alkylene monomers and can be unsubstituted or substituted fluorinated ethylene. In one embodiment, the fluoro

20 monomer is a substituted fluorinated ethylene bearing a substituent (R) such as -CF<sub>2</sub>-CRF-, -CHF-CRF-, -CH<sub>2</sub>-CRF-, -CF<sub>2</sub>-CRH-, and -CFH-CRH-. R can be

hydrogen, Cl, Br, I, methyl, ethyl, n-propyl, isopropyl, short chain alkyl groups, phenyl, substituted phenyl, cyclic alkyl, heterocyclic, heteroaryl, fluorinated short chain alkyl groups, fluorinated phenyl, fluorinated cyclic alkyl, fluorinated heterocyclic, or combinations thereof. Some exemplary fluorinated alkylene  
5 monomers include tetrafluoroethylene, trifluoroethylene, vinylidene fluoride, chlorotrifluoroethylene, pentafluoropropene, hexafluoropropene, vinyl fluoride, and -CHF-CHF-.

The hydrocarbon monomers can be any hydrocarbon vinyl monomers or substituted hydrocarbon vinyl monomers capable of forming biocompatible  
10 polymers. The hydrocarbon vinyl monomers generally have the formulas  $\text{CHR}=\text{CH}_2$  or  $\text{CR}_2=\text{CH}_2$  in which R can be hydrogen, methyl, ethyl, n-propyl, isopropyl, short chain alkyl groups, phenyl, substituted phenyl, cyclic alkyl, heterocyclic, heteroaryl, or combinations thereof. Representative hydrocarbon vinyl monomers include isobutylene, styrene, methyl styrene, and alkyl substituted  
15 styrene. Other hydrocarbon monomers that will yield biocompatible polymers include, but are not limited to, ethylene, propylene, butylene.

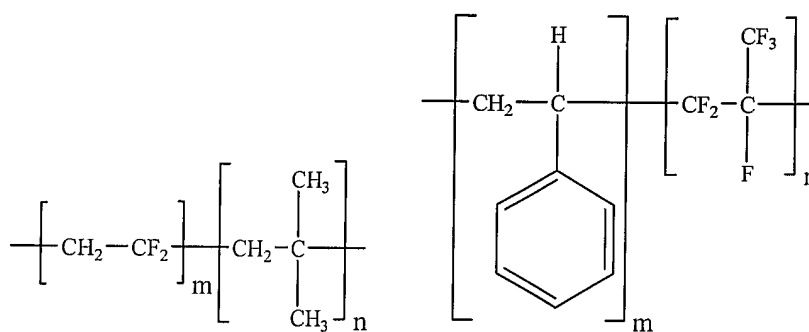
In the polymer of Formula I, the fluoro monomers generally account for about 25.01 mole% to about 99.99 mole%, or more narrowly, 50.01 mole% to about 94.99% of the total repeating units forming the polymer, and the  
20 hydrocarbon monomers generally account for about 0.01 mole% to about 74.99 mole% mole%, or more narrowly 5.01 mole% to about 49.99 mole% of the total repeating units forming the polymer. By varying the mole percentages of the two



components of the polymer, one can fine-tune physical properties of the polymer.

The polymer described herein can be a random or block copolymer.

In one embodiment, the polymer of formula I has a structure of formula II or formula III:



5

Formula II

or

Formula III

The polymer described herein can be synthesized by methods known in the art (see, for example, D. Braun, et al., Polymer Synthesis: Theory and Practice. Fundamentals, Methods, Experiments. 3<sup>rd</sup> Ed., Springer, 2001; Hans R. Kricheldorf, Handbook of Polymer Synthesis, Marcel Dekker Inc., 1992). For example, one method that can be used to make the polymer can be free radical methods (see, for example, D. Braun, et al., Polymer Synthesis: Theory and Practice. Fundamentals, Methods, Experiments. 3<sup>rd</sup> Ed., Springer, 2001; Hans R. Kricheldorf, Handbook of Polymer Synthesis, Marcel Dekker Inc., 1992). Polymerization in solvent can also be used to synthesize the polymer described herein.

15

Copolymerization prevents phase separation on a large scale. For systems where the reactivity ratios greatly differ, a random polymerization will result in more and more of a block structure. Otherwise, polymerizations that proceed step-

wise via the formation of prepolymers may be used to achieve block structures (See, for example, J. Kopecek, et al., Prog. Polym. Sci, 9:34 (1983)).

#### Polymer blends

In another embodiment, the polymer of formulae I-III can be blended with  
5 another biocompatible polymer to form a coating material for an implantable device. The biocompatible polymer can be biodegradable or nondegradable. Representative examples of these biocompatible polymers include, but are not limited to, poly(ester amide), polyesters, polyhydroxyalkanoates (PHA), poly(3-hydroxyalkanoates) such as poly(3-hydroxypropanoate), poly(3-hydroxybutyrate),  
10 poly(3-hydroxyvalerate), poly(3-hydroxyhexanoate), poly(3-hydroxyheptanoate) and poly(3-hydroxyoctanoate), poly(4-hydroxyalkanoates) 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 herein or  
15 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  
20 acid-co-trimethylene carbonate), polyphosphoester, polyphosphoester urethane, poly(amino acids), polycyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), polyurethanes, polyphosphazenes, silicones, polyolefins, polyisobutylene and ethylene-alphaolefin copolymers, poly(methylmethacrylate),

poly(ethyl methacrylate), poly(isopropyl methacrylate), poly(*n*-propyl methacrylate), poly(*n*-butyl methacrylate), methacrylic polymers and copolymers, acrylic polymers and copolymers, vinyl halide polymers and copolymers, such as polyvinyl chloride, poly(vinylidene fluoride), poly(vinylidene fluoride-co-  
5 hexafluoropropylene), polyvinyl ethers such as polyvinyl methyl ether, 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  
10 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), epoxy resins, polyurethanes, rayon, rayon-triacetate, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane,  
15 cellulose nitrate, cellulose propionate, cellulose ethers, carboxymethyl cellulose, polyethers such as poly(ethylene glycol) (PEG), copoly(ether-esters), e.g., copoly(ethylene oxide-co-lactic acid) (PEO/PLA), polyalkylene oxides such as poly(ethylene oxide) and poly(propylene oxide), polyalkylene oxalates, phosphoryl choline, choline, poly(aspirin), polymers and co-polymers of hydroxyl bearing  
20 monomers such as hydroxyethyl methacrylate (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),  
5 polydimethylsiloxane-co-PEG (PDMS-PEG), poly(vinylidene fluoride)-PEG (PVDF-PEG), PLURONIC<sup>™</sup> 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,  
10 heparin, fragments and derivatives of heparin, glycosamino glycan (GAG), GAG derivatives, polysaccharide, elastin, chitosan, alginate, and combinations thereof. In some embodiments, the polymer can exclude any one of the aforementioned polymers.

As used herein, the terms poly(D,L-lactide) (PDLL), poly(L-lactide) (PLL),  
15 poly(D,L-lactide-co-glycolide) (PDLLG), and poly(L-lactide-co-glycolide) (PLLG) are used interchangeably with the terms poly(D,L-lactic acid) (PDLLA), poly(L-lactic acid) (PLLA), poly(D,L-lactic acid-co-glycolic acid) (PDLLAGA), and poly(L-lactic acid-co-glycolic acid) (PLLAGA), respectively.

#### Bioactive Agents

20 In accordance with a further embodiment of the invention, the polymer or polymer blend described herein can form a coating that may optionally include one or more active agents. The bioactive agent can be any agent that is biologically active, for example, a therapeutic, prophylactic, or diagnostic agent.

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. Nucleic acid sequences include genes, antisense molecules which bind to complementary DNA to inhibit transcription, and ribozymes. Compounds with a wide range of molecular weight can be encapsulated, for example, between 100 and 500,000 grams or more per mole. Examples of suitable materials include proteins such as antibodies, receptor ligands, and enzymes, peptides such as adhesion peptides, saccharides and polysaccharides, synthetic organic or inorganic drugs, and nucleic acids. Examples of materials which can be encapsulated include enzymes, blood clotting factors, inhibitors or clot dissolving agents such as streptokinase and tissue plasminogen activator, antigens for immunization, hormones and growth factors, polysaccharides such as heparin, oligonucleotides such as antisense oligonucleotides and ribozymes and retroviral vectors for use in gene therapy. The polymer can also be used to encapsulate cells and tissues. Representative diagnostic agents are agents detectable by x-ray, fluorescence, magnetic resonance imaging, radioactivity, ultrasound, computer tomography (CT) and positron emission tomography (PET). Ultrasound diagnostic agents are typically a gas such as air, oxygen or perfluorocarbons.

In the case of controlled release, a wide range of different bioactive agents can be incorporated into a controlled release device. These include hydrophobic, hydrophilic, and high molecular weight macromolecules such as proteins. The

bioactive compound can be incorporated into polymeric coating in a percent loading of between 0.01% and 70% by weight, more preferably between 5% and 50% by weight.

In one embodiment, the bioactive agent can be for inhibiting the activity of  
5 vascular smooth muscle cells. More specifically, the bioactive agent can be aimed at inhibiting abnormal or inappropriate migration and/or proliferation of smooth muscle cells for the inhibition of restenosis. The bioactive agent can also include any substance capable of exerting a therapeutic or prophylactic effect in the practice of the present invention. For example, the bioactive agent can be for  
10 enhancing wound healing in a vascular site or improving the structural and elastic properties of the vascular site. Examples of active agents include antiproliferative substances such as actinomycin D, or derivatives and analogs thereof (manufactured by Sigma-Aldrich 1001 West Saint Paul Avenue, Milwaukee, WI 53233, or COSMEGEN available from Merck). Synonyms of actinomycin D  
15 include dactinomycin, actinomycin IV, actinomycin I<sub>1</sub>, actinomycin X<sub>1</sub>, and actinomycin C<sub>1</sub>. The bioactive agent can also fall under the genus of antineoplastic, anti-inflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, antiallergic and antioxidant substances. Examples of such antineoplastics and/or antimitotics include paclitaxel, (e.g. TAXOL<sup>®</sup> by Bristol-  
20 Myers Squibb Co., Stamford, Conn.), docetaxel (e.g. Taxotere<sup>®</sup>, from Aventis S.A., Frankfurt, Germany) methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin hydrochloride (e.g. Adriamycin<sup>®</sup> from Pharmacia & Upjohn, Peapack N.J.), and mitomycin (e.g. Mutamycin<sup>®</sup> 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  
5 antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and thrombin inhibitors such as Angiomax<sup>®</sup> (Biogen, Inc., Cambridge, Mass.). Examples of such cytostatic or antiproliferative agents include angiopeptin, angiotensin converting enzyme inhibitors such as captopril (e.g. Capoten<sup>®</sup> and Capozide<sup>®</sup> from Bristol-Myers  
10 Squibb Co., Stamford, Conn.), cilazapril or lisinopril (e.g. Prinivil<sup>®</sup> and Prinzide<sup>®</sup> from Merck & Co., Inc., Whitehouse Station, NJ), calcium channel blockers (such as nifedipine), colchicine, proteins, peptides, 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  
15 Mevacor<sup>®</sup> 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), and nitric oxide. An example of an antiallergic agent is  
20 permirolast potassium. Other therapeutic substances or agents which may be appropriate agents include alpha-interferon, genetically engineered epithelial cells, anti-inflammatory agents, steroidal anti-inflammatory agents, non-steroidal anti-inflammatory agents, antivirals, anticancer drugs, anticoagulant agents, free radical

scavengers, estradiol, antibiotics, nitric oxide donors, super oxide dismutases, super oxide dismutases mimics, 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl (4-amino-TEMPO), 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, cytostatic agents, prodrugs thereof, co-drugs thereof, or a combination thereof.

The foregoing substances are listed by way of example and 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 dosage or concentration of the bioactive agent required to inhibit the desired cellular activity of the vascular region 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 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

As used herein, an implantable device may be any suitable medical  
5 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), artificial heart valves, closure devices for patent foramen ovale, cerebrospinal fluid shunts, pacemaker electrodes, and endocardial leads (e.g., FINELINE and ENDOTAK, available from Guidant  
10 Corporation, Santa Clara, CA). 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  
15 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  
20 10% molybdenum. Devices made from bioabsorbable or biostable polymers could also be used with the embodiments of the present invention.

#### Method of Use

In accordance with embodiments of the invention, a coating of the various

described embodiments can be formed on an implantable device or prosthesis, e.g., a stent. For coatings including one or more active agents, the agent will retain on the medical device such as a stent during delivery and expansion of the device, and released at a desired rate, and for a predetermined duration of time at the site of

5 implantation. Preferably, the medical device is a stent. A stent having the above-described coating is useful for a variety of medical procedures, including, by way of 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 occluded regions of blood

10 vessels caused by abnormal or inappropriate migration and proliferation of smooth muscle cells, atherosclerosis, 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

15 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, which allows a stent in its collapsed configuration to be inserted

20 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

coating may then be expanded at the desired area of treatment. A post-insertion angiogram may also be utilized to confirm appropriate positioning.

### EXAMPLES

The embodiments of the present invention will be illustrated by the following set forth prophetic examples. All parameters and data are not to be construed to unduly limit the scope of the embodiments of the invention.

#### **Example 1: Synthesis of poly(block-vinylidene fluoride-co-block-isobutylene)**

Fluoropolymers are typically synthesized by free radical polymerization, using suspension or emulsion techniques, while polyisobutylene is typically produced via cationic polymerization methods (see G. Odian, Principles of Polymerization, 3<sup>rd</sup> Ed., John Wiley & Sons, NY, 1991). However, fluoropolymers can also be synthesized by atom transfer radical polymerization (ATRP) using iodine or bromine functional initiators. These polymerizations result in PVDF with terminal iodine or bromine groups. These endgroups can then be used directly, or functionalized, to serve as carbocationic initiators for isobutylene. A block copolymer can be made by first synthesizing a bromo-terminated poly(vinylidene fluoride) via ATRP techniques (see Z. Zhang, et al. "Synthesis of fluorine-containing block copolymers via ATRP 1. Synthesis and characterization of PSt-PVDF-PSt triblock copolymers", Polymer (40) (1999) 1341-1345). The resulting bromo-terminated PVDF can then be used as an initiator in a cationic polymerization catalyzed by a lewis acid such as titanium tetrachloride, titanium tetrabromide, or aluminum trichloride (see J. P. Kennedy, et al. "Design Polymers

by carbocationic Macromolecular Engineering”, Hanser, NY, Munich, 1992). A useful weight ratio of vinylidene fluoride to isobutylene is 75/25.

**Example 2. Synthesis of poly(vinylidene fluoride-co-styrene)**

Both monomers are amenable to free radical polymerization. This  
5 polymerization can be via suspension or emulsion polymerization techniques. Useful initiators are peroxides, organic soluble peroxides, persulfate compounds, and azo compounds. Redox systems such as compounds containing ferrous, sulfite, or bisulfite ions can be used to produce desirable initiation rates at low temperatures. One useful route is suspension polymerization in an autoclave. A  
10 vinylidene fluoride/styrene copolymer dispersion can be prepared having a composition of 90% vinylidene fluoride and 10% styrene by weight. To a 10 gallon glass-lined autoclave is added 5 gallons of deionized water, and charged with 2.2 kg of vinylidene fluoride (VDF) and 0.24 kg of styrene. After sparging with nitrogen to remove all oxygen, and with rapid stirring, a solution of 20 gm of  
15 a 70% solution of tertiary butyl hydroperoxide (TBHP) that is diluted to 100 ml with deionized water is added. Next, a solution of 15 gm of sodium metabisulfite (MBS), and 2.2 gm of ferrous sulfate heptahydrate, dissolved in 100 ml of deionized water is added. The autoclave is maintained at 15-20°C. After addition of the initial catalysts, 300 ml of perfluorinated ammonium octoanate catalyst (20%  
20 active solids) is charged into the autoclave. The polymerization is continued by slow addition of two separate solutions consisting of 100 gm of TBHP diluted to 700 ml with deionized water and 80 gm of MBS diluted to 750 ml with deionized water. These initiators are added at a rate of 1.8 ml/min. After consumption of the

initial charge of VDF and styrene, 18 kg of VDF and 2 kg of styrene are added over a period of 5 hours. The autoclave is vented, yielding a polymer dispersion in water which is isolated by sieving and rinsed.

**Example 3: Coating a stent with the composition of example 2**

5           A composition can be prepared by mixing the following components:

(a) about 2.0 % (w/w) of poly(butyl methacrylate) (PBMA), and

(b) the balance a 50/50 (w/w) blend of acetone and cyclohexanone. The composition can be applied onto the surface of bare 12 mm small VISION™ stent (Guidant Corp.). The coating can be sprayed and dried to form a primer layer. A spray coater can be used having a 0.014 round nozzle maintained at ambient temperature with a feed pressure 2.5 psi (0.17 atm) and an atomization pressure of about 15 psi (1.02 atm). About 20 µg of the coating can be applied at per one spray pass. About 80 µg of wet coating can be applied, and the stent can be dried for about 10 seconds in a flowing air stream at about 50°C between the spray passes. The stents can be baked at about 80°C for about one hour, yielding a drug reservoir layer composed of approximately 60 µg of PBMA.

A second composition can be prepared by mixing the following components:

(a) about 2.0 % (w/w) of the polymer of example 2;

(b) about 1.0% (w/w) of everolimus,

20           (c) the balance a 50/50 (w/w) blend of acetone and dimethylformamide.

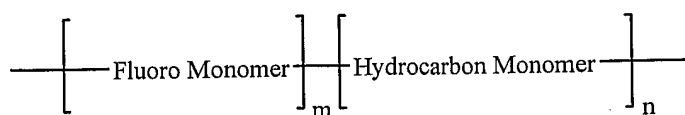
The second composition can be applied onto the dried primer layer to form a drug reservoir layer using the same spraying technique and equipment used for applying the reservoir. About 200  $\mu\text{g}$  of wet coating can be applied followed by drying and baking at about 50°C for about 2 hours, yielding a dry drug reservoir layer having solids content of about 180  $\mu\text{g}$  and containing about 60  $\mu\text{g}$  of everolimus.

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 biocompatible polymer comprising fluorinated monomers and hydrocarbon monomers,  
 wherein the fluorinated monomers form about 25.01 mole% to about 99.99 mole% repeating units of the polymer, and  
 wherein the hydrocarbon monomers form about 74.99 mole% to about 0.01 mole% repeating units of the polymer.
2. A biocompatible polymer comprising fluorinated monomers and hydrocarbon monomers,  
 wherein the fluorinated monomers form about 50.01 mole% to about 94.99 mole% units of the polymer, and  
 wherein the hydrocarbon monomers form about 49.99 mole% to about 5.01 mole% repeating units of the polymer.
3. The biocompatible polymer of claim 1, having the structure of formula I:



Formula I

wherein m and n are positive integers ranging from 1 to 100,000,

wherein the fluoro monomers are fluorinated alkylene monomers, and

wherein the hydrocarbon monomers are hydrocarbon vinyl monomers.

4. The biocompatible polymer of claim 3,

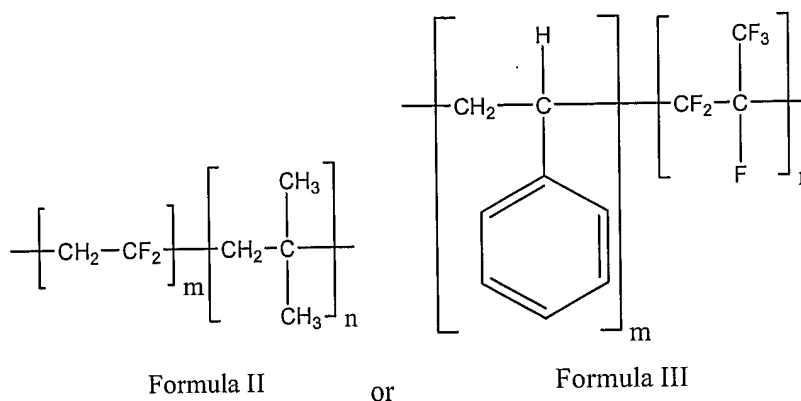
wherein the fluoro monomers are selected from the group consisting of  $-\text{CF}_2-$ ,  $\text{CF}_2-$ ,  $-\text{CH}_2-\text{CF}_2-$ ,  $-\text{CH}_2-\text{CHF}-$ ,  $-\text{CHF}-\text{CHF}-$ ,  $-\text{CClF}-\text{CF}_2-$ ,  $-\text{CF}_2-\text{C}(\text{CF}_3)\text{F}-$ ,  $-\text{CHF}-\text{C}(\text{CF}_3)\text{F}-$ ,  $-\text{CF}_2-\text{C}(\text{CF}_3)\text{H}-$ ,  $-\text{CF}_2-\text{CRF}-$ ,  $-\text{CHF}-\text{CRF}-$ ,  $-\text{CF}_2-\text{CRH}-$ ,  $-\text{CH}_2-\text{CRF}-$ , and  $-\text{CFH}-\text{CRH}-$  where R are hydrogen, Cl, Br, I, methyl, ethyl, n-propyl, isopropyl, short chain alkyl groups, phenyl, substituted phenyl, cyclic alkyl, heterocyclic, heteroaryl, fluorinated short chain alkyl groups, fluorinated phenyl, fluorinated cyclic alkyl, fluorinated heterocyclic, or combinations thereof, and

wherein the hydrocarbon monomers can be  $\text{CHR}=\text{CH}_2$  or  $\text{CR}_2=\text{CH}_2$  in which R can be hydrogen, methyl, ethyl, n-propyl, isopropyl, short chain alkyl groups, phenyl, substituted phenyl, cyclic alkyl, heterocyclic, heteroaryl, or combinations thereof.

5. The biocompatible polymer of claim 3 wherein the hydrocarbon monomer is one or more isobutylene, styrene, methyl styrene, alkyl substituted styrene, ethylene, propylene, and butylenes.

6. The biocompatible polymer of claim 3 having a structure of any of formulae II-III:





wherein m and n are positive integers ranging from 1 to 100,000.

7. A biocompatible polymer blend comprising the biocompatible polymer of claim 1 and at least one other biocompatible polymer.

8. A biocompatible polymer blend comprising the biocompatible polymer of claim 3 and at least one other biocompatible polymer.

9. A biocompatible polymer blend comprising the biocompatible polymer of claim 4 and at least one other biocompatible polymer.

10. The polymer blend of claim 9, wherein the other biocompatible polymer is selected from the group consisting of poly(ester amide), polyesters, polyhydroxyalkanoates (PHA), poly(3-hydroxyalkanoates), poly(3-hydroxypropanoate), poly(3-hydroxybutyrate), poly(3-hydroxyvalerate), poly(3-hydroxyhexanoate), poly(3-hydroxyheptanoate), poly(3-hydroxyoctanoate), poly(4-hydroxyalknaotes), poly(4-hydroxybutyrate), poly(4-hydroxyvalerate), poly(4-hydroxyhexanote), poly(4-hydroxyheptanoate), poly(4-hydroxyoctanoate) copolymers including 3-hydroxyalkanoate, 4-hydroxyalkanoate monomers described 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 carbonate), polyphosphoester, polyphosphoester urethane, poly(amino acids), polycyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), polyurethanes, polyphosphazenes, silicones, polyolefins, polyisobutylene and ethylene-alphaolefin copolymers, methacrylic polymers and copolymers, acrylic polymers and copolymers, poly(methylmethacrylate), poly(ethyl methacrylate), poly(isopropyl methacrylate), poly(n-propyl methacrylate), poly(n-butyl methacrylate), vinyl halide polymers and copolymers polyvinyl chloride, poly(vinylidene fluoride), poly(vinylidene fluoride-co-hexafluoropropylene), polyvinyl ethers polyvinyl methyl ether, polyvinylidene halides, polyvinylidene chloride, polyacrylonitrile, polyvinyl ketones, polyvinyl aromatics, polystyrene, polyvinyl esters, polyvinyl acetate, copolymers of vinyl monomers, ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers, polyamides, Nylon 66 and polycaprolactam, alkyd resins, polycarbonates, polyoxymethylenes, polyimides, polyethers, poly(glyceryl sebacate), poly(propylene fumarate), epoxy resins, polyurethanes, rayon, rayon-triacetate, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose

propionate, cellulose ethers, carboxymethyl cellulose, polyethers, poly(ethylene glycol) (PEG), copoly(ether esters), copoly(ethylene oxide-co-lactic acid) (PEO/PLA), polyalkylene oxides, poly(ethylene oxide), poly(propylene oxide), polyalkylene oxalates, phosphoryl choline, choline, poly(aspirin), polymers and co-polymers of hydroxyl bearing monomers, polymers and copolymers of hydroxyethyl methacrylate (HEMA), polymers and copolymers of hydroxypropyl methacrylate (HPMA), polymers and copolymers of hydroxypropylmethacrylamide, polymers and copolymers of PEG acrylate (PEGA), polymers and copolymers of PEG methacrylate, polymers and copolymers of 2-methacryloyloxyethylphosphorylcholine (MPC), polymers and copolymers of *n*-vinyl pyrrolidone (VP), polymers and copolymers of carboxylic acid bearing monomers, polymers and copolymers of methacrylic acid (MA), polymers and copolymers of acrylic acid (AA), polymers and copolymers of alkoxyethacrylate, polymers and copolymers of alkoxyacrylate, polymers and copolymers of 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, 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, and combinations thereof.

11. An implantable device having a biocompatible coating thereon, wherein the biocompatible coating comprises the biocompatible polymer of claim 1.

12. An implantable device having a biocompatible coating thereon, wherein the biocompatible coating comprises the biocompatible polymer of claim 2.

13. An implantable device having a biocompatible coating thereon, wherein the biocompatible coating comprises the biocompatible polymer of claim 3.

14. An implantable device having a biocompatible coating thereon, wherein the biocompatible coating comprises the biocompatible polymer of claim 4.

15. An implantable device having a biocompatible coating thereon, wherein the biocompatible coating comprises the biocompatible polymer of claim 5.

16. An implantable device having a biocompatible coating thereon, wherein the biocompatible coating comprises the biocompatible polymer of claim 6.

17. An implantable device having a biocompatible coating thereon, wherein the biocompatible coating comprises the polymer blend of claim 7.

18. An implantable device having a biocompatible coating thereon, wherein the biocompatible coating comprises the polymer blend of claim 10.

19. The implantable device of claim 13, which is a drug-delivery stent, wherein the coating further comprises a bioactive agent.

20. The drug-delivery stent of claim 19, 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), 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 a combination thereof.

21. A stent formed of a material comprising the composition of claim 1.

22. A stent formed of a material comprising the composition of claim 3.

23. A stent formed of a material comprising the composition of claim 10.

24. The stent of claim 23, further comprises a bioactive agent.

25. A method of treating a disorder in a patient comprising implanting in the patient the implantable device of claim 13, 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, claudication, anastomotic proliferation for vein and artificial grafts, bile duct obstruction, ureter obstruction, tumor obstruction, and combinations thereof.

26. A method of treating a disorder in a patient comprising implanting in the patient the implantable device of claim 20, 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, claudication, anastomotic proliferation for vein and artificial grafts, bile duct obstruction, ureter obstruction, tumor obstruction, and combinations thereof.