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(54) Title: COATED MEDICAL DEVICES FOR THE PREVENTION AND TREATMENT OF VASCULAR DISEASE

(57) Abrégé/Abstract:
A drug and drug delivery system may be utilized in the treatment of vascular disease. A local delivery system is coated with rapamycin or other suitable drug, agent or compound and delivered intraluminally for the treatment and prevention of neointimal hyperplasia following percutaneous transluminal coronary angiography. The local delivery of the drugs or agents provides for increased effectiveness and lower systemic toxicity.

ABSTRACT

A drug and drug delivery system may be utilized in the treatment of vascular disease. A local delivery system is coated with rapamycin or other suitable drug, agent or compound and delivered intraluminally for the treatment and prevention of neointimal hyperplasia following percutaneous transluminal coronary angiography. The local delivery of the drugs or agents provides for increased effectiveness and lower systemic toxicity.

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COATED MEDICAL DEVICES FOR THE PREVENTION AND TREATMENT OF VASCULAR DISEASE

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of Provisional Application Number No. 60/381,986, filed May 20, 2002 and is a continuation-in-part application of U.S. Application Serial Number 09/850,293, filed on May 7, 2001, which is a continuation-in-part application of U.S. Application Serial Number 09/575,480, filed on May 19, 2000 which claims the benefit of U.S. Provisional Application No. 60/204,417, filed May 12, 2000.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to drugs and coated medical devices for the prevention and treatment of vascular disease, and more particularly to drugs and drug coated medical devices for the prevention and treatment of neointimal hyperplasia, specifically edge lumen loss and target lesion restenosis.

2. Discussion of the Related Art

Many individuals suffer from circulatory disease caused by a progressive blockage of the blood vessels that perfuse the heart and other major organs. More severe blockage of blood vessels in such individuals often leads to hypertension, ischemic injury, stroke, or myocardial infarction. Atherosclerotic lesions, which limit or obstruct coronary blood flow, are the major cause of ischemic heart disease. Percutaneous transluminal coronary angioplasty is a medical procedure whose purpose is to increase blood flow through an artery. Percutaneous transluminal coronary angioplasty is the predominant treatment for coronary vessel stenosis. The increasing use of this procedure is

attributable to its relatively high success rate and its minimal invasiveness compared with coronary bypass surgery. A limitation associated with percutaneous transluminal coronary angioplasty is the abrupt closure of the vessel which may occur immediately after the procedure, and restenosis which occurs gradually following the procedure. Additionally, restenosis is a chronic problem in patients who have undergone saphenous vein bypass grafting. The mechanism of acute occlusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets and fibrin along the damaged length of the newly opened blood vessel.

Restenosis after percutaneous transluminal coronary angioplasty is a more gradual process initiated by vascular injury. Multiple processes, including thrombosis, inflammation, growth factor and cytokine release, cell proliferation, cell migration and extracellular matrix synthesis each contribute to the restenotic process.

While the exact mechanism of restenosis is not completely understood, the general aspects of the restenosis process have been identified. In the normal arterial wall, smooth muscle cells proliferate at a low rate, approximately less than 0.1 percent per day. Smooth muscle cells in the vessel walls exist in a contractile phenotype characterized by eighty to ninety percent of the cell cytoplasmic volume occupied with the contractile apparatus. Endoplasmic reticulum, Golgi, and free ribosomes are few and are located in the perinuclear region. Extracellular matrix surrounds the smooth muscle cells and is rich in heparin-like glycosylaminoglycans which are believed to be responsible for maintaining smooth muscle cells in the contractile phenotypic state (Campbell and Campbell, 1985).

Upon pressure expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the vessel wall become injured, initiating a thrombotic and inflammatory response. Cell derived growth factors such as platelet derived growth factor, basic fibroblast growth factor, epidermal

growth factor, thrombin, etc., released from platelets, invading macrophages and/or leukocytes, or directly from the smooth muscle cells provoke a proliferative and migratory response in medial smooth muscle cells. These cells undergo a change from the contractile phenotype to a synthetic phenotype characterized by only a few contractile filament bundles, extensive rough endoplasmic reticulum, Golgi and free ribosomes. Proliferation/migration usually begins within one to two days post-injury and peaks several days thereafter (Campbell and Campbell, 1987; Clowes and Schwartz, 1985).

Daughter cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate and secrete significant amounts of extracellular matrix proteins. Proliferation, migration and extracellular matrix synthesis continue until the damaged endothelial layer is repaired at which time proliferation slows within the intima, usually within seven to fourteen days post-injury. The newly formed tissue is called neointima. The further vascular narrowing that occurs over the next three to six months is due primarily to negative or constrictive remodeling.

Simultaneous with local proliferation and migration, inflammatory cells adhere to the site of vascular injury. Within three to seven days post-injury, inflammatory cells have migrated to the deeper layers of the vessel wall. In animal models employing either balloon injury or stent implantation, inflammatory cells may persist at the site of vascular injury for at least thirty days (Tanaka et al., 1993; Edelman et al., 1998). Inflammatory cells therefore are present and may contribute to both the acute and chronic phases of restenosis.

Numerous agents have been examined for presumed anti-proliferative actions in restenosis and have shown some activity in experimental animal models. Some of the agents which have been shown to successfully reduce the extent of intimal hyperplasia in animal models include: heparin and heparin fragments (Clowes, A.W. and Karnovsky M., Nature 265: 25-26, 1977; Guyton, J.R. et al., Circ. Res., 46: 625-634, 1980; Clowes, A.W. and Clowes, M.M.,

Lab. Invest. 52: 611-616, 1985; Clowes, A.W. and Clowes, M.M., Circ. Res. 58: 839-845, 1986; Majesky et al., Circ. Res. 61: 296-300, 1987; Snow et al., Am. J. Pathol. 137: 313-330, 1990; Okada, T. et al., Neurosurgery 25: 92-98, 1989), colchicine (Currier, J.W. et al., Circ. 80: 11-66, 1989), taxol (Sollot, S.J. et al., J. Clin. Invest. 95: 1869-1876, 1995), angiotensin converting enzyme (ACE) inhibitors (Powell, J.S. et al., Science, 245: 186-188, 1989), angiopeptin (Lundergan, C.F. et al. Am. J. Cardiol. 17(Suppl. B):132B-136B, 1991), cyclosporin A (Jonasson, L. et al., Proc. Natl., Acad. Sci., 85: 2303, 1988), goat-anti-rabbit PDGF antibody (Ferns, G.A.A., et al., Science 253: 1129-1132, 1991), terbinafine (Nemecek, G.M. et al., J. Pharmacol. Exp. Thera. 248: 1167-1174, 1989), trapidil (Liu, M.W. et al., Circ. 81: 1089-1093, 1990), tranilast (Fukuyama, J. et al., Eur. J. Pharmacol. 318: 327-332, 1996), interferon-gamma (Hansson, G.K. and Holm, J., Circ. 84: 1266-1272, 1991), rapamycin (Marx, S.O. et al., Circ. Res. 76: 412-417, 1995), corticosteroids (Colburn, M.D. et al., J. Vasc. Surg. 15: 510-518, 1992), see also Berk, B.C. et al., J. Am. Coll. Cardiol. 17: 111B-117B, 1991), ionizing radiation (Weinberger, J. et al., Int. J. Rad. Onc. Biol. Phys. 36: 767-775, 1996), fusion toxins (Farb, A. et al., Circ. Res. 80: 542-550, 1997) antisense oligonucleotides (Simons, M. et al., Nature 359: 67-70, 1992) and gene vectors (Chang, M.W. et al., J. Clin. Invest. 96: 2260-2268, 1995). Anti-proliferative action on smooth muscle cells *in vitro* has been demonstrated for many of these agents, including heparin and heparin conjugates, taxol, tranilast, colchicine, ACE inhibitors, fusion toxins, antisense oligonucleotides, rapamycin and ionizing radiation. Thus, agents with diverse mechanisms of smooth muscle cell inhibition may have therapeutic utility in reducing intimal hyperplasia.

However, in contrast to animal models, attempts in human angioplasty patients to prevent restenosis by systemic pharmacologic means have thus far been unsuccessful. Neither aspirin-dipyridamole, ticlopidine, anti-coagulant therapy (acute heparin, chronic warfarin, hirudin or hirulog), thromboxane receptor antagonism nor steroids have been effective in preventing restenosis, although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty (Mak and Topol, 1997; Lang et al., 1991; Popma et al., 1991).

The platelet GP II_6/III_a receptor, antagonist, Reopro® is still under study but has not shown definitive results for the reduction in restenosis following angioplasty and stenting. Other agents, which have also been unsuccessful in the prevention of restenosis, include the calcium channel antagonists, prostacyclin mimetics, angiotensin converting enzyme inhibitors, serotonin receptor antagonists, and anti-proliferative agents. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; anti-proliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Mak and Topol, 1997; Lang et al., 1991; Popma et al., 1991).

Additional clinical trials in which the effectiveness for preventing restenosis utilizing dietary fish oil supplements or cholesterol lowering agents has been examined showing either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Mak and Topol, 1997; Franklin and Faxon, 1993: Serruys, P.W. et al., 1993). Recent observations suggest that the antilipid/antioxidant agent, probucol may be useful in preventing restenosis but this work requires confirmation (Tardif et al., 1997; Yokoi, et al., 1997). Probucol is presently not approved for use in the United States and a thirty-day pretreatment period would preclude its use in emergency angioplasty. Additionally, the application of ionizing radiation has shown significant promise in reducing or preventing restenosis after angioplasty in patients with stents (Teirstein et al., 1997). Currently, however, the most effective treatments for restenosis are repeat angioplasty, atherectomy or coronary artery bypass grafting, because no therapeutic agents currently have Food and Drug Administration approval for use for the prevention of post-angioplasty restenosis.

Unlike systemic pharmacologic therapy, stents have proven effective in significantly reducing restenosis. Typically, stents are balloon-expandable slotted metal tubes (usually, but not limited to, stainless steel), which, when

expanded within the lumen of an angioplastied coronary artery, provide structural support through rigid scaffolding to the arterial wall. This support is helpful in maintaining vessel lumen patency. In two randomized clinical trials, stents increased angiographic success after percutaneous transluminal coronary angioplasty, by increasing minimal lumen diameter and reducing, but not eliminating, the incidence of restenosis at six months (Serruys et al., 1994; Fischman et al., 1994).

Additionally, the heparin coating of stents appears to have the added benefit of producing a reduction in sub-acute thrombosis after stent implantation (Serruys et al., 1996). Thus, sustained mechanical expansion of a stenosed coronary artery with a stent has been shown to provide some measure of restenosis prevention, and the coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs locally, at the site of injured tissue.

Accordingly, there exists a need for effective drugs and drug delivery systems for the effective prevention and treatment of neointimal thickening that occurs after percutaneous transluminal coronary angioplasty and stent implantation, primarily edge lumen loss.

SUMMARY OF THE INVENTION

The drugs and drug delivery systems of the present invention provide a means for overcoming the difficulties associated with the methods and devices currently in use as briefly described above.

The drugs and drug delivery systems of the present invention utilize a stent or graft in combination with rapamycin or other drugs/agents/compounds to prevent and treat neointimal hyperplasia, i.e. restenosis, following percutaneous transluminal coronary angioplasty and stent implantation. It has been determined that rapamycin functions to inhibit smooth muscle cell

proliferation through a number of mechanisms. It has also been determined that rapamycin eluting stent coatings produce superior effects in humans, when compared to animals, with respect to the magnitude and duration of the reduction in neointimal hyperplasia. Rapamycin administration from a local delivery platform also produces an anti-inflammatory effect in the vessel wall that is distinct from and complimentary to its smooth muscle cell anti-proliferative effect. In addition, it has also been demonstrated that rapamycin inhibits constrictive vascular remodeling in humans.

Other drugs, agents or compounds which mimic certain actions of rapamycin may also be utilized in combination with local delivery systems or platforms.

The local administration of drugs, agents or compounds to stented vessels have the additional therapeutic benefit of higher tissue concentration than that which would be achievable through the systemic administration of the same drugs, agents or compounds. Other benefits include reduced systemic toxicity, single treatment, and ease of administration. An additional benefit of a local delivery device and drug, agent or compound therapy may be to reduce the dose of the therapeutic drugs, agents or compounds and thus limit their toxicity, while still achieving a reduction in restenosis.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other features and advantages of the invention will be apparent from the following, more particular description of preferred embodiments of the invention, as illustrated in the accompanying drawings.

Figure 1 is a chart indicating the effectiveness of rapamycin as an anti-inflammatory relative to other anti-inflammatories.

Figure 2 is a view along the length of a stent (ends not shown) prior to expansion showing the exterior surface of the stent and the characteristic banding pattern.

Figure 3 is a perspective view of the stent of Figure 1 having reservoirs in accordance with the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The drug/drug combinations and delivery devices of the present invention may be utilized to effectively prevent and treat vascular disease, and in particular, vascular disease caused by injury. Various medical treatment devices utilized in the treatment of vascular disease may ultimately induce further complications. For example, balloon angioplasty is a procedure utilized to increase blood flow through an artery and is the predominant treatment for coronary vessel stenosis. However, as stated above, the procedure typically causes a certain degree of damage to the vessel wall, thereby potentially exacerbating the problem at a point later in time. Although other procedures and diseases may cause similar injury, exemplary embodiments of the present invention will be described with respect to the treatment of restenosis and related complications following percutaneous transluminal coronary angioplasty and other similar arterial/venous procedures.

While exemplary embodiments of the invention will be described with respect to the treatment of restenosis and related complications following percutaneous transluminal coronary angioplasty, it is important to note that the local delivery of drug/drug combinations may be utilized to treat a wide variety of conditions utilizing any number of medical devices, or to enhance the function and/or life of the device. For example, intraocular lenses, placed to restore vision after cataract surgery is often compromised by the formation of a secondary cataract. The latter is often a result of cellular overgrowth on the lens surface and can be potentially minimized by combining a drug or drugs

with the device. Other medical devices which often fail due to tissue in-growth or accumulation of proteinaceous material in, on and around the device, such as shunts for hydrocephalus, dialysis grafts, colostomy bag attachment devices, ear drainage tubes, leads for pace makers and implantable defibrillators can also benefit from the device-drug combination approach. Devices which serve to improve the structure and function of tissue or organ may also show benefits when combined with the appropriate agent or agents. For example, improved osteointegration of orthopedic devices to enhance stabilization of the implanted device could potentially be achieved by combining it with agents such as bone-morphogenic protein. Similarly, other surgical devices, sutures, staples, anastomosis devices, vertebral disks, bone pins, suture anchors, hemostatic barriers, clamps, screws, plates, clips, vascular implants, tissue adhesives and sealants, tissue scaffolds, various types of dressings, bone substitutes, intraluminal devices, and vascular supports could also provide enhanced patient benefit using this drug-device combination approach. Essentially, any type of medical device may be coated in some fashion with a drug or drug combination which enhances treatment over use of the singular use of the device or pharmaceutical agent.

In addition to various medical devices, the coatings on these devices may be used to deliver therapeutic and pharmacaeutic agents including: antiproliferative/antimitotic agents including natural products such as vinca alkaloids (i.e. vinblastine, vincristine, and vinorelbine), paclitaxel, epidipodophyllotoxins (i.e. etoposide, teniposide), antibiotics (dactinomycin (actinomycin D) daunorubicin, doxorubicin and idarubicin), anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin) and mitomycin, enzymes (L-asparaginase which systemically metabolizes L-asparagine and deprives cells which do not have the capacity to synthesize their own asparagine); antiplatelet agents such as G(GP) II_b/III_a inhibitors and vitronectin receptor antagonists; antiproliferative/antimitotic alkylating agents such as nitrogen mustards (mechlorethamine, cyclophosphamide and analogs, melphalan, chlorambucil), ethylenimines and methylmelamines (hexamethylmelamine and thiotepa), alkyl sulfonates-busulfan, nitrosoureas (carmustine (BCNU) and

analogs, streptozocin), trazanes - dacarbazinine (DTIC); antiproliferative/antimitotic antimetabolites such as folic acid analogs (methotrexate), pyrimidine analogs (fluorouracil, floxuridine, and cytarabine), purine analogs and related inhibitors (mercaptopurine, thioguanine, pentostatin and 2-chlorodeoxyadenosine {cladribine}); platinum coordination complexes (cisplatin, carboplatin), procarbazine, hydroxyurea, mitotane, aminoglutethimide; hormones (i.e. estrogen); anticoagulants (heparin, synthetic heparin salts and other inhibitors of thrombin); fibrinolytic agents (such as tissue plasminogen activator, streptokinase and urokinase), aspirin, dipyridamole, ticlopidine, clopidogrel, abciximab; antimigratory; antisecretory (breveldin); anti-inflammatory; such as adrenocortical steroids (cortisol, cortisone, fludrocortisone, prednisone, prednisolone, 6α-methylylprednisolone, triamcinolone, betamethasone, and dexamethasone), non-steroidal agents (salicylic acid derivatives i.e, aspirin; para-aminophenol derivaties i.e. acetominophen; indole and indene acetic acids (indomethacin, sulindac, and etodalac), heteroaryl acetic acids (tolmetin, diclofenac, and ketorolac), arylpropionic acids (ibuprofen and derivatives), anthranilic acids (mefenamic acid, and meclofenamic acid), enolic acids (piroxicam, tenoxicam, phenylbutazone, and oxyphenthatrazone), nabumetone, gold compounds (auranofin, aurothioglucose, gold sodium thiomalate); immunosuppressives; (cyclosporine, tacrolimus (FK-506), sirolimus (rapamycin), azathioprine, mycophenolate mofetil); angiogenic agents; vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF); angiotensin receptor blockers; nitric oxide donors; anti-sense oligionucleotides and combinations thereof; cell cycle inhibitors, mTOR inhibitors, and growth factor receptor signal transduction kinase inhibitors; retenoids; cyclin/CDK inhibitors; HMG co-enzyme reductase inhibitors (statins); and protease inhibitors.

As stated above, the proliferation of vascular smooth muscle cells in response to mitogenic stimuli that are released during balloon angioplasty and stent implantation is the primary cause of neointimal hyperplasia. Excessive neointimal hyperplasia can often lead to impairment of blood flow, cardiac ischemia and the need for a repeat intervention in selected patients in high risk

treatment groups. Yet repeat revascularization incurs risk of patient morbidity and mortality while adding significantly to the cost of health care. Given the widespread use of stents in interventional practice, there is a clear need for safe and effective inhibitors of neointimal hyperplasia and negative vascular remodeling.

Rapamycin is a macroyclic triene antibiotic produced by streptomyces hygroscopicus as disclosed in U.S. Patent No. 3,929,992. It has been found that rapamycin inhibits the proliferation of vascular smooth muscle cells *in vivo*. Accordingly, rapamycin may be utilized in treating intimal smooth muscle cell hyperplasia, restenosis and vascular occlusion in a mammal, particularly following either biologically or mechanically mediated vascular injury, or under conditions that would predispose a mammal to suffering such a vascular injury. Rapamycin functions to inhibit smooth muscle cell proliferation and does not interfere with the re-endothelialization of the vessel walls.

Rapamycin functions to inhibit smooth muscle cell proliferation through a number of mechanisms. In addition, rapamycin reduces the other effects caused by vascular injury, for example, inflammation. The operation and various functions of rapamycin are described in detail below. Rapamycin as used throughout this application shall include rapamycin, rapamycin analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin.

Rapamycin reduces vascular hyperplasia by antagonizing smooth muscle proliferation in response to mitogenic signals that are released during angioplasty. Inhibition of growth factor and cytokine mediated smooth muscle proliferation at the late G1 phase of the cell cycle is believed to be the dominant mechanism of action of rapamycin. However, rapamycin is also known to prevent T-cell proliferation and differentiation when administered systemically. This is the basis for its immunosuppresive activity and its ability to prevent graft rejection.

The molecular events that are responsible for the actions of rapamycin, a known anti-proliferative, which acts to reduce the magnitude and duration of neointimal hyperplasia, are still being elucidated. It is known, however, that rapamycin enters cells and binds to a high-affinity cytosolic protein called FKBP12. The complex of rapamycin and FKPB12 in turn binds to and inhibits a phosphoinositide (PI)-3 kinase called the "mammalian Target of Rapamycin" or mTOR. The mammalian Target of Rapamycin is a protein kinase that plays a key role in mediating the downstream signaling events associated with mitogenic growth factors and cytokines in smooth muscle cells and T lymphocytes. These events include phosphorylation of p27, phosphorylation of p70 s6 kinase and phosphorylation of 4BP-1, an important regulator of protein translation.

It is recognized that rapamycin reduces restenosis by inhibiting neointimal hyperplasia. However, there is evidence that rapamycin may also inhibit the other major component of restenosis, namely, negative remodeling. Remodeling is a process whose mechanism is not clearly understood but which results in shrinkage of the external elastic lamina and reduction in lumenal area over time, generally a period of approximately three to six months in humans.

Negative or constrictive vascular remodeling may be quantified angiographically as the percent diameter stenosis at the lesion site where there is no stent to obstruct the process. If late lumen loss is abolished *in-lesion*, it may be inferred that negative remodeling has been inhibited. Another method of determining the degree of remodeling involves measuring *in-lesion* external elastic lamina area using intravascular ultrasound (IVUS). Intravascular ultrasound is a technique that can image the external elastic lamina as well as the vascular lumen. Changes in the external elastic lamina proximal and distal to the stent from the post-procedural timepoint to four-month and twelve-month follow-ups are reflective of remodeling changes.

Evidence that rapamycin exerts an effect on remodeling comes from human implant studies with rapamycin coated stents showing a very low degree of restenosis *in-lesion* as well as *in-stent*. *In-lesion* parameters are usually measured approximately five millimeters on either side of the stent i.e. proximal and distal. Since the stent is not present to control remodeling in these zones which are still affected by balloon expansion, it may be inferred that rapamycin is preventing vascular remodeling.

The data in Table 1 below illustrate that *in-lesion* percent diameter stenosis remains low in the rapamycin treated groups, even at twelve months. Accordingly, these results support the hypothesis that rapamycin reduces remodeling.

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Angiographic *In-Lesion* Percent Diameter Stenosis (%, mean ± SD and "n=") In Patients Who Received a Rapamycin-Coated Stent

Coating Group	Post Placement	4 – 6 month Follow Up	12 month Follow Up
Brazil	10.6 ± 5.7 (30)	13.6 ± 8.6 (30)	22.3 ± 7.2 (15)
Netherlands	14.7 ± 8.8	22.4 ± 6.4	-

TABLE 1.0

Additional evidence supporting a reduction in negative remodeling with rapamycin comes from intravascular ultrasound data that was obtained from a first-in-man clinical program as illustrated in Table 2 below.

Matched IVUS data in Patients Who Received a Rapamycin-Coated Stent

IVUS Parameter	Post (n=)	4-Month Follow-Up (n=)	12-Month Follow-Up (n=)
Mean proximal vessel area (mm^2)	16.53 ± 3.53 (27)	16.31 ± 4.36 (28)	13.96 ± 2.26 (13)
Mean distal vessel area (mm^2)	13.12 ± 3.68 (26)	13.53 ± 4.17 (26)	12.49 ± 3.25 (14)

TABLE 2.0

The data illustrated that there is minimal loss of vessel area proximally or distally which indicates that inhibition of negative remodeling has occurred in vessels treated with rapamycin-coated stents.

Other than the stent itself, there have been no effective solutions to the problem of vascular remodeling. Accordingly, rapamycin may represent a biological approach to controlling the vascular remodeling phenomenon.

It may be hypothesized that rapamycin acts to reduce negative remodeling in several ways. By specifically blocking the proliferation of

fibroblasts in the vascular wall in response to injury, rapamycin may reduce the formation of vascular scar tissue. Rapamycin may also affect the translation of key proteins involved in collagen formation or metabolism.

Rapamycin used in this context includes rapamycin and all analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin.

In a preferred exemplary embodiment, the rapamycin is delivered by a local delivery device to control negative remodeling of an arterial segment after balloon angioplasty as a means of reducing or preventing restenosis. While any delivery device may be utilized, it is preferred that the delivery device comprises a stent that includes a coating or sheath which elutes or releases rapamycin. The delivery system for such a device may comprise a local infusion catheter that delivers rapamycin at a rate controlled by the administrator.

Rapamycin may also be delivered systemically using an oral dosage form or a chronic injectible depot form or a patch to deliver rapamycin for a period ranging from about seven to forty-five days to achieve vascular tissue levels that are sufficient to inhibit negative remodeling. Such treatment is to be used to reduce or prevent restenosis when administered several days prior to elective angioplasty with or without a stent.

Data generated in porcine and rabbit models show that the release of rapamycin into the vascular wall from a nonerodible polymeric stent coating in a range of doses (35-430 µg/15-18 mm coronary stent) produces a peak fifty to fifty-five percent reduction in neointimal hyperplasia as set forth in Table 3 below. This reduction, which is maximal at about twenty-eight to thirty days, is typically not sustained in the range of ninety to one hundred eighty days in the porcine model as set forth in Table 4 below.

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Animal Studies with Rapamycin-coated stents.
Values are mean ± Standard Error of Mean

Study	Duration	Stent[1]	Rapamycin	N	Neointimal Area (mm^2)	% Change From Polyme	% Change From Metal
Porcine							
98009	14 days	Metal		8	2.04 ± 0.17		
		1X + rapamycin	153 ug	8	1.66 ± 0.17*	-42%	-19%
		1X + TC300 + rapamycin	155 ug	8	1.51 ± 0.19*	-47%	-26%
99005	28 days	Metal		10	2.29 ± 0.21		
				9	3.91 ± 0.60**		
		1X + TC30 + rapamycin	130 ug	8	2.81 ± 0.34		+23%
		1X + TC100 + rapamycin	120 ug	9	2.62 ± 0.21		+14%
99006	28 days	Metal		12	4.57 ± 0.46		
		EVA/BMA 3X		12	5.02 ± 0.62		+10%
		1X + rapamycin	125 ug	11	2.84 ± 0.31* **	-43%	-38%
		3X + rapamycin	430 ug	12	3.06 ± 0.17* **	-39%	-33%
		3X + rapamycin	157 ug	12	2.77 ± 0.41* **	-45%	-39%
99011	28 days	Metal		11	3.09 ± 0.27		
				11	4.52 ± 0.37		
		1X + rapamycin	189 ug	14	3.05 ± 0.35		-1%
		3X + rapamycin/dex	182/363 ug	14	2.72 ± 0.71		-12%
99021	60 days	Metal		12	2.14 ± 0.25		
		1X + rapamycin	181 ug	12	2.95 ± 0.38		+38%
99034	28 days	Metal		8	5.24 ± 0.58		
		1X + rapamycin	186 ug	8	2.47 ± 0.33**		-53%
		3X + rapamycin/dex	185/369 ug	6	2.42 ± 0.64**		-54%
20001	28 days	Metal		6	1.81 ± 0.09		
		1X + rapamycin	172 ug	5	1.66 ± 0.44		-8%
20007							
	30 days	Metal		9	2.94 ± 0.43		
		1XTC + rapamycin	155 ug	10	1.40 ± 0.11*		-52%*
Rabbit							
99019	28 days	Metal		8	1.20 ± 0.07		
		EVA/BMA 1X		10	1.26 ± 0.16		+5%
		1X + rapamycin	64 ug	9	0.92 ± 0.14	-27%	-23%
		1X + rapamycin	196 ug	10	0.66 ± 0.12* **	-48%	-45%
99020	28 days	Metal		12	1.18 ± 0.10		
		EVA/BMA 1X + rapamycin	197 µg	8	0.81 ± 0.16		-32%

[1]Stent nomenclature: EVA/BMA 1X, 2X, and 3X signifies approx. 500µg, 1000µg, and 1500µg total mass (polymer + drug), respectively. TC, top coat of 30µg, 100µg, or 300µg drug-free BMA; Biphasic; 2 x 1X layers of rapamycin in EVA/BMA spearated by a 100µg drug-free BMA layer. [2]0.25mg/kg/d x 14 d preceeded by a loading dose of 0.5mg/kg/d x 3d prior to stent implantation.
*p<0.05 from EVA/BMA control. **p<0.05 from Metal;
#Inflammation score: (0 = essentially no intimal involvement; 1 = <25% intima involved;2= ≥25% intima involved; 3 = >50% intima involved).

TABLE 3.0

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180 day Porcine Study with Rapamycin-coated stents.
Values are mean ± Standard Error of Mean

Study	*Duration*	*Stent*[1]	*Rapamycin*	*N*	*Neointimal Area (mm^2)*	*% Change From*		*Inflammation Score #*
						Polyme	*Metal*	
20007	3 days	Metal		10	0.38 ± 0.06			1.05 ± 0.06
(ETP-2-002233-P)		1XTC + rapamycin	155 ug	10	0.29 ± 0.03		-24%	1.08 ± 0.04
	30 days	Metal		9	2.94 ± 0.43			0.11 ± 0.08
		1XTC + rapamycin	155 ug	10	1.40 ± 0.11*		-52%*	0.25 ± 0.10
	90 days	Metal		10	3.45 ± 0.34			0.20 ± 0.08
		1XTC + rapamycin	155 ug	10	3.03 ± 0.29		-12%	0.80 ± 0.23
		1X + rapamycin	171 ug	10	2.86 ± 0.35		-17%	0.60 ± 0.23
	180 days	Metal		10	3.65 ± 0.39			0.65 ± 0.21
		1XTC + rapamycin	155 ug	10	3.34 ± 0.31		-8%	1.50 ± 0.34
		1X + rapamycin	171 ug	10	3.87 ± 0.28		+6%	1.68 ± 0.37

TABLE 4.0

The release of rapamycin into the vascular wall of a human from a nonerodible polymeric stent coating provides superior results with respect to the magnitude and duration of the reduction in neointimal hyperplasia within the stent as compared to the vascular walls of animals as set forth above.

Humans implanted with a rapamycin coated stent comprising rapamycin in the same dose range as studied in animal models using the same polymeric matrix, as described above, reveal a much more profound reduction in neointimal hyperplasia than observed in animal models, based on the magnitude and duration of reduction in neointima. The human clinical response to rapamycin reveals essentially total abolition of neointimal hyperplasia inside the stent using both angiographic and intravascular ultrasound measurements. These results are sustained for at least one year as set forth in Table 5 below.

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Patients Treated (N=45 patients) with a Rapamycin-coated Stent

Effectiveness Measures	Sirolimus FIM (N=45 Patients, 45 Lesions)	95% Confidence Limit
Procedure Success (QCA)	100.0% (45/45)	[92.1%,100.0%]
4-month In-Stent Diameter Stenosis (%)		
Mean±SD (N)	4.8%±6.1% (30)	[2.6%,7.0%]
Range (min,max)	(-8.2%,14.9%)	
6-month In-Stent Diameter Stenosis (%)		
Mean±SD (N)	8.9%±7.6% (13)	[4.8%,13.0%]
Range (min,max)	(-2.9%,20.4%)	
12-month In-Stent Diameter Stenosis (%)		
Mean±SD (N)	8.9%±6.1% (15)	[5.8%,12.0%]
Range (min,max)	(-3.0%,22.0%)	
4-month In-Stent Late Loss (mm)		
Mean±SD (N)	0.00±0.29 (30)	[-0.10,0.10]
Range (min,max)	(-0.51,0.45)	
6-month In-Stent Late Loss (mm)		
Mean±SD (N)	0.25±0.27 (13)	[0.10,0.39]
Range (min,max)	(-0.51,0.91)	
12-month In-Stent Late Loss (mm)		
Mean±SD (N)	0.11±0.36 (15)	[-0.08,0.29]
Range (min,max)	(-0.51,0.82)	
4-month Obstruction Volume (%) (IVUS)		
Mean±SD (N)	10.48%±2.78% (28)	[9.45%,11.51%]
Range (min,max)	(4.60%,16.35%)	
6-month Obstruction Volume (%) (IVUS)		
Mean±SD (N)	7.22%±4.60% (13)	[4.72%,9.72%],
Range (min,max)	(3.82%,19.88%)	
12-month Obstruction Volume (%) (IVUS)		
Mean±SD (N)	2.11%±5.28% (15)	[0.00%,4.78%],
Range (min,max)	(0.00%,19.89%)	
6-month Target Lesion Revascularization (TLR)	0.0% (0/30)	[0.0%,9.5%]
12-month Target Lesion Revascularization (TLR)	0.0% (0/15)	[0.0%,18.1%]

QCA = Quantitative Coronary Angiography

SD = Standard Deviation

IVUS = Intravascular Ultrasound

TABLE 5.0

Rapamycin produces an unexpected benefit in humans when delivered from a stent by causing a profound reduction in in-stent neointimal hyperplasia that is sustained for at least one year. The magnitude and duration of this benefit in humans is not predicted from animal model data. Rapamycin used in

this context includes rapamycin and all analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin.

These results may be due to a number of factors. For example, the greater effectiveness of rapamycin in humans is due to greater sensitivity of its mechanism(s) of action toward the pathophysiology of human vascular lesions compared to the pathophysiology of animal models of angioplasty. In addition, the combination of the dose applied to the stent and the polymer coating that controls the release of the drug is important in the effectiveness of the drug.

As stated above, rapamycin reduces vascular hyperplasia by antagonizing smooth muscle proliferation in response to mitogenic signals that are released during angioplasty injury. Also, it is known that rapamycin prevents T-cell proliferation and differentiation when administered systemically. It has also been determined that rapamycin exerts a local inflammatory effect in the vessel wall when administered from a stent in low doses for a sustained period of time (approximately two to six weeks). The local anti-inflammatory benefit is profound and unexpected. In combination with the smooth muscle anti-proliferative effect, this dual mode of action of rapamycin may be responsible for its exceptional efficacy.

Accordingly, rapamycin delivered from a local device platform, reduces neointimal hyperplasia by a combination of anti-inflammatory and smooth muscle anti-proliferative effects. Rapamycin used in this context means rapamycin and all analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin. Local device platforms include stent coatings, stent sheaths, grafts and local drug infusion catheters or porous balloons or any other suitable means for the *in situ* or local delivery of drugs, agents or compounds.

The anti-inflammatory effect of rapamycin is evident in data from an experiment, illustrated in Table 6, in which rapamycin delivered from a stent was compared with dexamethasone delivered from a stent. Dexamethasone, a

potent steroidal anti-inflammatory agent, was used as a reference standard. Although dexamethasone is able to reduce inflammation scores, rapamycin is far more effective than dexamethasone in reducing inflammation scores. In addition, rapamycin significantly reduces neointimal hyperplasia, unlike dexamethasone.

Group Rapamycin Rap	N=	Neointimal Area (mm^2)	% Area Stenosis	Inflammation Score
Uncoated	8	5.24 ± 1.65	54 ± 19	0.97 ± 1.00
Dexamethasone (Dex)	8	4.31 ± 3.02	45 ± 31	0.39 ± 0.24
Rapamycin (Rap)	7	2.47 ± 0.94*	26 ± 10*	0.13 ± 0.19*
Rap + Dex	6	2.42 ± 1.58*	26 ± 18*	0.17 ± 0.30*

* = significance level P< 0.05

TABLE 6.0

Rapamycin has also been found to reduce cytokine levels in vascular tissue when delivered from a stent. The data in Figure 1 illustrates that rapamycin is highly effective in reducing monocyte chemotactic protein (MCP-1) levels in the vascular wall. MCP-1 is an example of a proinflammatory/chemotactic cytokine that is elaborated during vessel injury. Reduction in MCP-1 illustrates the beneficial effect of rapamycin in reducing the expression of proinflammatory mediators and contributing to the anti-inflammatory effect of rapamycin delivered locally from a stent. It is recognized that vascular inflammation in response to injury is a major contributor to the development of neointimal hyperplasia.

Since rapamycin may be shown to inhibit local inflammatory events in the vessel it is believed that this could explain the unexpected superiority of rapamycin in inhibiting neointima hyperplasia.

As set forth above, rapamycin functions on a number of levels to produce such desired effects as the prevention of T-cell proliferation, the

inhibition of negative remodeling, the reduction of inflammation, and the prevention of smooth muscle cell proliferation. While the exact mechanisms of these functions are not completely known, the mechanisms that have been identified may be expanded upon.

Studies with rapamycin suggest that the prevention of smooth muscle cell proliferation by blockade of the cell cycle is a valid strategy for reducing neointimal hyperplasia. Dramatic and sustained reductions in late lumen loss and neointimal plaque volume have been observed in patients receiving rapamycin delivered locally from a stent. The present invention expands upon the mechanism of rapamycin to include additional approaches to inhibit the cell cycle and reduce neointimal hyperplasia without producing toxicity.

The cell cycle is a tightly controlled biochemical cascade of events that regulate the process of cell replication. When cells are stimulated by appropriate growth factors, they move from G_0 (quiescence) to the G1 phase of the cell cycle. Selective inhibition of the cell cycle in the G1 phase, prior to DNA replication (S phase), may offer therapeutic advantages of cell preservation and viability while retaining anti-proliferative efficacy when compared to therapeutics that act later in the cell cycle i.e. at S, G2 or M phase.

Accordingly, the prevention of intimal hyperplasia in blood vessels and other conduit vessels in the body may be achieved using cell cycle inhibitors that act selectively at the G1 phase of the cell cycle. These inhibitors of the G1 phase of the cell cycle may be small molecules, peptides, proteins, oligonucleotides or DNA sequences. More specifically, these drugs or agents include inhibitors of cyclin dependent kinases (cdk's) involved with the progression of the cell cycle through the G1 phase, in particular cdk2 and cdk4.

Examples of drugs, agents or compounds that act selectively at the G1 phase of the cell cycle include small molecules such as flavopiridol and its structural analogs that have been found to inhibit cell cycle in the late G1

phase by antagonism of cyclin dependent kinases. Therapeutic agents that elevate an endogenous kinase inhibitory protein^{kip} called P27, sometimes referred to as P27^{kip1}, that selectively inhibits cyclin dependent kinases may be utilized. This includes small molecules, peptides and proteins that either block the degradation of P27 or enhance the cellular production of P27, including gene vectors that can transfact the gene to produce P27. Staurosporin and related small molecules that block the cell cycle by inhibiting protein kinases may be utilized. Protein kinase inhibitors, including the class of tyrphostins that selectively inhibit protein kinases to antagonize signal transduction in smooth muscle in response to a broad range of growth factors such as PDGF and FGF may also be utilized.

Any of the drugs, agents or compounds discussed above may be administered either systemically, for example, orally, intravenously, intramuscularly, subcutaneously, nasally or intradermally, or locally, for example, stent coating, stent covering or local delivery catheter. In addition, the drugs or agents discussed above may be formulated for fast-release or slow release with the objective of maintaining the drugs or agents in contact with target tissues for a period ranging from three days to eight weeks.

As set forth above, the complex of rapamycin and FKPB12 binds to and inhibits a phosphoinositide (PI)-3 kinase called the mammalian Target of Rapamycin or TOR. An antagonist of the catalytic activity of TOR, functioning as either an active site inhibitor or as an allosteric modulator, i.e. an indirect inhibitor that allosterically modulates, would mimic the actions of rapamycin but bypass the requirement for FKBP12. The potential advantages of a direct inhibitor of TOR include better tissue penetration and better physical/chemical stability. In addition, other potential advantages include greater selectivity and specificity of action due to the specificity of an antagonist for one of multiple isoforms of TOR that may exist in different tissues, and a potentially different spectrum of downstream effects leading to greater drug efficacy and/or safety.

The inhibitor may be a small organic molecule (approximate mw<1000), which is either a synthetic or naturally derived product. Wortmanin may be an agent which inhibits the function of this class of proteins. It may also be a peptide or an oligonucleotide sequence. The inhibitor may be administered either sytemically (orally, intravenously, intramuscularly, subcutaneously, nasally, or intradermally) or locally (stent coating, stent covering, local drug delivery catheter). For example, the inhibitor may be released into the vascular wall of a human from a nonerodible polymeric stent coating. In addition, the inhibitor may be formulated for fast-release or slow release with the objective of maintaining the rapamycin or other drug, agent or compound in contact with target tissues for a period ranging from three days to eight weeks.

As stated previously, the implantation of a coronary stent in conjunction with balloon angioplasty is highly effective in treating acute vessel closure and may reduce the risk of restenosis. Intravascular ultrasound studies (Mintz et al., 1996) suggest that coronary stenting effectively prevents vessel constriction and that most of the late luminal loss after stent implantation is due to plaque growth, probably related to neointimal hyperplasia. The late luminal loss after coronary stenting is almost two times higher than that observed after conventional balloon angioplasty. Thus, inasmuch as stents prevent at least a portion of the restenosis process, the use of drugs, agents or compounds which prevent inflammation and proliferation, or prevent proliferation by multiple mechanisms, combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis.

The local delivery of drugs, agents or compounds from a stent has the following advantages; namely, the prevention of vessel recoil and remodeling through the scaffolding action of the stent and the drugs, agents or compounds and the prevention of multiple components of neointimal hyperplasia. This local administration of drugs, agents or compounds to stented coronary arteries may also have additional therapeutic benefit. For example, higher tissue concentrations would be achievable than that which would occur with systemic administration, reduced systemic toxicity, and single treatment and ease of

administration. An additional benefit of drug therapy may be to reduce the dose of the therapeutic compounds, thereby limiting their toxicity, while still achieving a reduction in restenosis.

There are a multiplicity of different stents that may be utilized following percutaneous transluminal coronary angioplasty. Although any number of stents may be utilized in accordance with the present invention, for simplicity, one particular stent will be described in exemplary embodiments of the present invention. The skilled artisan will recognize that any number of stents may be utilized in connection with the present invention.

A stent is commonly used as a tubular structure left inside the lumen of a duct to relieve an obstruction. Commonly, stents are inserted into the lumen in a non-expanded form and are then expanded autonomously, or with the aid of a second device in situ. A typical method of expansion occurs through the use of a catheter-mounted angioplasty balloon which is inflated within the stenosed vessel or body passageway in order to shear and disrupt the obstructions associated with the wall components of the vessel and to obtain an enlarged lumen. As set forth below, self-expanding stents may also be utilized.

Figure 2 illustrates an exemplary stent 100 which may be utilized in accordance with an exemplary embodiment of the present invention. The expandable cylindrical stent 100 comprises a fenestrated structure for placement in a blood vessel, duct or lumen to hold the vessel, duct or lumen open, more particularly for protecting a segment of artery from restenosis after angioplasty. The stent 100 may be expanded circumferentially and maintained in an expanded configuration, that is circumferentially or radially rigid. The stent 100 is axially flexible and when flexed at a band, the stent 100 avoids any externally-protruding component parts.

The stent 100 generally comprises first and second ends with an intermediate section therebetween. The stent 100 has a longitudinal axis and

comprises a plurality of longitudinally disposed bands 102, wherein each band 102 defines a generally continuous wave along a line segment parallel to the longitudinal axis. A plurality of circumferentially arranged links 104 maintain the bands 102 in a substantially tubular structure. Essentially, each longitudinally disposed band 102 is connected at a plurality of periodic locations, by a short circumferentially arranged link 104 to an adjacent band 102. The wave associated with each of the bands 102 has approximately the same fundamental spatial frequency in the intermediate section, and the bands 102 are so disposed that the wave associated with them are generally aligned so as to be generally in phase with one another. As illustrated in the figure, each longitudinally arranged band 102 undulates through approximately two cycles before there is a link to an adjacent band.

The stent 100 may be fabricated utilizing any number of methods. For example, the stent 100 may be fabricated from a hollow or formed stainless steel tube that may be machined using lasers, electric discharge milling, chemical etching or other means. The stent 100 is inserted into the body and placed at the desired site in an unexpanded form. In one embodiment, expansion may be effected in a blood vessel by a balloon catheter, where the final diameter of the stent 100 is a function of the diameter of the balloon catheter used.

It should be appreciated that a stent 100 in accordance with the present invention may be embodied in a shape-memory material, including, for example, an appropriate alloy of nickel and titanium. In this embodiment, after the stent 100 has been formed it may be compressed so as to occupy a space sufficiently small as to permit its insertion in a blood vessel or other tissue by insertion means, wherein the insertion means include a suitable catheter, or flexible rod. On emerging from the catheter, the stent 100 may be configured to expand into the desired configuration where the expansion is automatic or triggered by a change in pressure, temperature or electrical stimulation.

Figure 3 illustrates an exemplary embodiment of the present invention utilizing the stent 100 illustrated in Figure 2. As illustrated, the stent 100 may be modified to comprise a reservoir 106. Each of the reservoirs may be opened or closed as desired. These reservoirs 106 may be specifically designed to hold the drug, agent, compound or combinations thereof to be delivered. Regardless of the design of the stent 100, it is preferable to have the drug, agent, compound or combinations thereof dosage applied with enough specificity and a sufficient concentration to provide an effective dosage in the lesion area. In this regard, the reservoir size in the bands 102 is preferably sized to adequately apply the drug/drug combination dosage at the desired location and in the desired amount.

In an alternate exemplary embodiment, the entire inner and outer surface of the stent 100 may be coated with various drug and drug combinations in therapeutic dosage amounts. A detailed description of exemplary coating techniques is described below.

Rapamycin or any of the drugs, agents or compounds described above may be incorporated into or affixed to the stent in a number of ways and utilizing any number of biocompatible materials. In the exemplary embodiment, the rapamycin is directly incorporated into a polymeric matrix and sprayed onto the outer surface of the stent. The rapamycin elutes from the polymeric matrix over time and enters the surrounding tissue. The rapamycin preferably remains on the stent for at least three days up to approximately six months and more preferably between seven and thirty days.

Any number of non-erodible polymers may be utilized in conjunction with rapamycin. In the exemplary embodiment, the polymeric matrix comprises two layers. The base layer comprises a solution of ethylene-co-vinylacetate and polybutylmethacrylate. The rapamycin is incorporated into this layer. The outer layer comprises only polybutylmethacrylate and acts as a diffusion barrier to prevent the rapamycin from eluting too quickly and entering the surrounding tissues. The thickness of the outer layer or top coat determines the rate at

which the rapamycin elutes from the matrix. Essentially, the rapamycin elutes from the matrix by diffusion through the polymer molecules. Polymers tend to move, thereby allowing solids, liquids and gases to escape therefrom. The total thickness of the polymeric matrix is in the range from about 1 micron to about 20 microns or greater.

The ethylene-co-vinylacetate, polybutylmethacrylate and rapamycin solution may be incorporated into or onto the stent in a number of ways. For example, the solution may be sprayed onto the stent or the stent may be dipped into the solution. In a preferred embodiment, the solution is sprayed onto the stent and then allowed to dry. In another exemplary embodiment, the solution may be electrically charged to one polarity and the stent electrically changed to the opposite polarity. In this manner, the solution and stent will be attracted to one another. In using this type of spraying process, waste may be reduced and more control over the thickness of the coat may be achieved.

Since rapamycin acts by entering the surrounding tissue, it is preferably only affixed to the surface of the stent making contact with one tissue. Typically, only the outer surface of the stent makes contact with the tissue. Accordingly, in a preferred embodiment, only the outer surface of the stent is coated with rapamycin. For other drugs, agents or compounds, the entire stent may be coated.

It is important to note that different polymers may be utilized for different stents. For example, in the above-described embodiment, ethylene-co-vinylacetate and polybutylmethacrylate are utilized to form the polymeric matrix. This matrix works well with stainless steel stents. Other polymers may be utilized more effectively with stents formed from other materials, including materials that exhibit superelastic properties such as alloys of nickel and titanium.

In another exemplary embodiment, the rapamycin or other therapeutic agent may be incorporated into a film-forming polyfluoro copolymer comprising

an amount of a first moiety selected from the group consisting of polymerized vinylidenefluoride and polymerized tetrafluoroethylene, and an amount of a second moiety other than the first moiety and which is copolymerized with the first moiety, thereby producing the polyfluoro copolymer, the second moiety being capable of providing toughness or elastomeric properties to the polyfluoro copolymer, wherein the relative amounts of the first moiety and the second moiety are effective to provide the coating and film produced therefrom with properties effective for use in coating implantbale medical devices.

The present invention provides polymeric coatings comprising a polyfluoro copolymer and implantable medical devices, for example, stents coated with a film of the polymeric coating in amounts effective to reduce thrombosis and/or restenosis when such stents are used in, for example, angioplasty procedures. As used herein, polyfluoro copolymers means those copolymers comprising an amount of a first moiety selected from the group consisting of polymerized vinylidenefluoride and polymerized tetrafluoroethylene, and an amount of a second moiety other than the first moiety and which is copolymerized with the first moiety to produce the polyfluoro copolymer, the second moiety being capable of providing toughness or elastomeric properties to the polyfluoro copolymer, wherein the relative amounts of the first moiety and the second moiety are effective to provide coatings and film made from such polyfluoro copolymers with properties effective for use in coating implantable medical devices.

The film-forming biocompatible polymer coatings generally are applied to the stent in order to reduce local turbulence in blood flow through the stent, as well as adverse tissue reactions. The coatings and films formed therefrom also may be used to administer a pharmaceutically active material to the site of the stent placement. Generally, the amount of polymer coating to be applied to the stent will vary, depending on, among other possible parameters, the particular polyfluoro copolymer used to prepare the coating, the stent design and the desired effect of the coating. Generally, the coated stent will comprise from about 0.1 to about fifteen weight percent of the coating, and preferably

from about 0.4 to about ten weight percent. The polyfluoro copolymer coatings may be applied in one or more coating steps, depending on the amount of polyfluoro copolymer to be applied. Different polyfluoro copolymers may be used for different layers in the stent coating. In fact, in certain exemplary embodiments, it is highly advantageous to use a diluted first coating solution comprising a polyfluoro copolymer as a primer to promote adhesion of a subsequent polyfluoro copolymer coating layer that may include pharmaceutically active materials. The individual coatings may be prepared from different polyfluoro copolymers.

Additionally, a top coating may be applied to delay release of the pharmaceutical agent, or they could be used as the matrix for the delivery of a different pharmaceutically active material. Layering of coatings may be used to stage release of the drug or to control release of different agents placed in different layers.

Blends of polyfluoro copolymers may also be used to control the release rate of different agents or to provide a a desirable balance of coating properties, i.e., elasticity, toughness, etc., and drug delivery characteristics, for example, release profile. Polyfluoro copolymers with different solubilities in solvents may be used to build up different polymer layers that may be used to deliver different drugs or to control the release profile of a drug. For example, polyfluoro copolymers comprising 85.5/14.5 (wt/wt) of poly(vinylidinefluoride/HFP) and 60.6/39.4 (wt/wt) of poly(vinylidinefluoride/HFP) are both soluble in DMAc. However, only the 60.6/39.4 poly(vinylidinefloride) polyfluoro copolymer is soluble in methanol. So, a first layer of the 85.5/14.5 poly(vinylidinefluoride) polyfluoro copolymer comprising a drug could be over coated with a topcoat of the 60.6/39.4 poly(vinylidinefluoride) polyfluoro copolymer made with the methanol solvent. The top coating may be used to delay the drug delivery of the drug contained in the first layer. Alternately, the second layer could comprise a different drug to provide for sequential drug delivery. Multiple layers of different drugs could be provided by alternating layers of first one polyfluoro copolymer, then the other.

As will be readily appreciated by those skilled in the art, numerous layering approaches may be used to provide the desired drug delivery.

Coatings may be formulated by mixing one or more therapeutic agents with the coating polyfluoro copolymers in a coating mixture. The therapeutic agent may be present as a liquid, a finely divided solid, or any other appropriate physical form. Optionally, the coating mixture may include one or more additives, for example, nontoxic auxiliary substances such as diluents, carriers, excipients, stabilizers or the like. Other suitable additives may be formulated with the polymer and pharmaceutically active agent or compound. For example, a hydrophilic polymer may be added to a biocompatible hydrophobic coating to modify the release profile, or a hydrophobic polymer may be added to a hydrophilic coating to modify the release profile. One example would be adding a hydrophilic polymer selected from the group consisting of polyethylene oxide, polyvinyl pyrrolidone, polyethylene glycol, carboxylmethyl cellulose, and hydroxymethyl cellulose to a polyfluoro copolymer coating to modify the release profile. Appropriate relative amounts may be determined by monitoring the *in ivtro* and/or *in vivo* release profiles for the therapeutic agents.

The best conditions for the coating application are when the polyfluoro copolymer and pharmaceutic agent have a common solvent. This provides a wet coating that is a true solution. Less desirable, yet still usable, are coatings that contain the pharmaceutical agent as a solid dispersion in a solution of the polymer in solvent. Under the dispersion conditions, care must be taken to ensure that the particle size of the dispersed pharmaceutical powder, both the primary powder size and its aggregates and agglomerates, is small enough not to cause an irregular coating surface or to clog the slots of the stent that need to remain essentially free of coating. In cases where a dispersion is applied to the stent and the smoothness of the coating film surface requires improvement, or to be ensured that all particles of the drug are fully encapsulated in the polymer, or in cases where the release rate of the drug is to be slowed, a clear (polyfluoro copolymer only) topcoat of the same polyfluoro copolymer used to

provide sustained release of the drug or another polyfluoro copolymer that further restricts the diffusion to the drug out of the coating may be applied. The topcoat may be applied by dip, coating with mandrel to clear the slots. This method is disclosed in U.S. Patent No. 6,153,252. Other methods for applying the topcoat include spin coating and spray coating. Dip coating of the topcoat can be problematic if the drug is very soluble in the coating solvent, which swells the polyfluoro copolymer, and the clear coating solution acts as a zero concentration sink and redissolves previously deposited drug. The time spent in the dip bath may need to be limited so that the drug is not extracted out into the drug free bath. Drying should be rapid so that the previously deposited drug does not completely diffuse into the topcoat.

The amount of therapeutic agent will be dependent upon the particular drug employed and medical condition being treated. Typically, the amount of drug represents about 0.001 percent to about seventy percent of the total coating weight, and more typically about 0.001 percent to about sixty percent of the total coating weight. It is possible that the drug may represent as little as 0.001 percent to the total coating weight.

The quantity and type of polyfluoro copolymers employed in the coating film comprising the pharmaceutic agent will vary depending on the release profile desired and the amount of drug employed. The product may contain blends of the same or different polyfluoro copolymers having different molecular weights to provide the desired release profile or consistency to a given formulation.

Polyfluoro copolymers may release dispersed drug by diffusion. This can result in prolonged delivery (over, say approximately one to two-thousand hours, preferably two to eight-hundred hours) of effective amounts (0.001 $\mu g/cm^2$-min to 100 $\mu g/cm^2$-min) of the drug. The dosage may be tailored to the subject being treated, the severity of the affliction, the judgment of the prescribing physician, and the like.

Drug eluting stents, as described above, have demonstrated an ability to dramatically reduce late lumen loss and restenosis rates in patients with coronary artery disease based on data from randomized clinical trials. However, the ability of this technology to substantially eliminate the problem of restenosis has only recently been investigated in very large patient cohorts that examine longer and more complex lesions, including Type C lesions. Lesions may be classified as Type A, B or C, which is the American College of Cardiology/American Heart Association classification system. A Type A lesion is minimally complex, discrete (length <10 mm), concentric, readily accessible, non-angulated segment (<45°), smoother contour, little or no calcification, less than totally occlusive, not ostial in location, no major side branch involvement, and an absence of thrombus. A Type B lesion is moderately complex, tubular (length 10 mm to 20 mm), eccentric, moderate tortuosity of proximal segment, moderately angulated segment (>45°, <90°), irregular contour, moderate or heavy calcification, total occlusions <3 months old, ostial in location, bifurcation lesions requiring double guidewires, and some thrombus is present. A Type C lesion is severely complex, diffuse (length >2cm), excessive tortuosity of proximal segment, extremely angulated segments (>90°), total occlusions >3 months old and/or bridging collaterals, inability to protect major side branches, and degenerated vein grafts with friable lesions.

Initial quantitative results obtained with rapamycin eluting stents in the first large (one thousand one hundred patient) randomized multicenter trial representative of real world stenting conditions, i.e.,Type A, B, C lesions, reveal a phenomenon that suggests the depth and direction of drug penetration from the stent struts into the vessel wall may play an important role in eliminating lumen loss within the treated segment, which incorporates the in-stent region and the in-lesion region, which as explained above includes a length of vessel extending five mm past the ends of the stent. More importantly, the results indicate that drug penetration into the proximal and distal portions of the vessel beyond the stent edges, i.e., the five mm boarder region may be required to substantially eliminate restenosis caused by aggressive remodeling and neointimal hyperplasia. Essentially, it is preferable

that the drug coated stent of the present invention be used for the prevention of target lesion restenosis, wherein target lesion includes the stented region and areas extending past the stented region.

Angiographic results from the first four hundred patients followed up at eight months in the above-referenced large randomized multicenter trial demonstrate that in-stent late lumen loss is dramatically reduced (0.92 +/- 0.69 mm versus 0.14+/- 0.44 mm; bare stent versus rapamycin coated stent, $p<0.0001$) as is distal edge lumen loss (0.19+/- 0.61 mm versus 0.04 +/- 0.42 mm; bare stent versus rapamycin coated stent, $p<0.05$). In contrast, the proximal edge lumen loss (0.26+/- 0.55 mm versus 0.16 +/- 0.16 mm; bare stent versus rapamycin coated stent, $p=0.22$, ns) suggests that there is a somewhat diminished effect. This unexpected result suggests a need for an improved design of drug eluting stents to minimize edge lumen loss, particularly proximal to the stent, in addition to minimizing target lesion restenosis.

It is important to note that the above-described trials utilized the EVA/BMA coating described above.

One possible explanation for these results is the direction of blood flow relative to the stent. It may be possible for the blood to be carrying away a portion of the rapamycin as it elutes from the stent, thereby effectively reducing the concentration available for absorption into the tissue proximal to the stent.

Accordingly, in a preferred exemplary embodiment, a drug eluting stent should incorporate an improved drug release profile from the edges of the stent, particularly the proximal edge, to prevent or substantially reduce edge restenosis. Improvement in drug release should preferably lead to improved axial and radial drug distribution from the stent struts into the vessel segments outside the stented region or zone. These improvements may take any number of forms.

In one exemplary embodiment, the polymer/drug combination coating may be applied to the stent such that there is a higher concentration of the drug proximate to the edges of the stent, particularly the proximal two to three mm thereof. In other words, it is preferable that there be more drug on the ends of the stent, for example, from the ends of the stent extending up to three mm or more. This tailored or profiled coating technique may be achieved by increasing the mass of the coating on the edges by a predetermined percentage of, for example, at least ten percent to about three-hundred percent, or by increasing the concentration of the drug in the polymer, for example, from about thirty-three percent to about eighty percent. The increase in drug concentration depends on the drug and the particular coating selected. In another alternate exemplary embodiment where a topcoat is utilized as a diffusion barrier, the thickness of the topcoat in the regions proximate the edges of the stent may be reduced thereby increasing the rate of drug elution from the edges of the stent.

In yet another alternate exemplary embodiment, another drug, agent and/or compound with improved solubility may be used in combination with the stent. For example, a rapamycin analog having improved solubility and thus potentially greater tissue penetration may be utilized. A rapamycin analog may include any structural modification that altered physical and chemical properties but did not alter the fundamental mechanism of the drug; i.e. the inhibition of mTOR. It may also be possible to use a combination of drugs. For example, rapamycin may be utilized on a major portion of the stent and an analog as just described may be utilized in the remaining end portions.

In yet another alternate exemplary embodiment, another drug, agent and/or compound may be utilized in combination with rapamycin. This other drug, agent and/or compound may be utilized to improve drug permeability or enhance uptake of rapamycin into the vessel wall. The additional drug, agent and/or compound may simply provide this effect or augment the effect of rapamycin.

Although shown and described is what is believed to be the most pratical and preferred embodiments, it is apparent that departures from specific designs and methods described and shown will suggest themselves to those skilled in the art and may be used without departing from the spirit and scope of the invention. The present invention is not restricted to the particular constructions described and illustrated, but should be constructed to cohere with all modifications that may fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A method for the prevention of target lesion restenosis comprising the controlled delivery, by a profiled release from an intraluminal medical device, of one or more compounds in therapeutic dosage amounts.

2. The method for the prevention of target lesion restenosis according to Claim 1, wherein the profiled release from an intraluminal medical device of one or more compounds comprises:

coating a first portion of the stent with a first concentration of the one or more compounds in therapeutic dosage amounts; and

coating a second portion of the stent with a second concentration of the one or more compounds in therapeutic dosage amounts, wherein the second concentration is greater than the first concentration.

3. The method for the prevention of target lesion restenosis according to Claim 2, wherein the one or more compounds comprises rapamycin.

4. The method for the prevention of target lesion restenosis according to Claim 1, wherein the one or more compounds comprises rapamycin.

5. The method for the prevention of target lesion restenosis according to Claim 1, wherein the one or more compounds comprises analogs, derivatives and congeners that bind a high-affinity cytosolic protein, FKBP12, and possesses the same pharmacologic properties as rapamycin.

6. The method for the prevention of target lesion restenosis according to Claim 1, wherein the profiled release from an intraluminal medical device of one or more compounds comprises:

coating a first portion of the stent with a first concentration of the one or more compounds in therapeutic dosage amounts; and

coating a second portion of the stent with a second concentration of another of the one or more compounds in therapeutic dosage amounts.

7. The method for the prevention of target lesion restenosis according to Claim 6, wherein the one or more compounds comprises rapamycin.

8. The method for the prevention of target lesion restenosis according to Claim 7, wherein the another of the one or more compounds comprises a high solubility inhibitor of the mammalin Target of Rapamycin.

9. The method for the prevention of target lesion restenosis according to Claim 1, further comprising adding an agent to enhance tissue penetration of the one or more compounds.

10. The method for the prevention of target lesion restenosis according to Claim 1, wherein the profiled release from an intraluminal medical device of one or more compounds comprises:
coating a first portion of the stent with a first mass of the one or more compounds in therapeutic dosage amounts in combination with a polymer; and

coating a second portion of the stent with a second mass of the one or more compounds in therapeutic dosage amounts in combination with a polymer, wherein the second mass is greater than the first mass.

11. A drug delivery device comprising:
an intraluminal medical device; and

a therapeutic dosage of one or more compounds releasably affixed, in a predetermined profile, to the intraluminal medical device for the treatment of target lesion restenosis.

12. Drug delivery device according to Claim 11, wherein the intraluminal medical device comprises a stent.

13. The drug delivery device according to Claim 11, wherein the one or more compounds comprises rapamycin.

14. The drug delivery device according to Claim 11, wherein the one or more compounds comprises analogs, derivatives and congeners that bind a high-affinity cytosolic protein, FKBP12, and possesses the same pharmacologic properties as rapamycin.

15. The drug delivery device according to Claim 11, wherein the therapeutic dosage of one or more compounds releasably affixed, in a predetermined profile, to the intraluminal medical device comprises:

a first concentration of the one or more compounds affixed to a first portion of the intraluminal medical device; and

a second concentration of the one or more compounds affixed to a second portion of the intraluminal medical device, wherein the second concentration is greater than the first concentration.

16. The drug delivery device according to Claim 15, wherein the one or more compounds comprises rapamycin.

17. The drug delivery device according to Claim 11, wherein the therapeutic dosage of one or more compounds releasably affixed, in a predetermined profile, to the intraluminal medical device comprises:

a first concentration of the one or more compounds affixed to a first portion of the intraluminal medical device; and

a second concentration of another of one or more compounds affixed to a second portion of the intraluminal medical device.

18. The drug delivery device according to Claim 17, wherein the one or more compounds comprises rapamycin.

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19. The drug delivery device according to Claim 17, wherein the another of the one or more compounds comprises a high solubility inhibitor of the mammalian Target of Rapamycin.

20. The drug delivery device according to Claim 11, further comprising an agent for enhancing tissue penetration of the one or more compounds incorporated into the therapeutic dosage of one or more compounds releasably affixed in a predetermined profile to the intraluminal medical device.

21. The drug delivery device according to Claim 11, wherein the therapeutic dosage of one or more compounds releasably affixed, in a predetermined profile, to the intraluminal medical device comprises:

a first mass of the one or more compounds in combination with a polymer affixed to a first portion of the intraluminal medical device; and

a second mass of the one or more compounds in combination with a polymer affixed to a second portion of the intraluminal medical device, the second mass is greater than the first mass.

FIG. 1

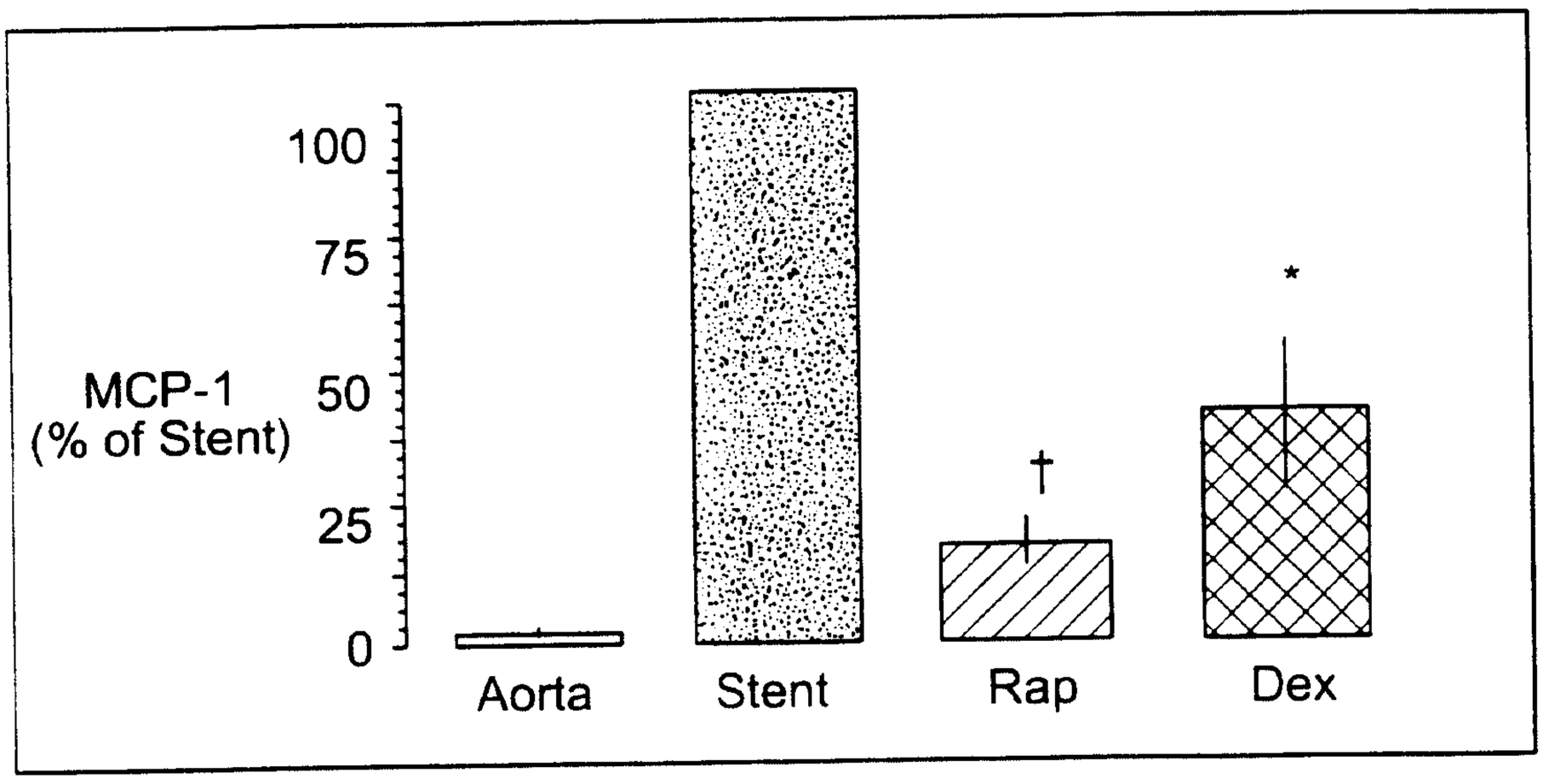

FIG. 2

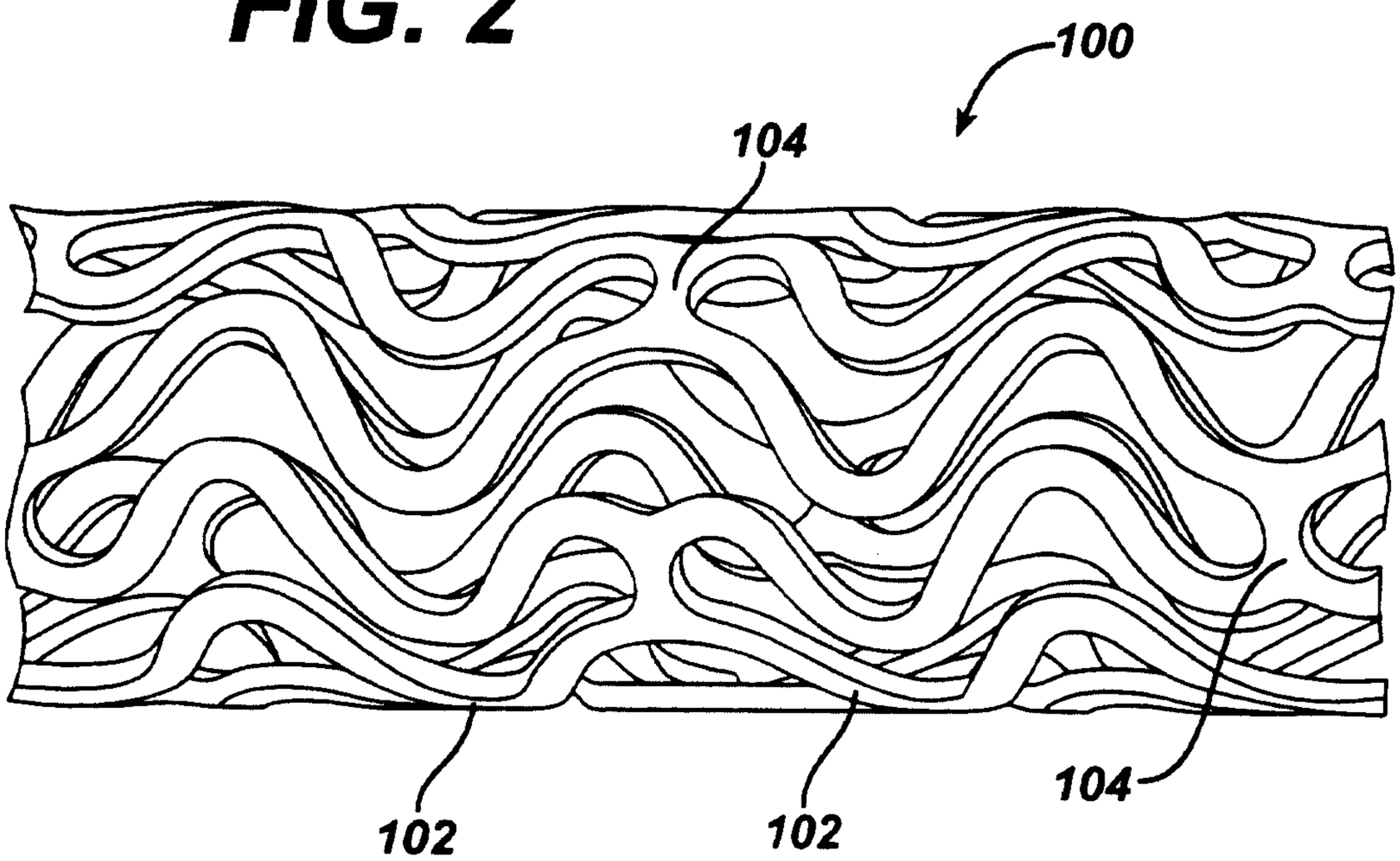
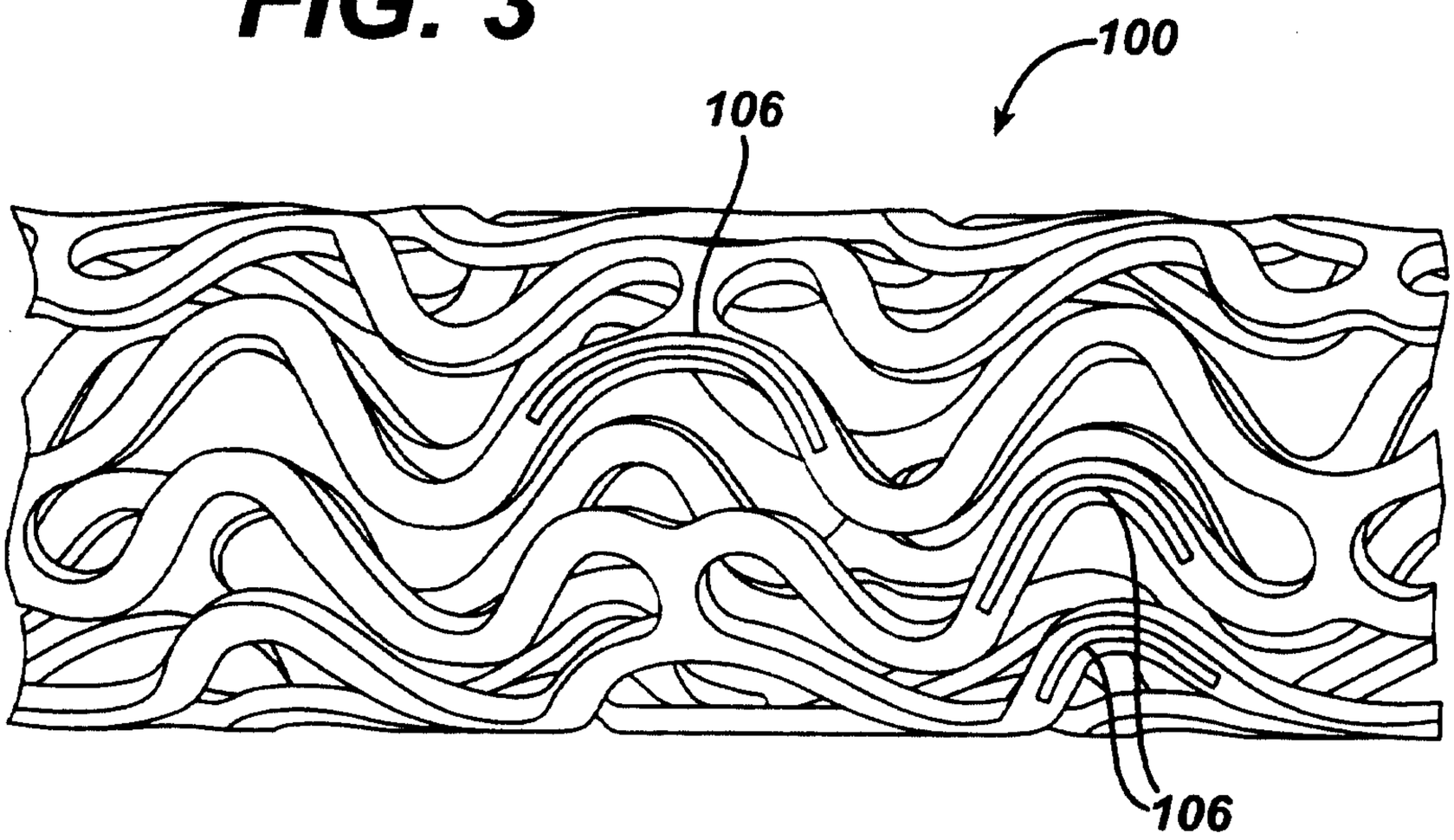
FIG. 3