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(54) **PROSTHETIC VALVE WITH SELECTIVELY POSITIONED BIOACTIVE AGENT**

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(60) Provisional application No. 60/616,512, filed on Oct. 6, 2004.

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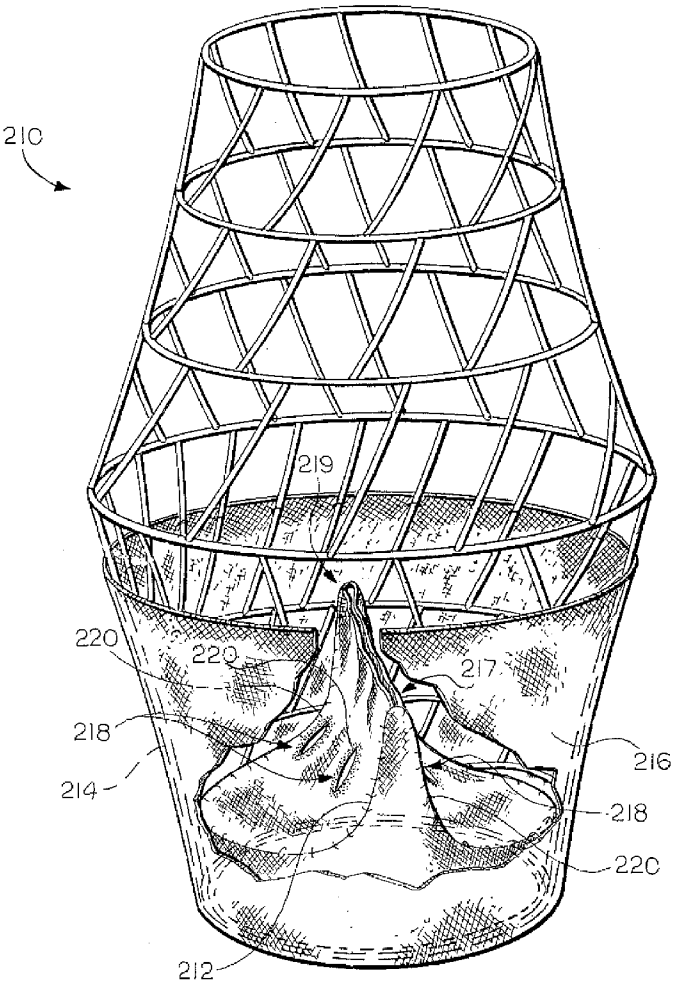
(57) **ABSTRACT**

A prosthetic valve includes a support frame, a leaflet attached to the support frame, and a bioactive agent associated with the leaflet. A first free edge of the leaflet permits fluid flow through a body vessel in a first direction and substantially prevents fluid flow through the body vessel in a second, opposite direction. A second free edge of the leaflet at least partially defines an opening for permitting a controlled amount of fluid flow through the body vessel.



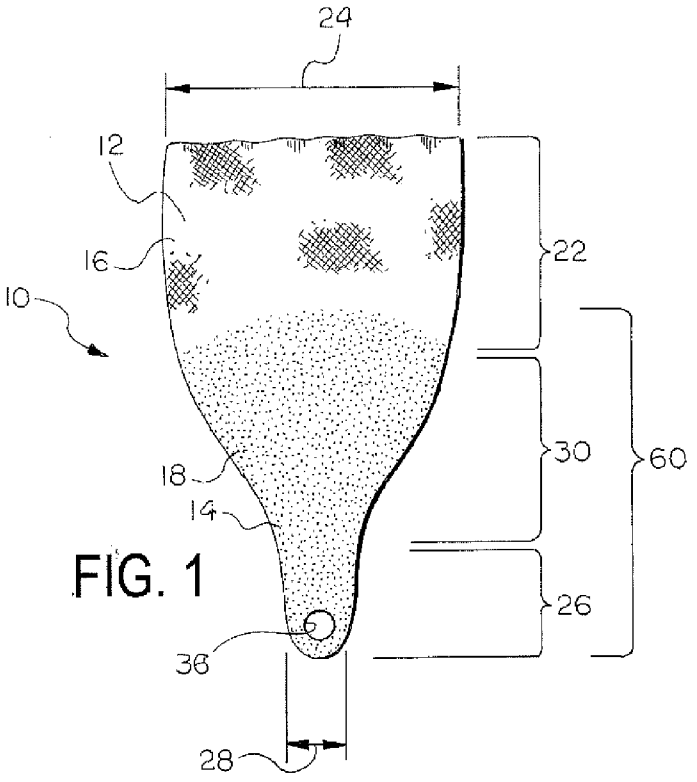


FIG. 1

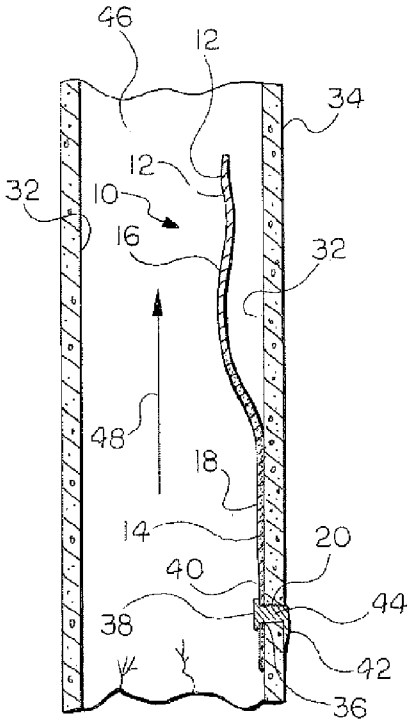


FIG. 2

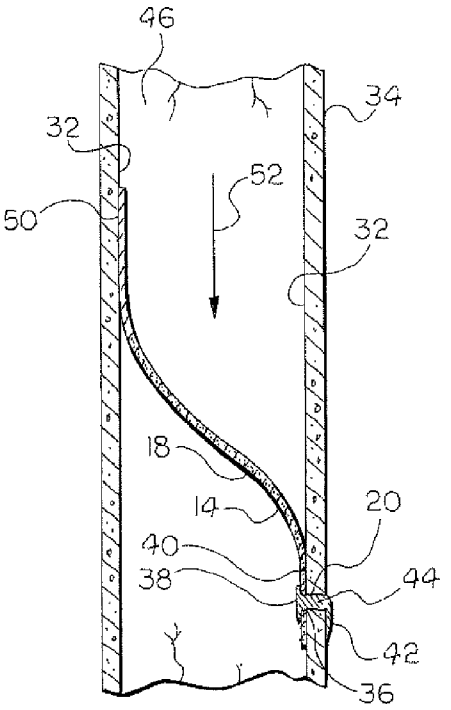


FIG. 3

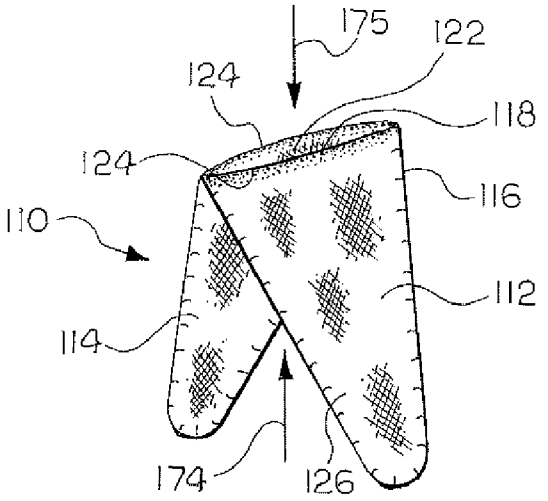

175
122
124
118
124
116
110
112
114
174
126

FIG. 4

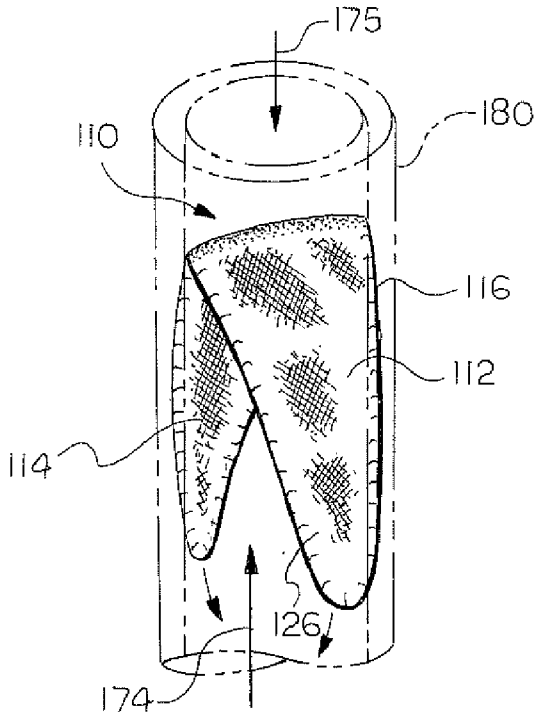

175
180
110
116
112
114
126
174

FIG. 5

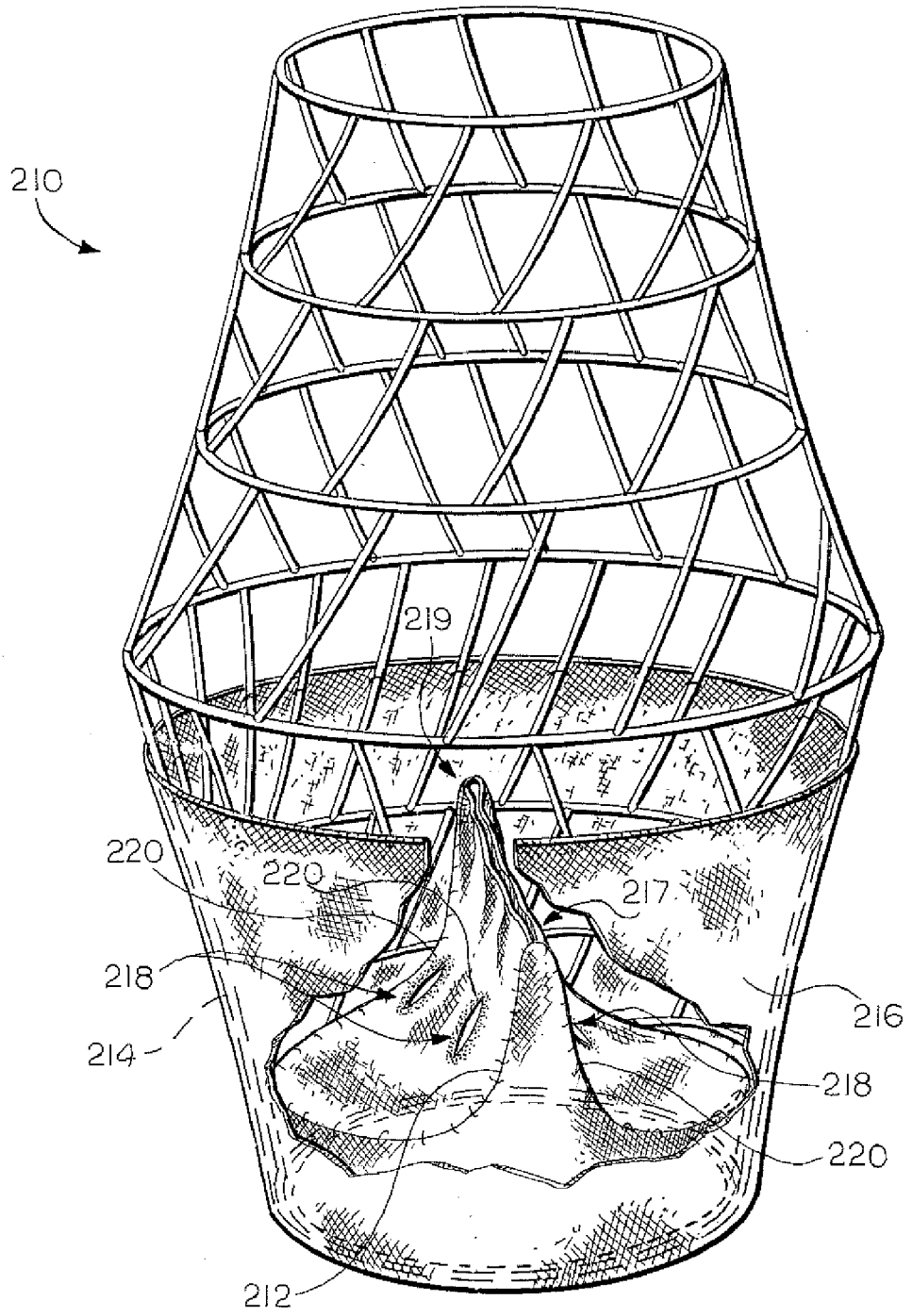


FIG. 6

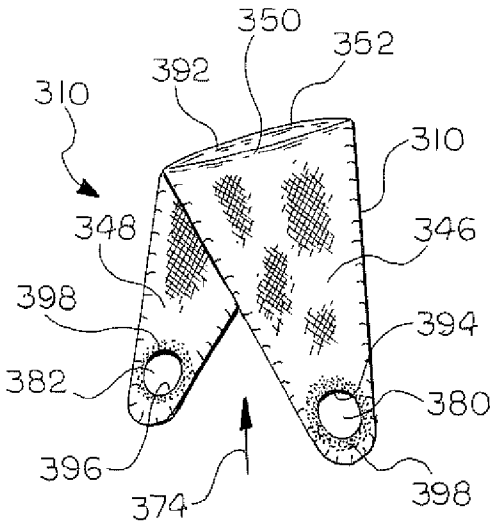


FIG. 7

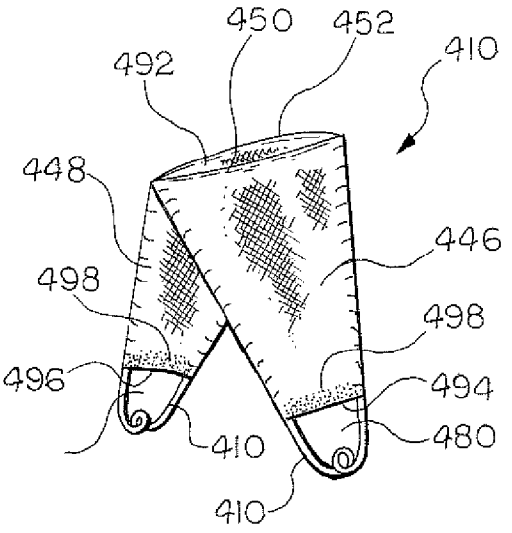


FIG. 8

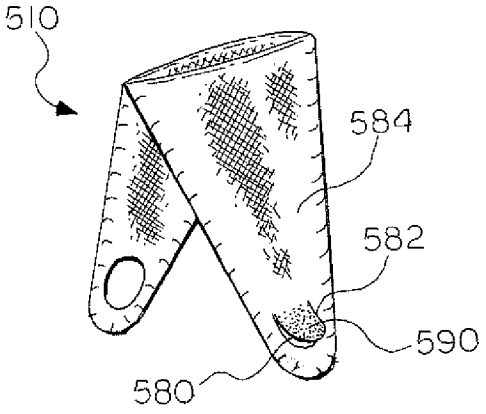


FIG. 9

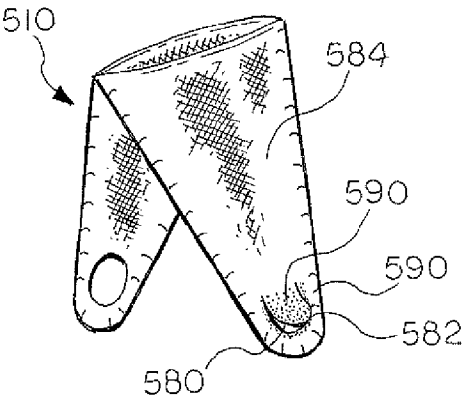


FIG. 10

PROSTHETIC VALVE WITH SELECTIVELY POSITIONED BIOACTIVE AGENT

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. patent application Ser. No. 11/244,991, filed on Oct. 6, 2005, currently pending, which claims priority to U.S. Provisional Application Ser. No. 60/616,512, filed on Oct. 6, 2004. The entire disclosure of each of these related applications is hereby incorporated by reference into this disclosure.

FIELD

[0002] Medical devices that include one or more bioactive agents are disclosed. Particular embodiments of the medical devices are intraluminal valve prostheses that include one or more bioactive agents.

BACKGROUND

[0003] Medical devices are used in the treatment of a wide variety of conditions. Bioactive agents can be associated with medical devices to provide a device that includes a particular biological effect upon implantation in a host.

[0004] Many vessels in animal bodies transport fluids from one bodily location to another. Frequently, fluid flows in a unidirectional manner along the length of the vessel. Varying fluid pressures over time, however, can introduce a reverse flow direction in the vessel. In some vessels, such as mammalian veins, natural valves are positioned along the length of the vessel and act as one-way check valves that open to permit the flow of fluid in the desired direction and close to prevent fluid flow in a reverse direction, i.e., retrograde flow. The valves can change from an open position in response to a variety of circumstances, including changes in the cross-sectional shape of the vessel and the fluid pressure within the vessel.

[0005] While natural valves may function for an extended time, some may lose effectiveness, which can lead to physical manifestations and pathology. For example, venous valves are susceptible to becoming insufficient due to one or more of a variety of factors. Over time, the vessel wall may stretch, affecting the ability of the valve leaflets to close. Furthermore, the leaflets may become damaged, such as by formation of thrombus and scar tissue, which may also affect the ability of the valve leaflets to close. Once valves are damaged, venous valve insufficiency may be present, which may lead to discomfort and possibly ulcers in the legs and ankles.

[0006] Current treatments for venous valve insufficiency include the use of compression stockings that are placed around the leg of a patient in an effort to force the vessel walls radially inward to restore valve function. Surgical techniques are also employed in which valves can be bypassed, eliminated, or replaced with autologous sections of veins having competent valves.

[0007] Minimally invasive techniques and instruments for placement of intraluminal medical devices have developed over recent years. A wide variety of treatment devices that utilize minimally invasive technology has been developed and includes stents, stent grafts, occlusion devices, infusion catheters and the like. Minimally invasive intravascular devices have especially become popular with the introduction of coronary stents to the U.S. market in the early 1990s. Coronary and peripheral stents have been proven to provide a superior means of maintaining vessel patency, and have become widely accepted in the medical community. Furthermore, the use of stents has been extended to treat aneurysms and to provide occlusion devices, among other uses.

[0008] Recently, prosthetic valves that are implantable by minimally invasive techniques have been developed. Frequently, a graft member is attached to a support frame and provides a valve function to the device. For example, the graft member can be in the form of a leaflet that is attached to a support frame and movable between first and second positions. In a first position, the valve is open and allows fluid flow to proceed through a vessel in a first direction, and in a second position the valve is closed to prevent fluid flow in a second, opposite direction. Examples of this type of prosthetic valve are described in commonly owned U.S. Pat. No. 6,508,833 to Pavcnik for a MULTIPLE-SIDED INTRALUMINAL MEDICAL DEVICE, United States Patent Application Publication No. 2001/0039450 to Pavcnik for an IMPLANTABLE VASCULAR DEVICE, and U.S. patent application Ser. No. 10/642,372, filed on Aug. 15, 2003, each of which is hereby incorporated by reference in its entirety. In other examples of prosthetic valves, a tube that terminates in leaflets is attached to one or more support frames to form a valve. The leaflets open to permit fluid flow in a first direction in response to fluid pressure on one side of the leaflets, and close to prevent fluid flow in a second, opposite direction in response to fluid pressure on opposite sides of the leaflets. An example of this configuration is provided in U.S. Pat. No. 6,494,909 to Greenhalgh for AN ENDOVASCULAR VALVE, which is hereby incorporated by reference in its entirety.

SUMMARY OF EXEMPLARY EMBODIMENTS

[0009] Medical devices that include one or more bioactive agents are disclosed. Particular embodiments of the invention relate to intraluminal valve prostheses that include one or more bioactive agents.

[0010] An intraluminal valve prostheses according to one exemplary embodiment comprises a graft member that comprises a bioactive agent.

[0011] Additional understanding of the invention can be obtained with review of the detailed description of exemplary embodiments, appearing below, and the appended drawings that illustrate various exemplary embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] FIG. **1** is a perspective view of a medical device according to a first exemplary embodiment.

[0013] FIG. **2** is a sectional view of a body vessel containing the medical device illustrated in FIG. **1**.

[0014] FIG. **3** is a sectional view of a body vessel containing the medical device illustrated in FIG. **1**.

[0015] FIG. **4** is a perspective view of a medical device according to a second exemplary embodiment.

[0016] FIG. **5** is a perspective view of the medical device illustrated in FIG. **4** disposed within in a body vessel.

[0017] FIG. **6** is a perspective view of a medical device according to a third exemplary embodiment.

[0018] FIG. **7** is a perspective view of a medical device according to a fourth exemplary embodiment.

[0019] FIG. **8** is a perspective view of a medical device according to a fifth exemplary embodiment.

[0020] FIG. **9** is a perspective view of a medical device according to a sixth exemplary embodiment.

[0021] FIG. **10** is a perspective view of a medical device according to a seventh exemplary embodiment.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

[0022] The following provides a detailed description of exemplary embodiments. The description is not intended to limit the scope of the invention, or its protection, in any manner, but rather serves to enable those skilled in the art to practice the invention.

[0023] The invention provides medical devices that can be used in a variety of applications. For example, a medical device according to the invention can be used to provide intraluminal support to a body vessel. Medical devices according to exemplary embodiments comprise prosthetic valves that can be used to regulate fluid flow through a body vessel. The prosthetic valves can be implanted in a body vessel, or in any other suitable environment, to regulate the flow of fluid. Valves according to the invention can also be implanted in ducts, canals, and other passageways in the body, as well as cavities and other suitable locations. Valves according to exemplary embodiments of the invention can be implanted in the vessels of the vasculature, such as veins, to regulate the flow of blood through the vessels.

[0024] As used herein, the term "implanted," and grammatically related terms, refers to the positioning of an item in a particular environment, either temporarily, semi-permanently, or permanently. The term does not require a permanent fixation of an item in a particular position.

[0025] FIGS. **1** through **3** illustrate a first exemplary embodiment. The medical device of this embodiment is a prosthetic valve **10** that can be used to regulate the flow of fluid through a body vessel. The valve **10** includes a graft member **12**, which can also be referred to as a leaflet, that has a base portion **14** and a valve portion **16**. The valve **10** also includes a means for maintaining an axial position of a portion of the leaflet **12** in a body vessel in which the valve **10** is implanted. A bioactive agent **18** is associated with the prosthetic valve **10**. As used herein, the phrase "associated with" refers to a spatial relationship between two items, such as a graft member and a bioactive agent. The phrase encompasses a spatial relationship in which one item is disposed on a surface of another, as well as a spatial relationship in which one item is disposed in a portion of another. Accordingly, in medical devices according to the invention, a bioactive agent can be disposed on a portion of the device, disposed within a portion of the device, or associated with the device in any other suitable manner.

[0026] Any suitable structure can be used as the means for maintaining an axial position of the leaflet **12** in a body vessel, and exemplary structure is illustrated in FIGS. **1** through **3**. The specific structure chosen for any particular valve according to the invention will depend on several considerations, including the nature of the leaflet and the vessel in which the valve will be implanted. The structure need only be able to substantially maintain a position of a portion of the leaflet on an axis of a vessel in which the leaflet is implanted while fluid flows through the vessel. Examples of suitable structures for the means for maintaining an axial position include barbs, integrally formed anchors, support frames, and their equivalents. In the embodiment illustrated in FIGS. **1** through **3**, the means for maintaining an axial position comprise a barb **20** that is structurally distinct from the leaflet **12**.

[0027] The leaflet **12** comprises a section of material. The leaflet **12** can be formed of any suitable material, and need only be biocompatible or be able to be made biocompatible and be able to perform as described herein. The leaflet **12** advantageously can be formed of a flexible material. Examples of suitable materials for the leaflet **12** include natural materials, synthetic materials, and combinations of natural and synthetic materials. Examples of suitable natural materials include extracellular matrix (ECM) materials, such as small intestine submucosa (SIS), and other bioremodellable materials, such as bovine pericardium. Other examples of ECM materials that can be used in the medical devices of the invention include stomach submucosa, liver basement membrane, urinary bladder submucosa, tissue mucosa, and dura mater. Examples of suitable synthetic materials include polymeric materials, such as expanded polytetrafluoroethylene and polyurethane. ECM materials are particularly well-suited materials for use in the leaflet **12** at least because of their abilities to remodel and to provide a scaffold onto which cellular in-growth can occur, eventually allowing the material to remodel into a structure of host cells. Resorbable materials, such as polyglycolic acid, polylactic acid, polycaprolactone and other suitable resorbable materials can also be used, including the resorbable materials listed below.

[0028] The leaflet **12** can have any suitable size and configuration, and the specific size and configuration chosen for the leaflet in a particular valve according to the invention will depend on several considerations, including the size, configuration, and/or nature of the vessel in which the valve will be implanted. In the embodiment illustrated in FIGS. **1** through **3**, the leaflet **12** includes a first portion **22** having a first width **24**, and a second portion **26** having a second width **28**. The first width **24** is greater than the second width **28**. Advantageously, the first portion **22** includes the valve portion **16**. Also advantageously, the second portion **26** includes the base portion **14**. In the illustrated embodiment, a transition region **30** is disposed between the first **22** and second **26** portions, and includes a width that tapers from the first width **24** to the second width **28**.

[0029] As best illustrated in FIGS. **2** and **3**, the base portion **14** provides a portion of the leaflet **12** that can be anchored to a wall **32** of a body vessel **34** in which the valve **10** is implanted. When the valve **10** is implanted in a body vessel, the base portion **14** remains substantially static, even as fluid flows through the body vessel **34**, because the base portion **14** is associated with a means for maintaining an axial position of a portion of the leaflet **12** in the body vessel. For example, in the illustrated embodiment, the base portion **14** defines an opening **36**. Barb **20** is partially disposed in the opening **36**, with a head **38** disposed adjacent one surface **40** of the leaflet **12**. An anchor portion **42** of the barb **20** is disposed external to the body vessel **34**, and a body portion **44** of the barb **20** is disposed within the opening **36** and through the wall **32** of the body vessel **34**. The head **38** and anchor portion **42** of the barb **20** can be compressed toward each other during implantation of the valve **10**.

[0030] The barb **20** can be formed of any suitable material, and need only be biocompatible or able to be made biocompatible. Also, the barb **20** can have any suitable size and configuration, and the specific size and configuration chosen for any particular valve according to the invention will depend on several considerations, including the nature of the

vessel in which the valve is being implanted. Also, the specific material used for the barb **20** can depend on the material used for the leaflet **12**. For example, in embodiments in which the leaflet **12** comprises a bioremodellable material, such as SIS, the barb **20** can be formed of a resorbable material. As used herein, the term "resorbable" refers to the ability of a material to be absorbed into a tissue and/or body fluid upon contact with the tissue and/or body fluid. The contact can be prolonged, and can be intermittent in nature. A number of resorbable materials are known in the art, and any suitable resorbable material can be used. Examples of suitable types of resorbable materials include resorbable homopolymers, copolymers, or blends of resorbable polymers. Specific examples of suitable resorbable materials include poly-alpha hydroxy acids such as polylactic acid, polylactide, polyglycolic acid (PGA), and polyglycolide; trimethylene carbonate; polycaprolactone; poly-beta hydroxy acids such as polyhydroxybutyrate and polyhydroxyvalerate; and other polymers such as polyphosphazines, polyorganophosphazines, polyanhydrides, polyesteramides, polyorthoesters, polyethylene oxide, polyester-ethers (e.g., polydioxanone) and polyamino acids (e.g., poly-L-glutamic acid or poly-L-lysine). There are also a number of naturally derived resorbable polymers that may be suitable, including modified polysaccharides, such as cellulose, chitin, and dextran, and modified proteins, such as fibrin and casein.

[0031] In embodiments in which the barb, or another suitable means for maintaining an axial position of the leaflet, comprises a resorbable material, the base portion **14** of the leaflet **12**, or a portion thereof, can eventually become incorporated into the wall **32** of the body vessel **34**, providing the desired anchoring function. Once the base portion **14** is sufficiently incorporated into the vessel wall **32**, additional anchoring, such as that provided by the barb **20**, may no longer be needed. If the barb **20** is formed of a resorbable material, the barb **20** would be eliminated gradually as the material of the barb **20** is absorbed, allowing the incorporated base portion **14** to perform the anchoring function.

[0032] The prosthetic valve **10** of this exemplary embodiment does not have a support frame, an optional element that may or may not be desirable in a particular embodiment.

[0033] As best illustrated in FIGS. **2** and **3**, the valve portion **16** is moveable between first and second positions when the valve **10** is implanted in a body vessel **34**. In the first position, illustrated in FIG. **2**, the valve portion **16** is positioned within the body vessel **34** so that an opening **46** is formed between the vessel wall **32** and the valve portion **16**. Fluid is able to flow through the body vessel **34** at the position of the valve **10** via the opening **46** in a first direction, represented by arrow **48**. As such, the leaflet **12** can be referred to as being in an open configuration and as permitting fluid flow through the body vessel **34** in the first direction **48**.

[0034] In the second position, illustrated in FIG. **3**, a surface **50** of the valve portion **16** is disposed adjacent a portion of the wall **32** of the body vessel **34**. In this configuration, the opening **46** of the first position, described above, is substantially eliminated. Accordingly, the leaflet **12** substantially prevents fluid flow through the body vessel **34** in a second, opposite direction, represented by arrow **52**. As such, the leaflet **12** can be referred to as being in a closed configuration.

[0035] The valve portion **16** can move between the first and second positions, i.e., between open and closed configurations, in response to a change in the direction of fluid flow through a body vessel in which the valve **10** is implanted, such as a change from flow in the first direction **48** to a flow in the second, opposite direction **52**. Also, the valve portion **16** can move between the first and second positions in response to a change in fluid pressure on one or more sides of the leaflet **12**.

[0036] In the embodiment illustrated in FIGS. **1** through **3**, the bioactive agent **18** is disposed on the leaflet **12**. As best illustrated in FIGS. **2** and **3**, the bioactive agent **18** can be disposed within a thickness of the leaflet **12**.

[0037] Any suitable bioactive agent can be used in the invention, and the specific bioactive agent, or bioactive agents, selected for any particular medical device according to the invention will depend upon several considerations, including the desired effect and the type of treatment and/or procedure in which the medical device is being used. Examples of suitable bioactives include heparin, covalent heparin or another thrombin inhibitor, hirudin, hirulog, argatroban, D-phenylalanyl-L-poly-L-arginyl chloromethyl ketone, or another antithrombogenic agent, or mixtures thereof; urokinase, streptokinase, a tissue plasminogen activator; or another thrombolytic agent, or mixtures thereof; a fibrinolytic agent; a vasospasm inhibitor; a calcium channel blocker; a nitrate, nitric oxide, a nitric oxide promoter or another vasodilator; an antimicrobial agent or antibiotic; aspirin, ticlopidine, a glycoprotein IIb/IIIa inhibitor or another inhibitor of surface glycoprotein receptors, or another antiplatelet agent; colchicine or another antimitotic, or another microtubule inhibitor, dimethylsulfoxide (DMSO), a retinoid or another antisecretory agent; cytochalasin or another actin inhibitor; or a remodeling inhibitor; deoxyribonucleic acid, an antisense nucleotide or another agent for molecular genetic intervention; methotrexate or another antimetabolite or antiproliferative agent; paclitaxel; tamoxifen citrate, Taxol® or derivatives thereof, or other anti-cancer chemotherapeutic agents; dexamethasone, dexamethasone sodium phosphate, dexamethasone acetate or another dexamethasone derivative, or another anti-inflammatory steroid or non-steroidal anti-inflammatory agent; cyclosporin, sirolimus, or another immunosuppressive agent; tripodal (aPDGF antagonist), angiopeptin (a growth hormone antagonist), angiogenin or other growth factors, or an anti-growth factor antibody, or another growth factor antagonist; dopamine, bromocriptine mesylate, pergolide mesylate or another dopamine agonist; ^{60}Co, ^{192}Ir, ^{32}P, ^{111}In, ^{90}Y, ^{99m}Tc or another radiotherapeutic agent; iodine-containing compounds, barium-containing compounds, gold, tantalum, platinum, tungsten or another heavy metal functioning as a radiopaque agent; a peptide, a protein, an enzyme, an extracellular matrix component, a cellular component or another biologic agent; captopril, enalapril or another angiotensin converting enzyme (ACE) inhibitor; ascorbic acid, alpha tocopherol, superoxide dismutase, deferoxamine, a 21-amino steroid (lasaroid) or another free radical scavenger, iron chelator or antioxidant; a ^{14}C—, ^{3}H—, ^{131}I—, ^{32}P— or ^{36}S-radiolabelled form or other radiolabelled form of any of the foregoing; estrogen or another sex hormone; AZT or other antipolymerases; acyclovir; famciclovir; rimantadine hydrochloride, ganciclovir sodium or other antiviral agents; 5-aminolevulinic acid, meta-tetrahydroxyphenylchlorin, hexadecaflouoro zinc phthalocyanine, tetramethyl hematoporphyrin, rhodamine 123 or other photodynamic therapy agents; an IgG2 Kappa antibody against Pseudomonas aeruginosa exotoxin A and reactive with A431 epidermoid carcinoma cells, monoclonal antibody against the noradrenergic enzyme dopamine betahydroxylase conjugated to saporin or other antibody tar-

get therapy agents; enalapril or other prodrugs; any endothelium progenitor cell attracting, binding and/or differentiating agents, including suitable chemoattractive agents and suitable polyclonal and monoclonal antibodies; cell migration inhibiting agents, such as smooth muscle cell migration inhibitors, such as Bamimistat, prolylhydrolase inhibitors, Probacol, c-proteinase inhibitors, halofuginone, and other suitable migration inhibitors; and gene therapy agents, or a mixture of any of these.

[0038] The bioactive agent **18** is disposed on a portion **60** of the leaflet **12**. The portion **60** can be any suitable portion of the leaflet **12**. Advantageously, the portion **60** is a portion of the leaflet **12** for which it is desirable to have the effect that the bioactive agent **18** is able to achieve within a biological system. For example, the prosthetic valve **10** illustrated in FIGS. **1** through **3** functions by moving between open and closed positions. As illustrated in FIGS. **2** and **3**, portions of the leaflet **12** makes contact with the vessel wall **32** during such movement. If the leaflet **12** comprises a material that may become temporarily or permanently adhered to or otherwise attached to the vessel wall **32** as a result of such contact, it may be desirable to protect one or more portions of the leaflet **12** during contact. A bioactive agent **18** that prevents cellular deposition, ingrowth, or proliferation can be placed on one or more portions of the leaflet **12** to achieve such protection. An antiproliferative bioactive agent, such as paclitaxel, is believed to be advantageous in this regard.

[0039] The use of a bioactive agent **18** to protect a portion of a valve leaflet **18** is particularly advantageous for leaflets that comprise a bioreodellable material. In these embodiments, the bioactive agent **18** protects a portion of the leaflet **18** while another portion begins the remodelling process. The protected portion **60** will begin the remodelling process as the bioactive agent **18** dissipates from the leaflet **18**. This may allow for selective protection and remodelling during a critical period, such as a period following implantation.

[0040] In the embodiment illustrated in FIGS. **1** through **3**, the portion **60** that includes the bioactive agent **18** is a portion that may contact the vessel wall **32** during valve function, such as base portion **14**. It is understood that the bioactive agent **18** can be disposed on one or more portions of a medical device without departing from the scope of the invention.

[0041] FIGS. **4** and **5** illustrate a second exemplary embodiment. The medical device according to this embodiment is a prosthetic valve **110** for regulating fluid flow through a body vessel. The valve **110** includes two leaflets **112**, **114** that are attached to a support frame **116**. Each leaflet **112**, **114** has a free edge **118**, **120** that is not attached to the support frame **116**. The free edges **118**, **120** cooperatively define valve orifice **122**. The leaflets **112**, **114** are both movable between first and second positions. In the first position, illustrated in FIG. **7**, the orifice **122** is open and allows fluid flow through the valve **110** in a first direction, represented by arrow **174**. In the second position, the free edges **118**, **120** of leaflets **112**, **114** come together to close the orifice **122** and substantially prevent fluid flow through the valve **110** in a second, opposite direction, represented by arrow **175**.

[0042] In this embodiment, a bioactive agent **124** is associated with each leaflet **112**, **114** adjacent the free edge **118**, **120**. Thus, the bioactive agent **124** is positioned adjacent the valve orifice **122**. A bioactive agent **124** positioned in this manner may confer a desired effect onto the leaflets **112**, **114** adjacent the valve orifice **122**. An antiproliferative agent, such as paclitaxel, may be used in this manner to delay remodelling of the free edges **118**, **120** of leaflets **112**, **114** formed of a remodellable material. Leaflets **112**, **114** with a bioactive agent positioned in this manner are expected to remodel at portions lacking the agent **124** first, such as base portion **126**, which may improve anchoring of the valve **110**.

[0043] FIG. **5** illustrates the prosthetic valve **110** disposed within a body vessel **180**. The valve **110** is shown in a closed configuration.

[0044] FIG. **6** illustrates a third exemplary embodiment. The medical device according to this embodiment is a prosthetic valve **210** for regulating fluid flow through a body vessel. The prosthetic valve **210** comprises a first tubular frame member **212** and a second tubular frame member **214** disposed circumferentially around the first tubular frame member **212**. A tubular graft member **216** is disposed about a portion of the first tubular frame member **212** and into a space between the frame members **212**, **214**. Opposing sides of one end **217** of the graft member **216** collapse onto the first tubular member **212** to close an opening **219** defined by the end of the graft member **216** and provide a valving function.

[0045] In this embodiment, the graft member **216** defines a plurality of openings **218**. The slits allow a controlled amount of retrograde flow through the valve **210** when the graft member **216** is in a closed configuration, as illustrated. This allowance of retrograde flow provides a beneficial flushing effect in the valve pocket, which may avoid pooling of fluid in the valve pocket. A bioactive agent **220** is associated with the graft member **216** adjacent the opening **218**. This positioning of the bioactive agent can provide a desired effect near the opening **218**, such as a delay in remodelling of a leaflet formed of a remodellable material, as described above.

[0046] It is understood that any suitable number, size, configuration, and positioning of openings **218** in the graft member **216** can be used.

[0047] FIG. **7** illustrates a fourth exemplary embodiment. The medical device according to this embodiment comprises a prosthetic valve **310**. The valve **310** includes two leaflets **346**, **348** that are attached to a support frame **310**. Each leaflet **346**, **348** has a free edge **350**, **352** that is not attached to the support frame **310**. The free edges **350**, **352** cooperatively define valve orifice **392**. The leaflets **346**, **348** are both movable between first and second positions. In the first position, illustrated in FIG. **7**, the orifice **392** is open and allows fluid flow through the valve **310** in a first direction, represented by arrow **374**. In the second position, the free edges **350**, **352** of leaflets **346**, **348** come together to close the orifice **392** and substantially prevent fluid flow through the device in a second, opposite direction. Each leaflet **346**, **348** defines an opening **380**, **382** that allows a controlled amount of retrograde flow to pass through the medical device **300** when the valve orifice **392** is closed. In this embodiment, each of the openings **380**, **382** is defined entirely by the respective leaflet **346**, **348**. Thus, one or more edges **394**, **396** of the leaflets **346**, **348** define each of the openings **380**, **382**. A bioactive agent **398** is associated with each leaflet **346**, **348** adjacent the respective opening **380**, **382**.

[0048] FIG. **8** illustrates a fifth exemplary embodiment. The medical device according to this embodiment comprises a prosthetic valve **410**. The prosthetic valve **410** of this embodiment is similar to the device illustrated in FIG. **7**, except that each opening **480**, **482** is partially defined by an edge **494**, **496** of a leaflet **446**, **448** and a portion of the support frame **410**. This configuration of the openings **480**, **482** may be advantageous if the valve leaflets **446**, **448** are formed of a

bioremodellable material or other material that can become adhered to or incorporated into a vessel wall following repeated and/or prolonged contact between the valve leaflets **446**, **448** and the vessel wall. Similar to the embodiment illustrated in FIG. **7**, free edges **450**, **452** of leaflets **446**, **448** define valve orifice **492** which opens and closes to regulate fluid flow through the device **400**. A bioactive agent **498** is associated with each leaflet **446**, **448** at the respective free edge **450**, **452** that partially defines the respective opening **480**, **482**.

[0049] FIG. **9** illustrates a sixth exemplary embodiment. The medical device according to this embodiment comprises a prosthetic valve **510**. The prosthetic valve **510** is similar to the valve **310** illustrated in FIG. **7**, except that the opening **580** that allows retrograde flow is defined by a flap **582** in the leaflet **584**. A flap configuration may allow retrograde flow to proceed through the opening, and minimize or prevent any antegrade flow from proceeding through the opening. As used herein, the term "flap" refers to a section of material that is connected to or integrally formed with adjacent material at one side or end, but is free of adjacent material at another side or end. The flap is a moveable section of material that is adjacent the opening. As the flap moves, it is able to temporarily and substantially close the opening. Specific examples of suitable shapes for the flap **582** include a partial square flap, a partial triangular flap, a partial ovoid flap, and a partial teardrop-shaped flap. The actual shape chosen for the flap will depend on various factors, including the desired quantity of retrograde flow, the size and configuration of the leaflet(s) of the medical device, the desired ability of the flap to close, and the size and configuration of the vessel in which the medical device will be employed. An optional support, such as a suture that traverses the opening **580**, can be added to prevent the flap **582** from inverting into the opening **580**.

[0050] A bioactive agent **590** is associated with the flap **582**. This positioning of the bioactive agent **590** may provide a desired effect at the flap **582**, such as a delay in remodelling as described above. Such a delay may be particularly desirable in embodiments that include a flap because it may allow the flap to open and close until the remainder of the leaflet has started or completed remodelling. Once the bioactive agent **590** has dissipated, the flap can remodel, which me result in permanent closure of the flap due to adherence to the remainder of the leaflet.

[0051] FIG. **10** illustrates an alternative configuration of the embodiment illustrated in FIG. **9**. As illustrated in FIG. **10**, the bioactive agent **590** also can be associated with the portion of the leaflet **584** that defines the opening **580** underlying the flap **582**. This positioning of the bioactive agent **590** may enhance the desired effect, such as a delay in remodeling near the opening **580**.

[0052] The foregoing detailed description provides exemplary embodiments of the invention and includes the best mode for practicing the invention. These embodiments are intended only to serve as examples of the invention, and not to limit the scope of the invention, or its protection, in any manner.

We claim:

1. A prosthetic valve for selectively permitting fluid flow through a body vessel, said prosthetic valve comprising:

a support frame;

a leaflet attached to the support frame and having first and second free edges, the first free edge adapted to move between first and second positions and to permit said fluid flow through said body vessel in a first direction and substantially prevent said fluid flow through said body vessel in a second, opposite direction, the second free edge at least partially defining an opening for permitting a controlled amount of said fluid flow through said body vessel; and

a bioactive agent associated with the second free edge;

wherein the first free edge is free of the bioactive agent.

2. The prosthetic valve of claim **1**, wherein the second free edge entirely defines the opening.

3. The prosthetic valve of claim **1**, wherein the second free edge and a portion of the support frame define the opening.

4. The prosthetic valve of claim **1**, wherein the leaflet defines a flap capable of substantially covering the opening.

5. The prosthetic valve of claim **1**, wherein the leaflet comprises a bioremodellable material.

6. The prosthetic valve of claim **1**, wherein the leaflet comprises an extracellular matrix material.

7. The prosthetic valve of claim **1**, wherein the leaflet comprises small intestine submucosa.

8. The prosthetic valve of claim **1**, wherein the bioactive agent is adapted to prevent cellular deposition, cellular ingrowth, or cellular proliferation.

9. The prosthetic valve of claim **1**, wherein the bioactive agent comprises an antiproliferative agent.

10. The prosthetic valve of claim **9**, wherein the bioactive agent comprises paclitaxel.

11. The prosthetic valve of claim **1**, wherein the bioactive agent comprises an anti-inflammatory agent.

12. The prosthetic valve of claim **1**, wherein the bioactive agent comprises one or more of a thrombin inhibitor, an antithrombogenic agent, a thrombolytic agent, a fibrinolytic agent, an antimicrobial agent, an antiplatelet agent, an antimitotic agent, a microtubule inhibitor, an antisecretory agent, an antimetabolite, a chemotherapeutic agent, an immunosuppressive agent, a growth factor, an anti-growth factor antibody, a growth factor antagonist, a dopamine agonist, a radiotherapeutic agent, a heavy metal functioning as a radiopaque agent, a biologic agent, a angiotensin converting enzyme (ACE) inhibitor, a free radical scavenger, an iron chelator; an antioxidant, a sex hormone, an antipolymerase, an antiviral, a photodynamic therapy agent, an antibody, a prodrug, a cell migration inhibiting agent, and a gene therapy agents.

13. The prosthetic valve of claim **1**, wherein the bioactive agent comprises one or more endothelium progenitor cell attracting, binding and/or differentiating agents.

14. The prosthetic valve of claim **13**, wherein the one or more endothelium progenitor cell attracting, binding and/or differentiating agents comprises one or more of a chemoattractive agent, a polyclonal antibody, and a monoclonal antibody.

15. The prosthetic valve of claim **1**, wherein the leaflet comprises a bioremodellable material and the bioactive agent is adapted to prevent cellular deposition, cellular ingrowth, or cellular proliferation.

16. The prosthetic valve of claim **1**, wherein the leaflet comprises a bioremodellable material and the bioactive agent comprises one or more endothelium progenitor cell attracting, binding and/or differentiating agents.

17. The prosthetic valve of claim **16**, wherein the one or more endothelium progenitor cell attracting, binding and/or differentiating agents comprises one or more of a chemoattractive agent, a polyclonal antibody, and a monoclonal antibody.

18. A prosthetic valve for selectively permitting fluid flow through a body vessel, said prosthetic valve comprising:

a support frame;

a first leaflet attached to the support frame and having first and second free edges, the second free edge at least partially defining a first opening for permitting a controlled amount of said fluid flow through said body vessel;

a second leaflet attached to the support frame and having third and fourth free edges, the fourth free edge at least partially defining a second opening for permitting a controlled amount of said fluid flow through said body vessel;

the first and third free edges cooperatively defining a valve orifice adapted to open to permit said fluid flow through said body vessel in a first direction and close to substantially prevent said fluid flow through said body vessel in a second, opposite direction;

a bioactive agent associated with at least one of the second and fourth free edges;

wherein at least one of the first and third free edges is free of the bioactive agent.

19. The prosthetic valve of claim **18**, wherein the second free edge entirely defines the first opening.

20. The prosthetic valve of claim **18**, wherein the second free edge and a portion of the support frame define the first opening.

21. A prosthetic valve for selectively permitting fluid flow through a body vessel, said prosthetic valve comprising:

a support frame having first and second portions;

a first leaflet attached to the support frame and having first and second free edges, the second free edge cooperating with the first portion of the support frame to define a first opening for permitting a controlled amount of said fluid flow through said body vessel;

a second leaflet attached to the support frame and having third and fourth free edges, the fourth free edge cooperating with the second portion of the support frame to define a second opening for permitting a controlled amount of said fluid flow through said body vessel;

the first and third free edges cooperatively defining a valve orifice adapted to open to permit fluid flow through said body vessel in a first direction and close to substantially prevent fluid flow through said body vessel in a second, opposite direction;

a bioactive agent associated with at least one of the second and fourth free edges;

wherein at least one of the first and third free edges is free of the bioactive agent.

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