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(71) Applicant *(for all designated States except US)*: **INNOVATIONAL HOLDINGS LLC** [US/US]; One Johnson & Johnson Plaza, New Brunswick, NJ 08933 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DANG, Diane, Mai Huong** [US/US]; 3907 Nelson Drive, Palo Alto, CA 94306 (US). **LITVACK, Frank** [US/US]; 3550 Wilshire Boulevard, #840, Los Angeles, CA 90010 (US). **LUK, Andrew, Sheung-king** [US/US]; 6512 Crestwood Drive, Castro Valley, CA 94552 (US). **SHANLEY, John, F.** [US/US]; 217 Yarborough Lane, Redwood City, CA 94061 (US). **PARKER, Theodore, L.** [US/US]; 634 Dunhill Drive, Danville, CA 94506 (US).

(74) Agent: **LYNCH, Cindy, A.**; Conor Medsystems Llc, Senior Patent Counsel, 1003 Hamilton Court, Menlo Park, CA 94025 (US).

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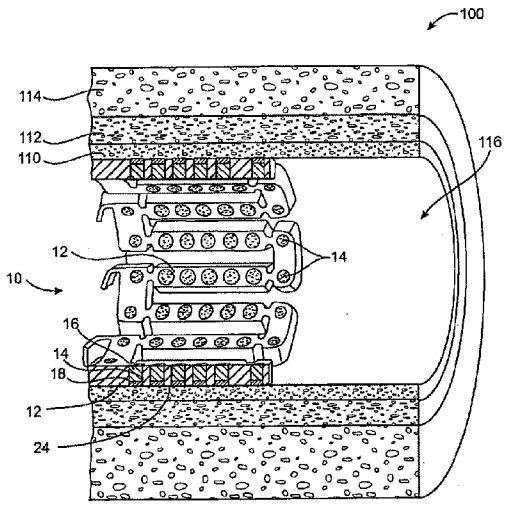
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(54) **Title:** METHOD AND APPARATUS FOR REDUCING INJURY FROM ACUTE MYOCARDIAL INFARCTION



(57) **Abstract:** A method and apparatus for the local delivery of therapeutic agents reduces myocardial tissue damage due to ischemia. A local delivery device is used for delivery of the therapeutic agents into a coronary artery which feeds the ischemic reperfused myocardial tissue. According to one example, an implantable medical device for delivering adenosine, agonists thereof, a PDE inhibitor, or combinations thereof locally to myocardial tissue includes a therapeutic dosage of adenosine, agonists thereof, a PDE inhibitor, or combinations thereof in a biocompatible polymer affixed to a stent. The therapeutic dosage of adenosine, agonists thereof, a PDE inhibitor, or combinations thereof is released from the stent at a therapeutic dosage and over an administration period effective to reduce ischemic and reperfusion injury of the myocardial tissue.

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METHOD AND APPARATUS FOR REDUCING INJURY FROM ACUTE MYOCARDIAL INFARCTION

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to methods and apparatus useful in the treatment of a patient who has suffered an acute myocardial infarction and other related events. Specifically the methods and apparatus described herein are useful in reducing infarct size, mitigating reperfusion injury, and mitigating long-term ischemia caused by acute myocardial infarction.

Brief Description of the Related Art

The reduction or cessation of blood flow to a vascular bed accounts for a variety of clinical events that require immediate intervention and restitution of adequate perfusion to the jeopardized organ or tissue. Different tissues can withstand differing degrees of ischemic injury. However, tissues may progress to irreversible injury and cellular necrosis if not reperfused.

Impaired perfusion of cardiac tissue (ischemia) results in a loss of the heart's ability to function properly as the tissue becomes oxygen- and energy-deprived. Permanent injury is directly related to the duration of oxygen deficiency which the myocardium experiences. Ischemia occurs when blood flow to an area of cells is insufficient to support normal metabolic activity. Surgical and percutaneous revascularization techniques following acute myocardial infarction (MI) are highly effective at treating ischemic myocardial tissue. In the case of an acute MI, the main blood flow is stopped by the blockage of a coronary artery and the tissue is perfused only through collateral arteries. If the ischemic condition persists for an extended period, the damage to cells within the ischemic zone progresses to irreversible injury and cellular necrosis. Reperfusion is the term used to describe the act of reestablishing blood flow and oxygen supply to ischemic tissue. Reperfusion is essential to the future survival of cells within an ischemic area. Reperfusion may be achieved by a blood flow recanalization therapy, generally including one of coronary angioplasty, administration of a

thrombolytic drug, coronary artery bypass surgery, or the like.

Timely reperfusion of ischemic myocardium limits infarct size and early reperfusion with angioplasty or thrombolytic therapy provides benefits of reduced myocardial damage, improved ventricular function, and reduced mortality in patients with acute MI. Myocardial salvage can, however, be compromised by such complications as coronary reocclusion and severe residual coronary stenosis.

Reperfusion of the ischemic myocardium does not alone return full functioning of the myocardium. In fact, it is well known that reperfusion itself can cause damage to many cells that survived the ischemic event. Studies have shown that reperfusion may accelerate death of irreversibly injured myocardium, and may also compromise survival of jeopardized, but still viable myocytes salvaged by reperfusion. These so-called reperfusion injuries may represent more than 50% of ultimate infarct size. A number of cellular mechanisms are believed to be responsible for ischemia-induced reperfusion injury. Development of adjuvant treatments to protect the post-ischemic myocardium and maximize benefits of coronary reperfusion has thus become a major target of modern cardiovascular research.

Compounds capable of minimizing and containing ischemic or reperfusion damage represent important therapeutic agents. In the past years, it has been demonstrated that the mortality rates following myocardial infarction and reperfusion can be further improved by delivery of drugs which optimize energy transfer in the post-ischemic heart tissue. For example, an arterial infusion of a combination of glucose, insulin, and potassium (GIK) after an acute myocardial infarction and reperfusion has been shown to provide an impact on the injured but viable myocardium tissue and reduced mortality.

The cardioprotective effect of adenosine and its analogs, derivatives, and adenosine receptor agonists has also been a subject of interest in recent years. Adenosine, an endogenous purine nucleoside, antagonizes many of the biochemical and physiological mechanisms implicated in ischemia-reperfusion injury and has been shown to reduce post-ischemic ventricular dysfunction and myocyte necrosis and apoptosis. The exact mechanism of the cardioprotective effect of adenosine is not fully understood, although inhibition of neutrophil activation and prevention of endothelial damage seem to play a major role.

Adenosine and its clinical effects have been examined in the AMISTAD phase I and phase II clinical trials (see Mahaffey *et al., J. Am. Coll. Cardio.* (1999) 34:1711, and Ross *et al., J. Am. Coll. Cardio.* (2002) 39:5). In these trials, adenosine was administered systemically via a 3 hour infusion, and achieved as much as a 67% relative reduction in infarct size as compared to a placebo group. When adeosine is delivered systemically by arterial infusion, however, the serum half life is less than 10 seconds due to cellular uptake. It is believed that less than 1% of the drug is bioavailable after 1 minute in circulation, resulting in the failure of a significant amount of infused drug to reach the target site.

In general, the compounds which have been used for reducing tissue damage after acute myocardial infarction have been delivered systemically, such as by arterial infusion. Systemic delivery of these compounds have significant drawbacks including the requirement for additional administration of protective agents to prevent damage to non-target tissues caused by the systemic delivery, or the failure of sufficient drug to reach the target site. Other drawbacks include the requirement for continuous administration and supervision, patient discomfort, high dosages required for systemic delivery, and side effects of the systemic delivery and high dosages.

SUMMARY OF THE INVENTION

The present invention relates to the local delivery of therapeutic agents which reduce myocardial tissue damage due to ischemia. The therapeutic agents are delivered locally to the myocardial tissue and over an administration period sufficient to achieve reduction in ischemic injury of the myocardial tissue.

In accordance with one aspect of the invention, a method for reducing tissue damage following ischemic injury includes identifying an implantation site within a blood vessel; delivering an expandable medical device containing a drug which preserves myocardial cell viability into the blood vessel to the selected implantation site; implanting the medical device at the implantation site; and locally delivering a therapeutic agent from the expandable medical device to tissue at the implantation site and to the blood vessels downstream of the implantation site over an administration period sufficient to reduce ischemic injury of the surrounding myocardial cells.

In accordance with another aspect of the invention, a method of delivering adenosine, a derivative thereof, a phosphodiesterase ("PDE") inhibitor, and combinations thereof locally to myocardial tissue to reduce tissue damage following myocardial infarction and reperfusion includes identifying an occlusion site within a blood vessel; treating the occlusion site to achieve reperfusion; and locally delivering adenosine, a derivative thereof, a PDE inhibitor, and combinations thereof to the tissue at or near the treated occlusion site and downstream of the occlusion site to reduce ischemic injury.

In accordance with an additional aspect of the invention, an implantable medical device for delivering adenosine, a derivative thereof, a PDE inhibitor, and combinations thereof locally to myocardial tissue includes an implantable medical device configured to be implanted within a coronary artery and a therapeutic dosage of adenosine, a derivative thereof, a PDE inhibitor, and combinations thereof in a biocompatible polymer affixed to the implantable medical device, wherein the therapeutic dosage of adenosine, a derivative thereof, a PDE inhibitor, and combinations thereof is released to the myocardial tissue at a dosage and over an administration period therapeutically effective to reduce ischemic injury of the myocardial tissue.

In accordance with a further aspect of the invention, an implantable medical device for delivering a therapeutic agent locally to myocardial tissue includes an implantable medical device configured to be implanted within a coronary artery, and a therapeutic dosage of a therapeutic agent for treatment of ischemic injury following acute myocardial infarction. The therapeutic agent is affixed to the implantable medical device in a manner such that the therapeutic agent is released to the myocardial tissue at a dosage and over an administration period therapeutically effective to reduce ischemic injury of the myocardial tissue.

In accordance with another aspect of the invention, a stent for delivering an adenosine, a receptor agonist locally to myocardial tissue includes a substantially cylindrical expandable device body configured to be implanted within a blood vessel, and a therapeutic dosage of adenosine receptor agonist in a biocompatible polymer affixed to the implantable medical device body.

Still other aspects, features, and attendant advantages of the present invention will become apparent to those skilled in the art from a reading of the following detailed

description of embodiments constructed in accordance therewith, taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention of the present application will now be described in more detail with reference to exemplary embodiments of the apparatus and method, given only by way of example, and with reference to the accompanying drawings, in which:

Fig. 1 illustrates a cross-sectional perspective view of a portion of an expandable medical device implanted in the lumen of an artery with a therapeutic agent arranged for delivery to the lumen of the artery;

FIG. 2 illustrates a perspective view of an expandable medical device showing a plurality of openings;

FIG. 3 illustrates an expanded side view of a portion of the expandable medical device of FIG. 2;

FIG. 4 illustrates an enlarged cross-section of an opening illustrating a therapeutic agent for directional delivery to a lumen of a blood vessel;

FIG. 5 illustrates an enlarged cross-section of an opening illustrating a first therapeutic agent provided for delivery to a lumen of the blood vessel and a second therapeutic agent provided for delivery to a wall of the blood vessel; and

FIG. 6 illustrates an enlarged cross-section of an opening illustrating first and second therapeutic agents for delivery to a lumen of the blood vessel.

FIG. 7 illustrates a graph of data of the total percentage of agent released versus time, for three examples of devices in accordance with the present invention.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

Referring to the drawing figures, like reference numerals designate identical or corresponding elements throughout the several figures.

Principles of the present invention relate to method and apparatus for treatment of acute ischemic syndromes including acute myocardial infarction. Methods and devices embodying some of these principles provide for delivery of therapeutic agents locally to the

myocardial tissue to limit the necrotic zone in ischemic injury and to reduce reperfusion injury after acute myocardial infarction. The local delivery of the therapeutic agents avoid the need for systemic delivery and associated need to administer additional protective agents to prevent damage to non-target tissues, and the need to deliver large amounts of the drug to achieve sufficient amounts of the drug at the target site and the concomitant side effects.

First, the following terms, as used herein, shall have the following meanings:

The terms "drug" and "therapeutic agent" are used interchangeably to refer to any therapeutically active substance that is delivered to a bodily conduit of a living being to produce a desired, usually beneficial, effect.

The term "matrix" or "biocompatible matrix" are used interchangeably to refer to a medium or material that, upon implantation in a subject, does not elicit a detrimental response sufficient to result in the rejection of the matrix. The matrix typically does not provide any therapeutic responses itself, though the matrix may contain or surround a therapeutic agent, and/or modulate the release of the therapeutic agent into the body. A matrix is also a medium that may simply provide support, structural integrity, or structural barriers. The matrix may be polymeric, non-polymeric, hydrophobic, hydrophilic, lipophilic, amphiphilic, and the like. The matrix may be bioresorbable or non-bioresorbable.

The term "bioresorbable" refers to a matrix, as defined herein, that can be broken down by either chemical or physical process, upon interaction with a physiological environment. The matrix can erode or dissolve. A bioresorbable matrix serves a temporary function in the body, such as drug delivery, and is then degraded or broken into components that are metabolizable or excretable, over a period of time from minutes to years, preferably less than one year, while maintaining any requisite structural integrity in that same time period.

The term “ischemia” refers to local hypoxia resulting from obstructed blood flow to an affected tissue.

The term “ischemic injury” as used herein refers to both injury due to obstructed blood flow and reperfusion injury caused by removal of the obstruction.

The term “openings” includes both through openings and recesses.

The term “pharmaceutically acceptable” refers to the characteristic of being non-toxic

to a host or patient and suitable for maintaining the stability of a beneficial agent and allowing the delivery of the beneficial agent to target cells or tissue.

The term "polymer" refers to molecules formed from the chemical union of two or more repeating units, called monomers. Accordingly, included within the term "polymer" may be, for example, dimers, trimers, and oligomers. The polymer may be synthetic, naturally-occurring or semisynthetic. In preferred form, the term "polymer" refers to molecules which typically have a molecular weight (M_W) greater than about 3000, and preferably greater than about 10,000, and a M_W that is less than about 10 million, preferably less than about a million, and more preferably less than about 200,000. Examples of polymers include, but are not limited to, poly-α-hydroxy acid esters such as, polylactic acid (PLLA or DLPLA), polyglycolic acid, polylactic-co-glycolic acid (PLGA), polylactic acid-co-caprolactone; poly (block-ethylene oxide-block-lactide-co-glycolide) polymers (PEO-block-PLGA and PEO-block-PLGA-block-PEO); polyethylene glycol and polyethylene oxide, poly (block-ethylene oxide-block-propylene oxide-block-ethylene oxide); polyvinyl pyrrolidone; polyorthoesters; polysaccharides and polysaccharide derivatives such as polyhyaluronic acid, poly (glucose), polyalginic acid, chitin, chitosan, chitosan derivatives, cellulose, methyl cellulose, hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, cyclodextrins and substituted cyclodextrins, such as beta-cyclo dextrin sulfo butyl ethers; polypeptides, and proteins such as polylysine, polyglutamic acid, albumin; polyanhydrides; polyhydroxy alkonoates such as polyhydroxy valerate, polyhydroxy butyrate, and the like.

The term "primarily" with respect to directional delivery, refers to an amount greater than 50% of the total amount of beneficial agent provided to a blood vessel.

The term "restenosis" refers to the renarrowing of an artery following an angioplasty procedure which may include stenosis following stent implantation.

Methods for Locally Delivering Drugs to Preserve Myocardial Cell Viability

Implantable medical devices in the form of stents, when implanted directly at or near a site of a previously occluded blood vessel, can be used to deliver therapeutic agents to the myocardial tissue at and downstream of the implantation site. The delivery of the agent

locally at the ischemic injury site improves the viability of the cells by reducing ischemic injury to the myocardial cells including reperfusion injury which may occur upon return of blood flow to the ischemic tissue. In cases where reperfusion therapy is performed by angioplasty, a stent is often delivered to the reopened occlusion site. A drug delivery stent for delivery of a therapeutic agent for treatment of ischemic injury can be implanted at the implantation site in the traditional manner after angioplasty. The drug delivery stent for delivery of the therapeutic agent implanted at or near the occlusion site following reperfusion therapy provides the advantage of reduction of ischemic injury including reduction of reperfusion injury without the difficulties associated with systemic delivery of the therapeutic agent.

The metabolic mechanisms of reperfusion injury are not completely clear. Lack of oxygen and accumulation of metabolic products change the energy transfer in the tissue. After reperfusion, the oxidation of glucose remains depressed, as does contractile function, and the generation of reactive oxygen species (ROS) can result. In addition, reperfusion damage occurs due to the inflammatory response. Reperfused ischemic tissue attracts leukocytes which release proteolytic enzymes and oxidants that in turn promote further inflammation followed by eventual healing and scarring. Therefore, anti-inflammatory drugs that dampen the inflammatory response can reduce reperfusion injury. Protease inhibitors, antioxidants, vasodilators, and other cardio-protective agents can also improve tissue function following reperfusion. Vasodilators, when delivered downstream of an occlusion, either acute or nonacute, can expand vessel dimensions and thus increase blood flow to an ischemic area.

The drugs which are particularly well suited for the reduction of ischemic injury following acute myocardial infarction or other ischemic injuries include, but are not limited to, vasodilators, such as adenosine and its analogs, derivatives, and adenosine receptor agonists, and dipyridamole; nitric oxide donors; phosphodiesterase inhibitors, including PDE-III active compounds and PDE-IV compounds; prostaglandins and their derivatives; antioxidants; membrane stabilizing agents; anti-TNF compounds; anti-inflamatories including dexamethasone, aspirin, pirfenidone, meclofenamic acid, and tranilast; hypertension drugs including Beta blockers, ACE inhibitors, and calcium channel blockers;

anti-metabolites, such as 2-CdA; vasoactive substances including vasoactive intestinal polypeptides (VIP); insulin; cell sensitizers to insulin including glitazides, glitazones and glitazars, P PAR agonists, and metformin; protein kinases; antisense oligonucleotides including resten-NG; immuno-suppressants including sirolimus, everolimus, tacrolimus, etoposide, and mitoxantrone; antithrombins; antiplatelet agents including tirofiban, eptifibatide, and abciximab; cardio protectants including, VIP, pituitary adenylate cyclase-activating peptide (PACAP), apoA-I milano, amlodipine, nicorandil, cilostaxone, dioxycycline, minocycline, imatinib, and thienopyridine; anti-leukocytes; cyclooxygenase inhibitors including COX-1 and COX-2 inhibitors; petidose inhibitors which increase glycolitic metabolism including omnipatrilat; and matrix metalloproteinase inhibitors, such as bastimastat and ilomastat.

Agents for the treatment of ischemic injury may also be delivered using a gene therapy-based approach in combination with an expandable medical device. Gene therapy refers to the delivery of exogenous genes to a cell or tissue, thereby causing target cells to express the exogenous gene product. Genes are typically delivered by either mechanical or vector-mediated methods. Mechanical methods include, but are not limited to, direct DNA microinjection, ballistic DNA-particle delivery, liposome-mediated transfection, and receptor-mediated gene transfer. Vector-mediated delivery typically involves recombinant virus genomes, including but not limited to retroviruses, adenoviruses, adeno-associated viruses, herpesviruses, vaccinia viruses, picornaviruses, alphaviruses, and papovaviruses.

According to one aspect of the invention, a stent or other local delivery device is used for local delivery of adenosine following acute MI and reperfusion. Adeosine is a purine nucleoside which is a catabolite of the body's energy-storing molecule ATP. Adenosine, known as a potent vasodialator, endogenously is known to inhibit enzyme release, and the generation of toxic oxygen species by activated neutrophils, inhibit neutrophil aggregation, as well as neutrophil adherence to, and injury of, endothelial cells, reduce ATP depletion during ischemia and improve repletion of ATP on reperfusion, stimulate myocardial glycolysis, normalize the oxygen supply/demand ratio through its vasodilatory and antiadrenergic properties, and inhibit platelet aggregation. Thus, the administration of exogenous adenosine can have protective effects during an ischemia-reperfusion event. Specifically, adenosine

administered during reperfusion can attenuate reperfusion injury and therefore, limits tissue injury as assessed by myocardial infarct size.

The adenosine for use in the present invention may be the molecule having the chemical structure 6-amino-9-beta-D-ribofuranosyl-9-H-purine ($C_{10}H_{13}N_5O_4$). Derivatives or analogs of adenosine may also be used, and include, but are not limited to, adenosine receptor agonists, or selective or non-selective adenosine receptor agonists. The adenosine or derivatives thereof may be administered singly or in any combination. The dosage of adenosine or derivatives delivered from a stent can range from 5μg to 2500μg, preferably 10μg to 1500μg, and most preferably 400-1000μg. The dosage may be a constant for all stent sizes. Alternatively, the dosage can vary for different size stents, with the preferred 400-1000μg dosage corresponding to a 3.0mm x 17mm expanded stent size. The dosage of adenosine or derivatives delivered locally by a coronary infusion catheter can range from 0.1 mg to 100 mg, preferably 0.5 mg to 20 mg, and can be delivered in a saline solution.

Adenosine exerts its physiological effects through activation of 4 types of purine receptors, designated A_1, A_{2A}, A_{2B}, and A_3. Adenosine A_{2A} receptors are located on blood vessels where they mediate vasodilation (Ueeda, M., et al., J. Med. Chem. 34:1334-1339 (1991); Ueeda, M., et al., J. Med. Chem. 34:1340-1344 (1991); Niiya, K., et al., J. Med. Chem. 35:4557-4561 (1992), Niiya, K., et al., J. Med. Chem. 35:4562-4566 (1992); and Glover, D. K., et al., Circulation 94:1726-1732 (1996)), on platelets where they mediate an inhibition of aggregation (Cristalli, G., et al., Arch. Pharmacol. 349:644-650 (1994); and Varani, K., et al., Biochem. Pharmacol. 48:1658-1661 (1994)) and on neutrophils where they mediate inhibition of adherence to endothelial cells and release of toxic oxygen products (Cronstein, B. N., et al., J. Clin. Invest. 85:1150-1157(1990), Cronstein, B. N., et al., J. Immunol. 148:2201-2206 (1992); and Sullivan, G. W., et al., Int. J. Immunopharmac. 17:793-803 (1995)). A compound that selectively activates only the A_{2A} adenosine receptors is expected to have anti-inflammatory actions in ischemic tissue by virtue of these properties. Activation of A_1 receptors on neutrophils promotes chemotaxis and thereby increases migration of neutrophils to the site of injury. In addition, activation of A_1 receptors increases adherence of neutrophils to the endothelium. Adenosine's actions at the A_1 receptor are therefore pro-inflammatory (Cronstein, B. N., et al., J. Clin. Invest. 85:1150-1157 (1990), and

Cronstein, B. N., et al., J. Immunol. 148:2201-2206 (1992)).

In vitro studies using human neutrophils have shown that A_{2A} selective agonists inhibit the release of oxygen free radicals and proteolytic enzymes from activated neutrophils and inhibit adherence of activated neutrophils to the endothelium (Cronstein, B. N., et al., J. Immunol. 148:2201-2206 (1992), Cronstein, B. N., et al., J. Clin. Invest. 85:1150-1157 (1990); and Sullivan, G. W., et al., Int. J. Immunopharmac. 17:793-803 (1995)). An A_{2A} selective agonist has also been shown to inhibit both the adhesion of activated canine neutrophils to canine cardiac myocytes and to reduce oxidative injury (Bullough, D. A., et al., J. Immunol. 155:2579-2586 (1995)). Studies in pigs have shown that there is an increase in platelet deposition and neutrophil adhesion at the site of arterial injury produced by balloon inflation during angioplasty (Merhi, Y., et al., Circulation 90:997-1002 (1994); and Provost, P. and Merhi, Y., J. Pharmacol. Exp. Ther. 277:17-21 (1996)).

The term "selective adenosine A_{2A} receptor agonist" refers to agonists that stimulate preferentially the adenosine A_{2A} receptor and do not substantially stimulate the adenosine A_1 receptor. Compounds may be chosen as selective A_{2A} agonists by testing for cardiovascular activity as described in Niiya, K., et al., *J. Med. Chem.* 35:4557-4561 (1992) and demonstrating an A_1/A_2 selectivity ratio, therein defined, as greater than approximately 100. Other assays can also be employed to screen for adenosine A_{2A} receptor agonism.

Examples of selective adenosine A_{2A} receptor agonists include: 2-(substituted amino)adenosine 5'-carboxamides, described in U.S. Pat. No. 4,968,697; 2-(substituted amino)adenosines, described in U.S. Pat. No. 5,034,381; imidazo-[4,5-b]-pyridine derivatives, described in U.S. Pat. No. 4,977,144; and 2-(substituted alkynyl)adenosines, described in U.S. Pat. No. 5,189,027. Additional examples of selective A_{2A} receptor agonists include 2-hydrazoadenosines, described in U.S. Pat. No. 5,278,150 and 2-aralkoxy and 2-alkoxy adenosines, described in U.S. Pat. No. 5,140,015.

Examples of agonists selective for adenosine A_{2A} receptors include, but are not limited to, 2-cyclohexylmethylenehydrazinoadenosine, 2-(3-cyclohexenyl)methylenehydrazinoadenosine, 2-isopropylmethylenehydrazinoadenosine, N-ethyl-1'-deoxy-1'-[6-amino-2-[(2-thiazolyl)ethynyl]-9 H-purin-9-yl]-.beta.-D-ribofuranuronamide, N-ethyl-1'-deoxy- 1'-[6-amino-2-[hexynyl]-9 H-purin-9-yl]-.beta.-D-

ribofuranuronamide, 2-(1 -hexyn-1-yl)adenosine-5'-N-methyluronamide, 5'-chloro-5'-deoxy-2-(1-hexyn-1-yl)adenosine, N^6 -[2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)adenosine, 2-(2-phenyl)ethoxyadenosine, 2-[2-(4-methylphenyl)ethoxy]adenosine, 2-[2-(4-fluorophenyl)ethoxy]adenosine, 2-(2-(2-naphthyl)ethoxy)adenosine, 2-[p-(2-carboxyethyl)phenethylamino-5'-N-ethylcarboxamidoadenosine (CGS-21680), 2-(2-cyclohexyl)ethoxyadenosine, 2-octynyladenosine (YT-146), 2-thiazolylethynyladenosine and 2-phenethylamino-5'-N-ethylcarboxamidoadenosine (CGS-21577), Binodenson (MRE-0470), Apadenoson (ATL-146e), Regadenoson (CVT-3146), and ATL-313 of Adenosine Therapeutics.

Further selective A_{2A} agonists include 2-cyclohexylmethylenehydrazinoadenosine, 2-(3-cyclohexenyl)methylenehydrazinoadenosine, 2-isopropylmethylenehydrazinoadenosine, 2-(2-phenyl)ethoxyadenosine, 2-(2-(4-methylphenyl)ethoxyadenosine, 2-(2-cyclohexyl)ethoxyadenosine, and 2-(2-(p-carboxyethyl)phenyl)ethylamino-5'-N-ethyl-carboxamidoadenosine.

The term "non-selective adenosine agonist" refers to agonists that bind to adenosine A_1, A_{2A}, and A_{2B} receptors. Compounds may be chosen as non-selective agonists by testing for cardiovascular activity as described in Ueeda, M., et al., J. Med. Chem. 34:1334-1339 (1991) and demonstrating an A_1 /A_2 selectivity ratio, therein defined, between about 5 and about 100. Examples of non-selective agonists include, but are not limited to, adenosine, 5'-N-ethylcarboxamidoadenosine (NECA), and 2-chloroadenosine.

Preferably the adenosine or derivative thereof is a stable form which is resistant to radiation. Adenosine in its crystalline form may be used for improved resistance to radiation. When the adenosine is combined with a polymer, an agent may be added to preserve bioactivity. Preferred polymers include, but are not limited to, water soluble polymers such as polyethylene glycol and polyethylene oxide, poly (block-ethylene oxide-block-propylene oxide-block-ethylene oxide); polyvinyl pyrrolidone (PVP); polyorthoesters; polysaccharides and polysaccharide derivatives such as polyhyaluronic acid, poly (glucose), polyalginic acid, chitin, chitosan, chitosan derivatives, cellulose, methyl cellulose, hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, cyclodextrins and substituted cyclodextrins, such as beta-cyclo dextrin sulfo butyl ethers; polypeptides, and proteins such as polylysine,

polyglutamic acid, albumin; and poly(ester-co-anhydride). Particularly preferred is PVP, which may be formulated as an adenosine/PVP matrix in a ratio of between about 50/50 and 90/10, and is best for its ability to maintain an amorphous condition.

In one examplary embodiment, adenosine and/or a derivative thereof can be combined with a hydrogel or proto-hydrogel matrix. The adenosine/hydrogel is loaded into the openings of a stent and dehydrated. Rehydration of the hydrogel causes the hydrogel to swell and allows the adenosine to be released from the hydrogel.

Although the delivery of adenosine or adenosine derivatives from a stent has been described herein primarily for delivery to the lumen of a blood vessel for reducing ischemic injury, adenosine or derivatives may also be delivered murally from the stent.

In another aspect of the invention, therapeutic agents which preserve or enhance endogenous adenosine levels may also be loaded onto the local delivery device. Such agents include phosphodiesterase (PDE) inhibitors, which act to preserve endogenous adenosine levels by blocking phosphorylation and loss of cAMP, which itself is derived from adenosine. Preferred phosphosdiesterase inhibitors include those of Type III, which include cilostazol, milrinone, inamrinone, cilostamide, saterinone, motapizone, lixazinone, enoximone (fenoximone), imazodan, pimobendan. Commercially, type III PDE inhibitors are known as Pletal, Primacor or Milrinone Lactate, and Amrinone Lactate. Other preferred PDE inhibitors include those of type IV, which can have cross-over PDE-III activity, and include ariflo and rolipram. Non-specific PDE inhibitors may also be used, and include theophylline, dipyridamole, and aminophylline. PDE inhibitors of type V may also be used, and include sildenafil and tadalafil. Commercially, type V PDE inhibitors are also known as Viagra and Cialis.

The PDE inhibitors of type III are particularly preferred, and in particular cilostazol. Cilostazol is widely used as an antiplatelet drug and appears to affect both vascular beds and cardiovascular function, such as vasodilation. This agent is also known to increase myocardioal contractile force and coronary blood flow, and to augment ischemia-induced increase in interstitial adenosine by limiting the conversion of cAMP to ADP. Other beneficial effects of cilostazol are that it reversibly moderates platelet aggregation induced by thrombin, shear stress, collagen, and ADP. The dosage of cilostazol may be between 10μg

and 800μg, preferably 100 μg to 600μg, most preferably about 500μg, for a 3mm x 17 mm stent; as will be immediately apparent, these dosage amounts will be different for different sized devices.

PDE inhibitors may be used as either stand alone therapeutic drugs for treating acute myocardial infarction, or in combination with adenosine and/or a derivative thereof. Particularly, PDE inhibitors are useful as a neuro-protectant for treating ischemic stroke or cerebral ischemia. PDE inhibitors may be administered alone or in combination with adenosine or its derivatives.

In one embodiment of the invention, a drug which is suited for the reduction of ischemic injury is delivered at or near the site of a reopened occlusion following myocardial infarction or other acute ischemic syndromes. The delivery of the drug at or near the site of the previous occlusion allows the drug to be delivered by the blood flow downstream to the reperfused tissue. The drug can be delivered by a stent containing drug in openings in the stent as described further below.

The drug can also be delivered by a drug coated stent, an implant, microspheres, a catheter, coils, or other local delivery means.

For example, microspheres, coils, liposomes, or other small drug carriers can be delivered locally at or near the site of a previous occlusion with a catheter or drug delivery stent. These small drug carriers are released and pass downstream into the myocardium where they may implant themselves delivering the drug directly to the ischemic tissue.

The drug can be released over an administration period which is dependent on the mode of action of the drug delivered. For example, adenosine may be delivered over an administration period from a few minutes up to weeks; preferably, adenosine is delivered over a period of at least 1 hour, more preferably at least 2 hours, and more preferably about 3 hours to about one week, most preferably about 10-62 hours. One possible *in vivo* release profile is about 25% in the first 30 minutes, an additional 25% by 2 hours, 75% by 24 hours, and 100% by 48 hours. The PDE inhibitor cilostazol is moderately hydrophobic, so it is suitable for a longer term delivery, such as up to several weeks. Alternatively, if administered in combination with adenosine, the release profile is optionally set up so that cilostazol elutes after adenosine. The dosage of cilostazol between 10μg and 800μg,

preferably 100 μg to 600μg, most preferably about 500μg on a 3 mm x 17 mm stent.

In one example, the drug for reduction of ischemic injury is delivered from a stent primarily in a luminal direction with minimal drug being delivered directly from the stent in the direction of the vessel wall. This stent may be placed alone in the occlusion or may be placed in addition to another stent (bare stent or drug delivery stent) placed in connection with an angioplasty procedure. The stent for delivery of ischemic injury treatment agent may be placed within or adjacent another previously placed stent. The implantation site for the stent may be at or near the site of the occlusion. An implantation site may also be selected at or near a location of a plaque rupture site or a vessel narrowing.

The present invention is also particularly well suited for the delivery of a second therapeutic agent primarily from a mural side of a stent for treatment of a condition such as restenosis in addition to the first agent delivered primarily from the luminal side of the stent for reduction of ischemic injury. The primarily murally delivered agents may include antineoplastics, antiangiogenics, angiogenic factors, antirestenotics, anti-thrombotics, such as heparin, anti-inflammatories, such as Pimecrolimus, antiproliferatives, such as paclitaxel and Rapamycin and derivatives thereof.

In the dual agent example, a drug suited for the reduction of ischemic injury is delivered primarily luminally from a stent while a drug for the treatment of restenosis is delivered primarily murally from the stent. In one likely example, the first drug for the reduction of ischemic injury is delivered at a first delivery rate for a first administration period, such as over a period of about 1 to about 48 hours, while the second drug for the treatment of restenosis is delivered *in vivo* at a second delivery rate for a second administration period, such as over a period of about 2 days or longer, preferably about 10 days or longer, and more preferably about 30 days or longer. For example, paclitaxel may be delivered for a period of up to 5 to 6 months, and pimecrolimus may be delivered for up to 4 to 5 months.

In another dual agent delivery example, two agents for treatment of ischemic injury are both delivered primarily luminally. The two agents may be delivered over different administration periods depending on the mode of action of the agents. For example, a fast acting agent may be delivered over a short period of a few minutes while a slower acting

agent is delivered over several hours or days.

It is preferred that adenosine and/or a derivative thereof be delivered primarily luminally. If delivered in combination with a PDE inhibitor, then the PDE inhibitor should also be delivered luminally. In addition, the PDE inhibitor may be delivered locally by the same drug delivery stent as the adenosine or by another local delivery vehicle, such as another stent, catheter, or implant. The PDE inhibitor can also serve a second function in treatment of another condition, for example dipyridamole can act as a PDE inhibitor to treat ischemia or reperfusion injury and as an anti-thrombotic agent.

In another example, the local delivery of a therapeutic agent suited for the reduction of ischemic injury is used in combination with one or more systemically delivered therapeutic agents, such as lidocaine, heparin, other anti-thrombotic agents, and the like.

In addition, other therapeutic agents for use in combination may be delivered locally by the same drug delivery stent or by another local delivery vehicle, such as another stent, catheter, or implant.

Some of the therapeutic agents for use with the present invention which may be transmitted primarily luminally, primarily murally, or both may, for example, take the form of small molecules, peptides, lipoproteins, polypeptides, polynucleotides encoding polypeptides, lipids, protein-drugs, protein conjugate drugs, enzymes, oligonucleotides and their derivatives, ribozymes, other genetic material, cells, antisense oligonucleotides, monoclonal antibodies, platelets, prions, viruses, bacteria, eukaryotic cells such as endothelial cells, stem cells, ACE inhibitors, monocyte/macrophages and vascular smooth muscle cells. Such agents can be used alone or in various combinations with one another. For instance, anti-inflammatories may be used in combination with antiproliferatives to mitigate the reaction of tissue to the antiproliferative. The therapeutic agent may also be a pro-drug, which metabolizes into the desired drug when administered to a host. In addition, therapeutic agents may be pre-formulated as microcapsules, microspheres, microbubbles, liposomes, niosomes, emulsions, dispersions or the like before they are incorporated into the matrix. Therapeutic agents may also be radioactive isotopes or agents activated by some other form of energy such as light or ultrasonic energy, or by other circulating molecules that can be systemically administered.

Exemplary classes of therapeutic agents include antiproliferatives, antithrombins (i.e., thrombolytics), immunosuppressants, antilipid agents, anti-inflammatory agents, antineoplastics including antimetabolites, antiplatelets, angiogenic agents, anti-angiogenic agents, vitamins, antimitotics, metalloproteinase inhibitors, NO donors, nitric oxide release stimulators, anti-sclerosing agents, vasoactive agents, endothelial growth factors, beta blockers, AZ blockers, hormones, statins, insulin growth factors, antioxidants, membrane stabilizing agents, calcium antagonists (i.e., calcium channel antagonists), retinoids, anti-macrophage substances, antilymphocytes, cyclooxygenase inhibitors, immunomodulatory agents, angiotensin converting enzyme (ACE) inhibitors, anti-leukocytes, high-density lipoproteins (HDL) and derivatives, cell sensitizers to insulin, prostaglandins and derivatives, anti-TNF compounds, hypertension drugs, protein kinases, antisense oligonucleotides, cardio protectants, petidose inhibitors (increase blycolitic metabolism), endothelin receptor agonists, interleukin-6 antagonists, anti-restenotics, vasodilators, and other miscellaneous compounds.

Antiproliferatives include, without limitation, paclitaxel, actinomycin D, rapamycin, everolimus, ABT-578, tacrolimus, cyclosporin, and pimecrolimus.

Antithrombins include, without limitation, heparin, aspirin, sulfinpyrazone, ticlopidine, ABCIXIMAB, eptifibatide, tirofiban HCL, coumarines, plasminogen, α_2-antiplasmin, streptokinase, urokinase, bivalirudin, tissue plasminogen activator (t-PA), hirudins, hirulogs, argatroban, hydroxychloroquin, BL-3459, pyridinolcarbamate, Angiomax, and dipyridamole.

Immunosuppressants include, without limitation, cyclosporine, rapamycin and tacrolimus (FK-506), ABT-578, everolimus, etoposide, and mitoxantrone.

Antilipid agents include, without limitation, HMG CoA reductase inhibitors, nicotinic acid, probucol, and fibric acid derivatives (e.g., clofibrate, gemfibrozil, gemfibrozil, fenofibrate, ciprofibrate, and bezafibrate).

Anti-inflammatory agents include, without limitation, pimecrolimus, salicylic acid derivatives (e.g., aspirin, insulin, sodium salicylate, choline magnesium trisalicylate, salsalate, dflunisal, salicylsalicylic acid, sulfasalazine, and olsalazine), para-amino phenol derivatives (e.g., acetaminophen), indole and indene acetic acids (e.g., indomethacin, sulindac, and etodolac), heteroaryl acetic acids (e.g., tolmetin, diclofenac, and ketorolac),

arylpropionic acids (e.g., ibuprofen, naproxen, flurbiprofen, ketoprofen, fenoprofen, and oxaprozin), anthranilic acids (e.g., mefenamic acid and meclofenamic acid), enolic acids (e.g., piroxicam, tenoxicam, phenylbutazone and oxyphenthatrazone), alkanones (e.g., nabumetone), glucocorticoids (e.g., dexamethaxone, prednisolone, and triamcinolone), pirfenidone, and tranilast.

Antineoplastics include, without limitation, nitrogen mustards (e.g., mechlorethamine, cyclophosphamide, ifosfamide, melphalan, and chlorambucil), methylnitrosoureas (e.g., streptozocin), 2-chloroethylnitrosoureas (e.g., carmustine, lomustine, semustine, and chlorozotocin), alkanesulfonic acids (e.g., busulfan), ethylenimines and methylmelamines (e.g., triethylenemelamine, thiotepa and altretamine), triazines (e.g., dacarbazine), folic acid analogs (e.g., methotrexate), pyrimidine analogs (5-fluorouracil, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, cytosine arabinoside, 5-azacytidine, and 2',2'-difluorodeoxycytidine), purine analogs (e.g., mercaptopurine, thioguanine, azathioprine, adenosine, pentostatin, cladribine, and erythrohydroxynonyladenine), antimitotic drugs (e.g., vinblastine, vincristine, vindesine, vinorelbine, paclitaxel, docetaxel, epipodophyllotoxins, dactinomycin, daunorubicin, doxorubicin, idarubicin, epirubicin, mitoxantrone, bleomycins, plicamycin and mitomycin), phenoxodiol, etoposide, and platinum coordination complexes (e.g., cisplatin and carboplatin).

Antiplatelets include, without limitation, insulin, dipyridamole, tirofiban, eptifibatide, abciximab, and ticlopidine.

Angiogenic agents include, without limitation, phospholipids, ceramides, cerebrosides, neutral lipids, triglycerides, diglycerides, monoglycerides lecithin, sphingosides, angiotensin fragments, nicotine, pyruvate thiolesters, glycerol-pyruvate esters, dihydoxyacetone-pyruvate esters and monobutyrin.

Anti-angiogenic agents include, without limitation, endostatin, angiostatin, fumagillin and ovalicin.

Vitamins include, without limitation, water-soluble vitamins (e.g., thiamin, nicotinic acid, pyridoxine, and ascorbic acid) and fat-soluble vitamins (e.g., retinal, retinoic acid, retinaldehyde, phytonadione, menaqinone, menadione, and alpha tocopherol).

Antimitotics include, without limitation, vinblastine, vincristine, vindesine, vinorelbine, paclitaxel, docetaxel, epipodophyllotoxins, dactinomycin, daunorubicin, doxorubicin, idarubicin, epirubicin, mitoxantrone, bleomycins, plicamycin and mitomycin.

Metalloproteinase inhibitors include, without limitation, TIMP-1, TIMP-2, TIMP-3, and SmaPI.

NO donors include, without limitation, L-arginine, amyl nitrite, glyceryl trinitrate, sodium nitroprusside, molsidomine, diazeniumdiolates, S-nitrosothiols, and mesoionic oxatriazole derivatives.

NO release stimulators include, without limitation, adenosine.

nti-sclerosing agents include, without limitation, collagenases and halofuginone.

Vasoactive agents include, without limitation, nitric oxide, adenosine, nitroglycerine, sodium nitroprusside, hydralazine, phentolamine, methoxamine, metaraminol, ephedrine, trapadil, dipyridamole, vasoactive intestinal polypeptides (VIP), arginine, and vasopressin.

Endothelial growth factors include, without limitation, VEGF (Vascular Endothelial Growth Factor) including VEGF-121 and VEG-165, FGF (Fibroblast Growth Factor) including FGF-1 and FGF-2, HGF (Hepatocyte Growth Factor), and Ang1 (Angiopoietin 1).

Beta blockers include, without limitation, propranolol, nadolol, timolol, pindolol, labetalol, metoprolol, atenolol, esmolol, and acebutolol.

Hormones include, without limitation, progestin, insulin, the estrogens and estradiols (e.g., estradiol, estradiol valerate, estradiol cypionate, ethinyl estradiol, mestranol, quinestrol, estrond, estrone sulfate, and equilin).

Statins include, without limitation, mevastatin, lovastatin, simvastatin, pravastatin, atorvastatin, and fluvastatin.

Insulin growth factors include, without limitation, IGF-1 and IGF-2.

Antioxidants include, without limitation, vitamin A, carotenoids and vitamin E.

Membrane stabilizing agents include, without limitation, certain beta blockers such as propranolol, acebutolol, labetalol, oxprenolol, pindolol and alprenolol.

Calcium antagonists include, without limitation, amlodipine, bepridil, diltiazem,

felodipine, isradipine, nicardipine, nifedipine, nimodipine and verapamil.

Retinoids include, without limitation, all-trans-retinol, all-trans-14-hydroxyretroretinol, all-trans-retinaldehyde, all-trans-retinoic acid, all-trans-3,4-didehydroretinoic acid, 9-cis-retinoic acid, 11-cis-retinal, 13-cis-retinal, and 13-cis-retinoic acid.

Anti-macrophage substances include, without limitation, NO donors.

Anti-leukocytes include, without limitation, 2-CdA, IL-1 inhibitors, anti-CD116/CD18 monoclonal antibodies, monoclonal antibodies to VCAM, monoclonal antibodies to ICAM, and zinc protoporphyrin.

Cyclooxygenase inhibitors include, without limitation, Cox-1 inhibitors and Cox-2 inhibitors (e.g., CELEBREX® and VIOXX®).

Immunomodulatory agents include, without limitation, immunosuppressants (see above) and immunostimulants (e.g., levamisole, isoprinosine, Interferon alpha, and Interleukin-2).

ACE inhibitors include, without limitation, benazepril, captopril, enalapril, fosinopril sodium, lisinopril, quinapril, ramipril, spirapril, and 2B3 ACE inhibitors.

Cell sensitizers to insulin include, without limitation, glitazones, P PAR agonists and metformin.

Antisense oligonucleotides include, without limitation, resten-NG.

Cardio protectants include, without limitation, VIP, pituitary adenylate cyclase-activating peptide (PACAP), apoA-I milano, amlodipine, nicorandil, cilostaxone, and thienopyridine.

Petidose inhibitors include, without limitation, omnipatrilat.

Anti-restenotics include, without limitation, include vincristine, vinblastine, actinomycin, epothilone, paclitaxel, paclitaxel derivatives (e.g., docetaxel), rapamycin, rapamycin derivatives, everolimus, tacrolimus, ABT-578, and pimecrolimus.

PPAR gamma agonists include, without limitation, farglitizar, rosiglitazone, muraglitazar, pioglitazone, troglitazone, and balaglitazone.

Miscellaneous compounds include, without limitation, Adiponectin.

Agents may also be delivered using a gene therapy-based approach in

combination with an expandable medical device. Gene therapy refers to the delivery of exogenous genes to a cell or tissue, thereby causing target cells to express the exogenous gene product. Genes are typically delivered by either mechanical or vector-mediated methods.

Some of the agents described herein may be combined with additives which preserve their activity. For example additives including surfactants, antacids, antioxidants, and detergents may be used to minimize denaturation and aggregation of a protein drug. Anionic, cationic, or nonionic detergents may be used. Examples of nonionic additives include but are not limited to sugars including sorbitol, sucrose, trehalose; dextrans including dextran, carboxy methyl (CM) dextran, diethylamino ethyl (DEAE) dextran; sugar derivatives including D-glucosaminic acid, and D-glucose diethyl mercaptal; synthetic polyethers including polyethylene glycol (PEF and PEO) and polyvinyl pyrrolidone (PVP); carboxylic acids including D-lactic acid, glycolic acid, and propionic acid; detergents with affinity for hydrophobic interfaces including n-dodecyl-β-D-maltoside, n-octyl-β-D-glucoside, PEO-fatty acid esters (e.g. stearate (myrj 59) or oleate), PEO-sorbitan-fatty acid esters (e.g. Tween 80, PEO-20 sorbitan monooleate), sorbitan-fatty acid esters (e.g. SPAN 60, sorbitan monostearate), PEO-glyceryl-fatty acid esters; glyceryl fatty acid esters (e.g. glyceryl monostearate), PEO-hydrocarbon-ethers (e.g. PEO-10 oleyl ether; triton X-100; and Lubrol. Examples of ionic detergents include but are not limited to fatty acid salts including calcium stearate, magnesium stearate, and zinc stearate; phospholipids including lecithin and phosphatidyl choline; CM-PEG; cholic acid; sodium dodecyl sulfate (SDS); docusate (AOT); and taumocholic acid.

Some of the agents described herein may be combined with additives which preserve their activity. For example, additives including surfactants, antacids, antioxidants, and detergents may be used to minimize denaturation and aggregation of a protein drug. Additives such as antacids and antioxidants may also be used with non-protein drugs.

Anionic, cationic, or nonionic detergents may be used. Examples of nonionic additives include but are not limited to sugars including sorbitol, sucrose, trehalose; dextrans including dextran, carboxy methyl (CM) dextran, diethylamino ethyl (DEAE) dextran, and acid scavengers; sugar derivatives including D-glucosaminic acid, and D-glucose diethyl

mercaptal; synthetic polyethers including polyethylene glycol (PEO) and polyvinyl pyrrolidone (PVP); carboxylic acids including D-lactic acid, glycolic acid, and propionic acid; detergents with affinity for hydrophobic interfaces including n-dodecyl-β-D-maltoside, n-octyl-β-D-glucoside, PEO-fatty acid esters (e.g. stearate (myrj 59) or oleate), PEO-sorbitan-fatty acid esters (e.g. Tween 80, PEO-20 sorbitan monooleate), sorbitan-fatty acid esters (e.g. SPAN 60, sorbitan monostearate), PEO-glyceryl-fatty acid esters; glyceryl fatty acid esters (e.g. glyceryl monostearate), PEO-hydrocarbon-ethers (e.g. PEO-10 oleyl ether; triton X-100; and Lubrol.

Examples of ionic detergents include but are not limited to fatty acid salts including calcium stearate, magnesium stearate, and zinc stearate; phospholipids including lecithin and phosphatidyl choline; CM-PEG; cholic acid; sodium dodecyl sulfate (SDS); docusate (AOT); and taumocholic acid.

Implantable Medical Devices with Openings

FIG. 1 illustrates an expandable medical device 10 in the form of a stent implanted in a lumen 116 of an artery 100. A wall of the artery 100 includes three distinct tissue layers, the intima 110, the media 112, and the adventitia 114. When the expandable medical device 10 is implanted in an artery at an occlusion site, a therapeutic agent delivered from the expandable medical device to the lumen 116 of the artery 100 is distributed locally to the tissue at the site of the occlusion and downstream by the blood flow.

One example of an expandable medical device 10, as shown in FIGS. 1-3, includes large, non-deforming struts 12, which can contain openings 14 without compromising the mechanical properties of the struts, or the device as a whole. The non-deforming struts 12 may be achieved by the use of ductile hinges 20 (see FIGS. 2, 3) which are described in detail in U.S. Patent No. 6,241,762, which is incorporated herein by reference in its entirety. The openings 14 serve as large, protected reservoirs for delivering various beneficial agents to the device implantation site.

The relatively large, protected openings 14, as described herein, make the expandable medical device of the present invention particularly suitable for delivering large amounts of therapeutic agents, larger molecules or genetic or cellular agents, and for

directional delivery of agents. The large non-deforming openings 14 in the expandable device 10 form protected areas or receptors to facilitate the loading of such an agent, and to protect the agent from abrasion, extrusion, or other degradation during delivery and implantation.

FIG. 1 illustrates an expandable medical device for directional delivery of a therapeutic agent 16. The openings 14 contain the therapeutic agent 16 for delivery to the lumen 116 of the blood vessel and an optional cap 18 in or adjacent the mural side 24 of the openings.

The volume of beneficial agent that can be delivered using openings 14 is about 3 to 10 times greater than the volume of a 5 micron coating covering a stent with the same stent/vessel wall coverage ratio. This much larger beneficial agent capacity provides several advantages. The larger capacity can be used to deliver multi-drug combinations, each with independent release profiles, for improved efficacy. Also, larger capacity can be used to provide larger quantities of less aggressive drugs and to achieve clinical efficacy without the undesirable side-effects of more potent drugs, such as retarded healing of the endothelial layer.

FIG. 4 shows a cross section of a portion of a medical device 10 in which one or more beneficial agents have been loaded into an opening 14 in multiple deposits. Although multiple discrete deposits are shown for ease of illustration, the deposits may be discrete layers with independent compositions or blended to form a continuous polymer matrix and agent inlay. For example, the deposits can be deposited separately in layers of a drug, polymer, solvent composition which are then blended together in the openings by the action of the solvent. The agent may be distributed within an inlay uniformly or in a concentration gradient. Examples of some methods of creating such layers and arrangements of layers are described in U.S. Patent Publication No. 2002/0082680, published on June 27, 2002, which is incorporated herein by reference in its entirety. The use of drugs in combination with polymers within the openings 14 allows the medical device 10 to be designed with drug release kinetics tailored to the specific drug delivery profile desired.

Another aspect of the present invention includes that the configurations of the drug matrix 16, cap 18, and base 22 preferably generally conform to one or more of the

following constraints. The therapeutic agent matrix 16 optionally occupies between about 40% to about 60% of the volume of a hole 14, and the drug, e.g., adenosine, is heavily loaded in the matrix. By way of non-limiting example, adenosine is loaded between 50% and 95% of the matrix, the balance being, e.g., PVP. The cap 18 optionally occupies between about 5% and about 20% of the volume of the hole 14; by way of non-limiting example, the cap can be formed of combination of Pimecrolimus with a polymer, e.g., PLGA. The base 22 optionally occupies between about 15% to about 30% of the hole 14, and can be formed of one of numerous materials. When the total volume percentages of the matrix 16, cap 18, and base 22 together, relative to the volume of the hole 14, is less than 100%, the hole is merely underfilled.

According to one example, the total depth of the opening 14 is about 50 to about 140 microns, and the typical deposit thickness would be about 2 to about 50 microns, preferably about 12 microns. Each typical deposit is thus individually about twice as thick as the typical coating applied to surface-coated stents. There can be at least two and preferably about five to twelve such deposits in a typical opening, with a total beneficial agent thickness about 4 to 28 times greater than a typical surface coating. According to one embodiment of the present invention, the openings have an area of at least 5 x 10-6 square inches, and preferably at least 10 x 10-6 square inches.

In the example of FIG. 4, the mural side of the openings are provided with a cap 18 which is a deposit of polymer or other material having an erosion rate which is sufficiently slow to allow substantially all of the therapeutic agent in the therapeutic agent matrix 16 to be delivered from the luminal side of the opening prior to complete erosion of the cap 18. The cap 18 prevents loss of the beneficial agent during transport, storage, and during the stent implantation procedure. However, the cap 18 may be omitted where mural and luminal delivery of the agent is acceptable.

In one example, the cap 18 and/or a base 22 may be formed by a material soluble in a different solvent from the therapeutic agent matrix 16 to prevent intermixing of deposits. For example, where one or more deposits of therapeutic agent and matrix have been deposited in the openings in a solvent (e.g., Adenosine, PDE inhibitor, and PVP in water), it may be desirable to select a different polymer and solvent combination (e.g., PLGA in

DMSO) for the barrier to prevent the therapeutic agent from mixing into the barrier. Another deposit, such as a cap, may be formed by a third non-mixing polymer and solvent combination (e.g., PLGA in anisole). In addition to the barrier and cap, other therapeutic agent deposits, protective layers, or separating layers may also be formed of non-mixing polymer/solvent systems in this manner.

The base 22 can be provided which serves as a seal during filling of the openings, as well as constraining the contents of the hole 14 at least until the device is implanted. The base 22 is preferably a rapidly degrading biocompatible material.

Since each deposit of both the cap 18 and therapeutic agent 16 is created independently, individual chemical compositions and pharmacokinetic properties can be imparted to each deposit. Numerous useful arrangements of such deposits can be formed, some of which will be described below. Changes in the agent concentration between deposits can be used to achieve a desired delivery profile. For example, a decreasing release of drug for about 24 hours can be achieved. In another example, an initial burst followed by a constant release for about one week can be achieved. Substantially constant release rates over time period from a few hours to months can be achieved. The deposits may be solid, porous, or filled with other drugs or excipients.

FIG. 5 is a cross sectional view of a portion of an expandable medical device 10 including two or more therapeutic agents. Dual agent delivery systems such as that shown in FIG. 5 can deliver two or more therapeutic agents in different directions for the treatment of different conditions or stages of conditions. For example, a dual agent delivery system may deliver different agents in the luminal and mural directions for treatment of ischemia and restenosis from the same drug delivery device.

In FIG. 5, an antirestenotic agent 32 is provided at the mural side of the device 10 in one or more deposits and a therapeutic agent 36 for reducing ischemic injury is provided at the luminal side of the device in one or more deposits. A separating deposit 34 can be provided between the agents. A separating deposit 34 can be particularly useful when the administration periods for the two agents are substantially different and delivery of one of the agents will be entirely completed while the other agent continues to be delivered. The separating deposit 34 can be any biocompatible material, which is optionally degradable at a

rate which is equal to or longer than the longer of the administration periods of the two agents.

FIG. 6 illustrates an expandable medical device 10 including an inlay 40 formed of a biocompatible matrix with first and second agents provided in the matrix for delivery according to different agent delivery profiles. As shown in FIG. 6, a first drug illustrated by Os is provided in the matrix with a concentration gradient such that the concentration of the drug is highest adjacent the cap 18 at the mural side of the opening and is lowest at the luminal side of the opening. The second drug illustrated by Δs is relatively concentrated in an area close to the luminal side of the opening. This configuration illustrated in FIG. 6 results in delivery of two different agents with different delivery profiles from the same inlay 40. The two different agents can be agents which treat ischemic injury by different modes of action, such as adenosine, PDE inhibitors, and VIP.

In the embodiments described above, the therapeutic agent can be provided in the expandable medical device in a biocompatible matrix. The matrix can be bioerodible as those described below or can be a permanent part of the device from which the therapeutic agent diffuses. One or more base, separating and cap deposits can be used to separate therapeutic agents within the openings, to provide directional delivery, or to prevent the therapeutic agents from degradation or delivery prior to implantation of the medical device.

The invention will be further described with reference to the following non-limiting examples:

Examples:

Example 1:

To test the clinical viability of the drug-loaded stent, a porcine coronary balloon infarct model may be employed. The swine model of a heart attack created by a catheter balloon occlusion simulates the human condition of a heart attack. Juvenile farm swine, 25-30kg in weight, 2-3 months in age can be employed. The drug-loaded stent will be prepared with a fomulation containing approximately 500μg adenosine.

Pre-surgical procedures:

All animals will be pre-medicated once daily with oral atenolol and amiodarone (drugs that control heart rhythms and inhibit irregular heartbeats) for seven days prior to and the morning of surgery. The animals will also be pre-medicated once daily with aspirin and Plavix (drugs that prevent blood clots) for three days prior to and the morning of surgery. A pain reliever (Carprofen) will be administered orally the morning of surgery to help control post-operative pain. The animals will be fasted overnight.

The animal will be immobilized with intramuscular acepromazine, ketamine, and/or atropine. Anesthesia will be induced with IV thiopental, followed by intubation and ventilation. Anesthesia will be maintained with isoflurane.

Blood samples will be drawn pre-implantation, at 24 hr post-implantation and at termination, to an external lab for creatine kinase (CK) assay.

Procedure for Catheterization and Stent Implantation:

The surgical procedure using aseptic technique will be performed under inhaled anesthesia maintenance. An incision is made in the neck to expose the carotid (neck) artery and the vessel surgically isolated and controlled proximally and distally. A catheter will be inserted into the neck artery and a coronary angiogram will be performed. Heparin is to be administered. Heparin may be re-administered one hour following initial dose. Lidocaine will be given.

An appropriately sized vascular access sheath will be inserted into the artery. A guiding catheter of appropriate shape will be placed into the left or right coronary artery ostia. Once coronary access is achieved, IC nitroglycerine is to be administered prior to baseline cineangiography; thereafter, cineangiography is performed. All animals will have a heart attack induced. The heart attack is induced by using an appropriately sized balloon catheter, which upon inflation within the coronary artery, causes a blockage in the middle portion of the (e.g., left) anterior descending artery (distal to the first septal perforator and first diagonal branch). Before the full infarct begins, animals may be subjected to a pre-conditioning period, with the following steps:

Step	Preconditioning protocol
1	Inflate balloon for 30 sec
2	Deflate balloon for 1 min
3	Inflate balloon for 45 sec
4	Deflate balloon for 1 min
5	Inflate balloon for 1 min
6	Deflate balloon for 1 min

The balloon catheter is left inflated for one hour. During induction of the heart attack, the animals will additionally be given IV heparin in order to prevent blood clots from forming in the coronary arteries. If the animal develops abnormal ventricular heart beats during the heart attack, lidocaine will be given. After the period of balloon inflation, all animals will have a left ventricular angiogram for analysis of ejection fraction and regional wall motion.

After the heart attack has developed, the drug-loaded coronary stent will be implanted in the artery as closely as possible to the area of occlusion created by the balloon. Following stent implantation, the catheters, guidewire, and access sheaths, used to implant the stent, are to be withdrawn, and the vessel will be ligated. The subcutaneous tissue and skin will be closed in standard fashion.

Daily Observations, Care, and Follow-up:

At follow up (72 hours post infarct and stent implantation) the animals will undergo angiography using the same techniques as described above. Following angiography the pigs will be euthanized while under deep anesthesia, and their hearts will be removed for analysis.

Data Analysis:

The tetrazolium staining method will be used to determine infract size. Evans blue stains all perfused tissue blue. Tetrazolium stains living tissue red. Formalin fixes the colors and makes the unstained myocardium pale tan. Thus, the tissue perfused during coronary occlusion is not at risk and is blue. The tissue not infarcted within the area at risk is red. The infracted tissue is pale tan.

However, beyond 3 days after infarct the assessment becomes less reliable due to scar shrinkage. Therefore, to calculate the region at risk, just prior to sacrifice it may be necessary to re-occlude the coronary and infuse dye to stain all perfused (not at risk) areas of the heart.

Methods:

To Mark the risk zone: Prior to sacrifice repeat angiogram. Wire LAD and reinflate balloon at same site of previous infarction (may need to do preconditioning like during primary infarction). Intravenous infusion of 5% Evans blue solution. Infuse KCL cardioplegia (Sacrifice animal) and deflate balloon.

Removing / Slicing the Heart: Remove heart; rinse with saline; cut away atria +/- RV; slice heart parallel to AV groove; wrap the heart in clear food wrap; freeze at 20°C x 1-2 hours; once solid, cut 1cm slices.

Incubating the slices: Incubated in the 1% tetrazolium stain at a temperature of 37°C; water bath or by heating the tetrazolium cocktail over a hot plate on a low setting and carefully monitoring the temperature with a thermometer. Once the temperature has been established, add the heart slices and agitate them at least once a minute. Keep turning the slices. Incubate for 15-20 minutes. The surviving tissue should turn a deep red. After color established, fix the slice in 10% formalin for ~20 minutes.

The living tissue is colored and the infarcted tissue is a pale tan color.

Trace and photograph: Directly trace or take digital photo's of basal surface of the slices.

Planimetry of the infarcts: digitize images and analyze with computer software. Software determination of the area at risk (AR) and area of necrosis (AN); calculate total heart volume (HV). Normalize areas to slice weight for volume estimation. AN/AR = % of risk area infracted, this would be the goal primary endpoint.

Example 2:

In this example, a drug delivery stent substantially equivalent to the stent illustrated in FIGS. 2 and 3, having an expanded size of about 3 mm X 17 mm, is loaded with

adenosine in the following manner. The stent is positioned on a mandrel and an optional quick degrading layer is deposited into the openings in the stent. The quick degrading layer is a mixture of low molecular weight PLGA with PVP, provided on the luminal side to protect the subsequent layers during transport, storage, and delivery.

The layers described herein are deposited in a dropwise manner and are delivered in liquid form by use of a suitable organic solvent, such as DMSO, NMP, or DMAc. A plurality of layers of adenosine and low molecular weight PLGA matrix are then deposited into the openings to form an inlay of drug for the reduction of ischemic injury. The adenosine and polymer matrix are combined and deposited in a manner to achieve a drug delivery profile which results in about 25% of the total drug released in about the first 30 minutes, about 50% released in about 2 hours, about 75% released in about 24 hours, and essentially 100% released in about 48 hours. A barrier layer of moderate or high molecular weight PLGA, a slow degrading polymer, is deposited over the adenosine layers to prevent the adenosine from migrating to the mural side of the stent and the vessel walls. The degradation rate of the barrier layer is selected so that the cap layer does not degrade substantially until after the about 48 hour administration period.

The adenosine dosage provided on the stent is about 500 micrograms, which is calculated based on reported studies on systemic infusions of adenosine, taking in to account the degradation rate. The total dosage on the stent may range from about 5 micrograms to about 1500 micrograms, preferably about 200 to about 600 micrograms.

The drug delivery stent is installed in the patient's vasculature, more particularly at a vascular location at, upstream, or downstream of an occlusion site, in a well known manner, and the adenosine is delivered intraluminally from the stent downstream for local delivery via the bloodstream to the ischemic (or anoxic) myocardial tissue. The vascular location at which the drug delivery stent is installed is selected so that the amount of adenosine delivered to the myocardial tissue of interest is a therapeutically effective amount, based on the known degradation, absorption, and diffusion rates, particularly advantageously co-selected with the rate at which and amount of adenosine is delivered from the stent so that adverse effects from overdosage of the agent are mitigated or completely avoided. By way of non-limiting examples, the drug delivery stent is preferably installed anywhere in the

coronary arteries, including the right coronary artery (RCA), the circumflex, the left anterior descending (LAD), and all branches off of these three main coronary arteries.

Example 3:

In this example, a drug delivery stent substantially equivalent to the stent illustrated in FIGS. 2 and 3, having an expanded size of about 3 mm X 17 mm, is loaded with adenosine and cilostazol in the following manner. The stent is positioned on a mandrel and an optional quick degrading layer is deposited into the openings in the stent. The quick degrading layer is low molecular weight PVP-PLGA provided on the luminal side to protect the subsequent layers during transport, storage, and delivery.

The layers described herein are deposited in a dropwise manner and are delivered in liquid form by use of a suitable organic solvent, such as DMSO, NMP, or DMAc. A plurality of layers of adenosine and low molecular weight PLGA matrix are then deposited into the about half of the openings to form an inlay of drug for the reduction of ischemic injury. A plurality of layers of cilostazol and low molecular weight PLGA matrix are then deposited into the remaining half of the openings. The adenosine/polymer matrix are combined and deposited in a manner to achieve a drug delivery profile which results in about 25% of the total drug released in about the first 30 minutes, about 50% released in about 2 hours, about 75% released in about 24 hours, and essentially 100% released in about 48 hours. The cilostazol/polymer matrix are deposited in a manner to achieve a drug delivery profile which is slowly released over several weeks, and possibly not starting release until the adenosine is released after 48 hours. A barrier layer of moderate or high molecular weight PLGA, a slow degrading polymer, is deposited over the adenosine and cilostazol layers to prevent the drugs from migrating to the mural side of the stent and the vessel walls. The degradation rate of the barrier layer is selected so that the cap layer does not degrade substantially until after the about 48 hour administration period.

The adenosine dosage provided on the stent is about 500 micrograms, which is calculated based on reported studies on systemic infusions of adenosine, taking in to account the degradation rate. The total dosage on the stent may range from about 5 micrograms to about 1500 micrograms, preferably about 200 to about 600 micrograms. The cilostazol

dosage provided on the stent is about 200 μg for a 3x17mm stent.

The drug delivery stent is installed in the patient's vasculature, more particularly at a vascular location at, upstream, or downstream of an occlusion site, in a well known manner, and the adenosine and cilostazol are delivered intraluminally from the stent downstream for local delivery via the bloodstream to the ischemic (or anoxic) myocardial tissue. The vascular location at which the drug delivery stent is installed is selected so that the amounts of adenosine and cilostazol delivered to the myocardial tissue of interest are therapeutically effective amounts, based on the known degradation, absorption, and diffusion rates, particularly advantageously co-selected with the rates at which and amounts of adenosine and cilostazol are delivered from the stent so that adverse effects from overdosage of these agents are mitigated or completely avoided. By way of non-limiting examples, the drug delivery stent is preferably installed anywhere in the coronary arteries, including the right coronary artery (RCA), the circumflex, the left anterior descending (LAD), and all branches off of these three main coronary arteries.

Example 4:

Two lay-up models configured substantially as illustrated in FIG. 4 herein were built with the following specifications: a base occupying 30% of the hole, formed of a mixture of PLGA 50/50 (50%) and PVP (50%); a drug matrix occupying 50% of the volume of the hole, formed of a mixture of 80% adenosine (500 μg total drug load) and 20% PVP; and a cap occupying 10-20% of the volume of the hole, formed of a mixture of 95% pimecrolimus (240 μg)and 5% PLGA 50/50.

Example 5:

Two stents configured substantially as illustrated in FIG. 4 herein were built with the following specifications: a base occupying about 30% of the volume of the hole, formed of PLGA 50/50; a drug matrix occupying about 50% of the volume of the hole, formed of a mixture of 80% adenosine (500 μg total drug load) and 20% PVP; and a cap occupying about 10-20% of the volume of the hole, formed of a mixture of 95% pimecrolimus (240 μg)and 5% PLGA 50/50.

Example 6:

Two stents configured substantially as illustrated in FIG. 4 herein were built with the following specifications: a base occupying about 22% of the hole, formed of PLGA 85/15; a drug matrix occupying about 50% of the volume of the hole, formed of a mixture of 80% adenosine (400 μg total drug load) and 20% PVP; and a cap occupying about 10-20% of the volume of the hole, formed of a mixture of 95% pimecrolimus (240 μg)and 5% PLGA 50/50.

For each of Examples 4-6, the time-release percentage (release kinetics, RK) profiles of the two devices were determined, and are illustrated in FIG. 7. Because each Example involved building two devices, the data for each lay-up example was averaged to arrive at the data points in FIG. 7.

The release kinetics (RK) of adenosine from a stent is determined by extracting drug from the stent release medium such as phosphate buffered saline (PBS) at selected time intervals and measuring the amount released by HPLC as described below. The total drug load (TDL) of adenosine from a stent is determined by extracting all the polymer and drug from the stent in a solvent such as dimethyl sulfoxide (DMSO) or acetonitrile and measuring the amount of drug in the sample by HPLC. The amount of Adenosine in a solution sample is determined by High Pressure Liquid Chromatography (HPLC). The following conditions are used:

Analysis Column: Phenomenex Synergy_Hydro RP HPLC Column (150 mm X 4.6 mm 4 micron particle)

Mobile phase: Water (0.1% glacial acetic acid in water, adjusted to pH 5.0 with 50% NaOH) / Acetonitrile :: 95% vol. / 5% vol.

Flow Rate: 1.0 mL / minute

Temperature: 35°C ambient

Detection wavelength: 259 nm

Injection volume: 10 μL

Retention time: 6.5 minutes

Example 7:

A control bare metal stent is compared with a local catheter delivered intra coronary bolus of 3 mg of adenosine in one milliliter of saline plus a bare metal stent in the porcine model described in Example 1. The resulting % infarct in at risk area for the adenosine bolus group of 5 pigs was about 28% as opposed to about 48% for the control group. The % infarct was normalized for the weight of the porcine heart. Thus, the local delivery of adenosine provided a significant decrease in the infarct size in the porcine model of acute myocardial infarction.

While the invention has been described in detail with reference to exemplary embodiments thereof, it will be apparent to one skilled in the art that various changes can be made, and equivalents employed, without departing from the scope of the invention. Each of the aforementioned documents is incorporated by reference herein in its entirety.

WHAT IS CLAIMED IS:

1. A method of delivering a therapeutic agent locally to myocardial tissue to reduce tissue damage following myocardial infarction and reperfusion, the method comprising:

identifying an occlusion site within a blood vessel;

treating the occlusion site to achieve reperfusion; and

locally delivering an effective amount of the therapeutic agent to myocardial tissue located downstream of the treated occlusion site to reduce ischemic injury;

wherein said therapeutic agent is selected from the group consisting of adenosine, a derivative thereof, a PDE inhibitor, and combinations thereof.

2. The method of claim 1, further comprising:

implanting an implantable medical device, the implantable medical device comprising said therapeutic agent; and

wherein locally delivering the therapeutic agent comprises delivering from the implantable medical device.

3. The method of Claim 1, further comprising:

implanting a stent having a therapeutic dosage of the therapeutic agent affixed thereto; and

implanting the stent at or near the occlusion site.

4. The method of Claim 1, wherein locally delivering the therapeutic agent comprises delivering with a catheter to the occlusion site.

5. The method of Claim 4, wherein the therapeutic agent is adenosine or a derivative thereof delivered in a bolus of about 0.5 to about 20 milligrams.

6. The method of Claim 1, wherein locally delivering the therapeutic agent comprises delivering from one of spheres, coils, implants, and combinations thereof, located at or near the occlusion site.

7. The method of Claim 1, further comprising:

depositing the therapeutic agent and a biocompatible polymer matrix within openings in an implantable medical device for local delivery to the occlusion site.

8. The method of Claim 7, wherein the implantable medical device comprises a stent; and further comprising:

implanting the stent at or near the occlusion site.

9. The method of Claim 1, further comprising:

implanting an implantable medical device at or near the occlusion site;

wherein locally delivering comprises delivering the therapeutic agent from the implantable medical device and delivering an antirestenotic agent from the implantable medical device to the blood vessel wall at the occlusion site.

10. The method of Claim 9, wherein the antirestenotic agent is sirolimus.

11. The method of Claim 9, wherein the antirestenotic is pimecrolimus, zotorolimus or everolimus.

12. The method of Claim 1, wherein the therapeutic agent is the PDE inhibitor cilostazol.

13. The method of Claim 1, wherein the therapeutic agent is an adenosine receptor agonist.

14. The method of Claim 13, wherein the adenosine receptor agonist is an A_{2a} adenosine receptor agonist.

15. An implantable medical device for delivering a therapeutic agent locally to myocardial tissue, the device comprising:

an implantable medical device configured to be implanted within a coronary artery; and

a therapeutic dosage of a therapeutic agent in a biocompatible polymer affixed to the implantable medical device, wherein the therapeutic dosage of therapeutic agent is configured and arranged to be released to the myocardial tissue at a therapeutic dosage and over an administration period effective to reduce ischemic injury of the myocardial tissue,

wherein said therapeutic agent is selected from the group consisting of adenosine, a derivative thereof, a PDE inhibitor, and combinations thereof.

16. The device of Claim 15, wherein the implantable medical device comprises a stent which is expandable within a coronary artery.

17. The device of Claim 15, further comprising:

openings formed in the implantable medical device; and

wherein the therapeutic agent and biocompatible polymer are deposited within the openings in the implantable medical device.

18. The device of Claim 15, wherein the therapeutic agent and biocompatible polymer are deposited on a surface of the implantable medical device.

19. The device of Claim 15, wherein the administration period is about 1 hour or more.

20. The device of Claim 15, wherein the administration period is about 3 hours to about one week.

21. The device of Claim 15, wherein the administration period is about 10 to 62 hours.

22. The device of Claim 15, wherein the therapeutic agent comprises an adenosine receptor agonist.

23. The device of Claim 22 , wherein the therapeutic dosage of adenosine receptor agonist is about 5 to about 1500 micrograms.

24. The device of Claim 22, wherein the therapeutic dosage of adenosine receptor agonist is about 10 to about 800 micrograms.

25. The device of Claim 15, wherein the therapeutic agent comprises a PDE inhibitor.

26. The device of Claim 25, wherein the PDE inhibitor is cilostazol.

27. The device of Claim 22, wherein the adenosine receptor agonist is an A_{2a} receptor agonist.

28. The device of Claim 27, wherein the A_{2a} adenosine receptor agonist is ATL 313.

29. The device of Claim 15, further comprising:

openings and a barrier layer in the implantable medical device, the barrier layer positioned to substantially prevent delivery of the therapeutic agent to the artery wall; and

wherein the therapeutic agent and biocompatible polymer are positioned within the openings in the implantable medical device.

30. The device of Claim 15, further comprising:

an antirestenotic composition.

31. The device of Claim 15, wherein the device is substantially cylindrical with a luminal side and a mural side.

32. The device of Claim 31, wherein the therapeutic agent is deposited on the implantable medical device for delivery primarily to the luminal side of the device and the antirestenotic composition is deposited on the implantable medical device for delivery primarily to the mural side of the device.

33. The device of Claim 15, wherein the therapeutic agent is adenosine or a derivative thereof and the dosage is at least 200 micrograms.

34. A stent for delivering a therapeutic agent locally to myocardial tissue, the stent comprising:

a substantially cylindrical expandable medical device body configured to be implanted within a blood vessel; and

a therapeutic dosage of an adenosine receptor agonist in a biocompatible polymer affixed to the implantable medical device body.

35. The stent of Claim 34, further comprising:

openings; and

wherein the adenosine receptor agonist and biocompatible polymer are deposited within the openings.

36. The stent of Claim 34, wherein the adenosine receptor agonist and biocompatible polymer are deposited on a surface of the stent.

37. The stent of Claim 34, wherein the therapeutic dosage is configured for delivery over an administration period of about 1 hour or more.

38. The stent of Claim 34, wherein the therapeutic dosage is configured for delivery over an administration period of about 10 to about 48 hours.

39. The stent of Claim 34, wherein the therapeutic dosage of adenosine receptor agonist is about 5 to about 1500 micrograms.

40. The stent of Claim 34, further comprising:

openings;

a barrier layer which substantially prevents delivery of the adenosine receptor agonist to the artery wall; and

wherein the adenosine receptor agonist and biocompatible polymer are deposited within the openings.

41. The stent of Claim 34, further comprising:

an antirestenotic composition.

42. The stent of Claim 41, wherein the stent comprises a luminal side and a mural side, and wherein the adenosine receptor agonist is deposited on the stent for delivery primarily to the luminal side of the stent and the antirestenotic composition is deposited on the stent for delivery primarily to the mural side of the stent.

43. The stent of Claim 34, wherein the therapeutic dosage of adenosine, a derivative thereof, or both, is about 50 to about 700 micrograms.

44. The stent of Claim 34, wherein the biocompatible polymer is a bioresorbable polymer.

45. A method of delivering a therapeutic agent locally to myocardial tissue to reduce tissue damage following myocardial infarction and reperfusion, the method comprising:

identifying an occlusion site within a blood vessel;

treating the occlusion site to achieve reperfusion; and

locally delivering an effective amount of the therapeutic agent to myocardial tissue located downstream of the treated occlusion site to reduce ischemic injury and/or reperfusion injury;

wherein said therapeutic agent binds to an adenosine receptor.

46. The method of Claim 44, wherein the therapeutic agent is adenosine or a derivative thereof delivered in a bolus of about 0.5 to about 20 milligrams.

47. The method of Claim 44, further comprising:

implanting a stent having a therapeutic dosage of the therapeutic agent affixed thereto; and

implanting the stent at or near the occlusion site.

48. The method of Claim 44, wherein locally delivering the therapeutic agent comprises delivering with a catheter to the occlusion site.

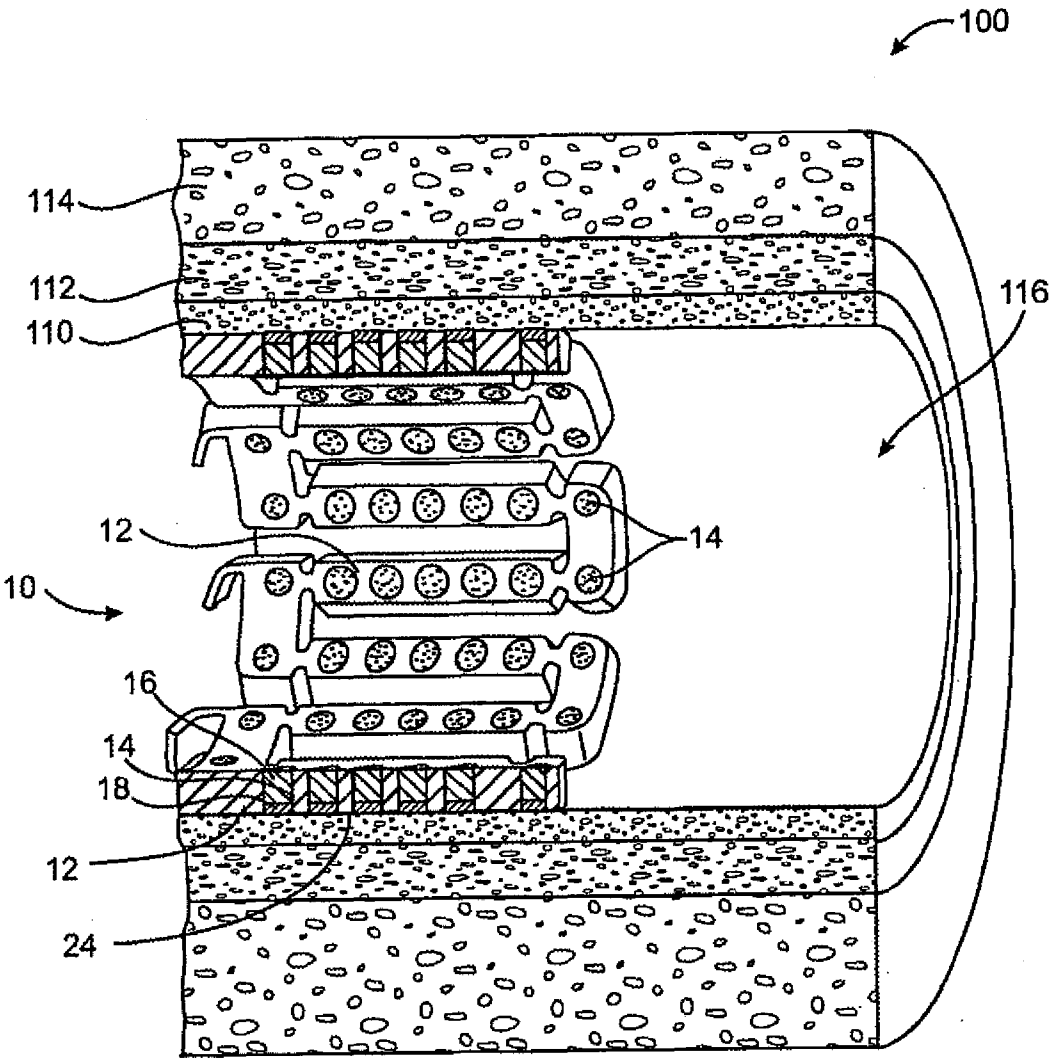


FIG. 1

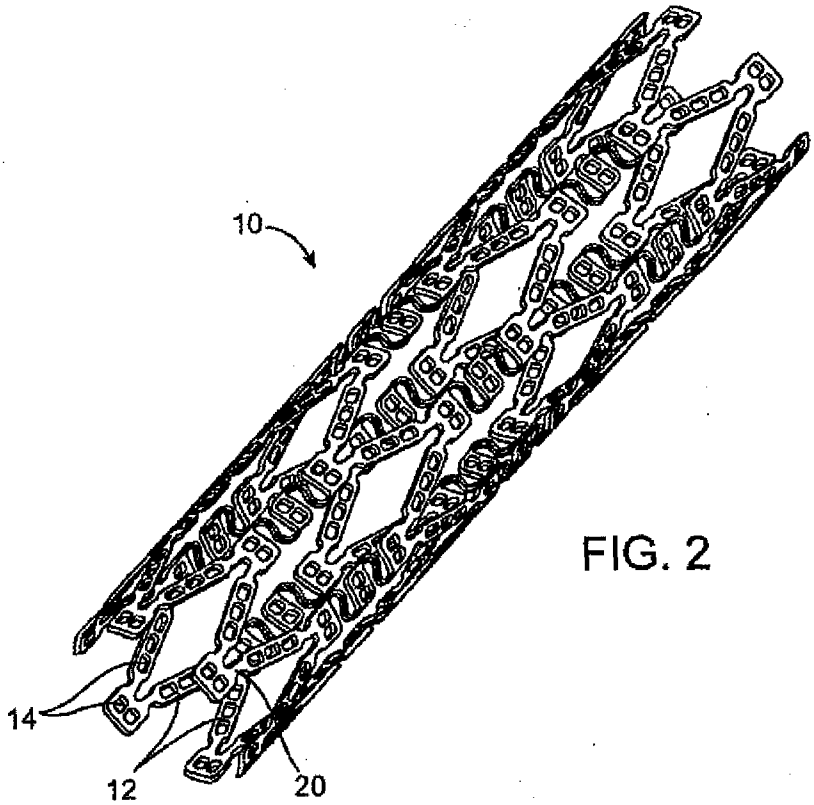


FIG. 2

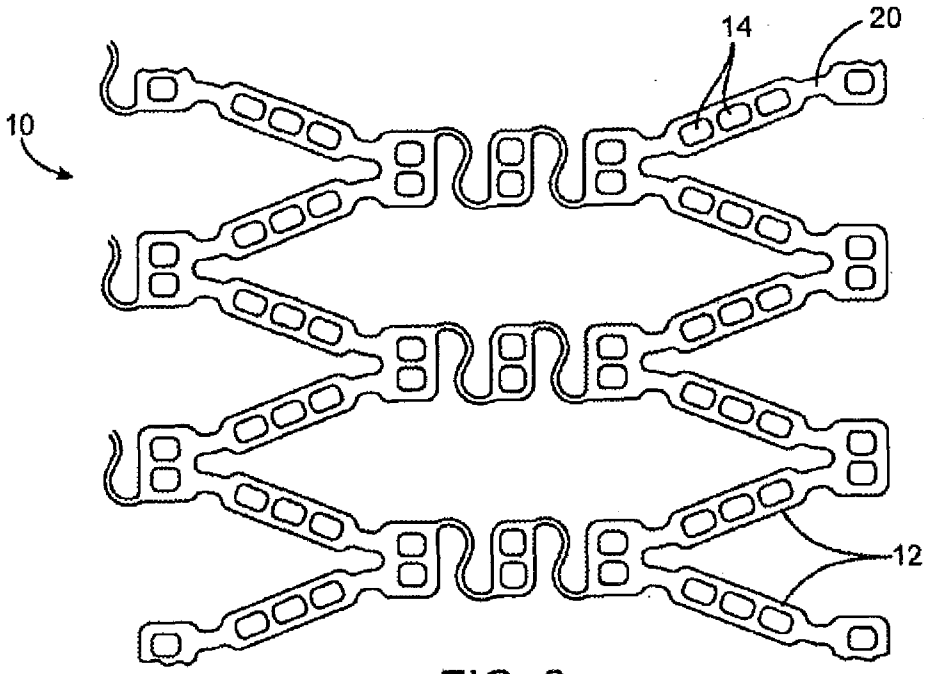


FIG. 3

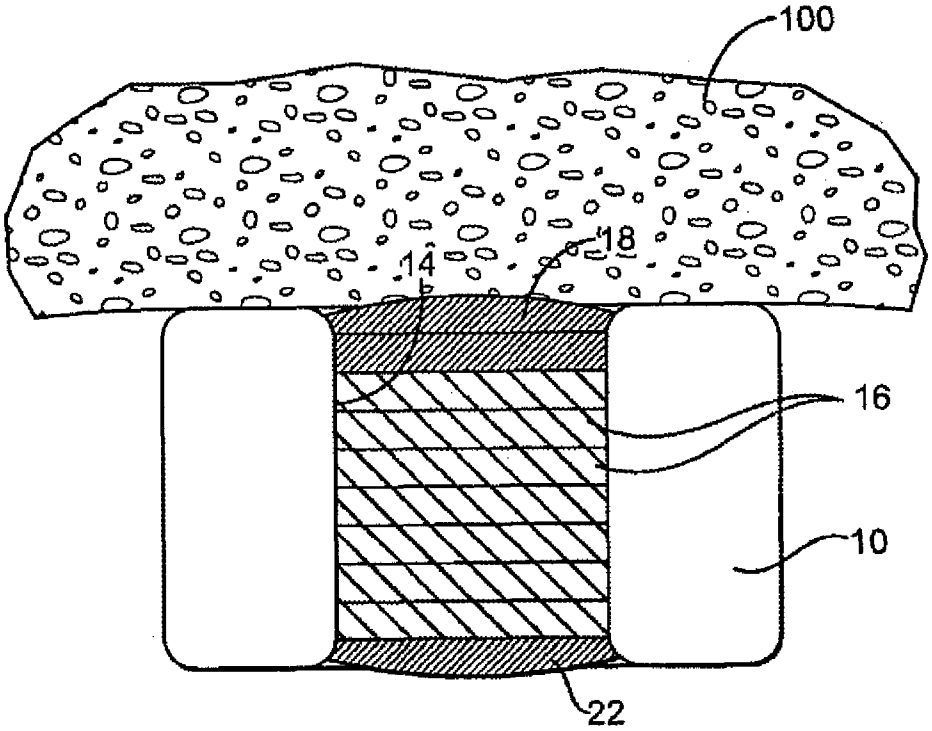


FIG. 4

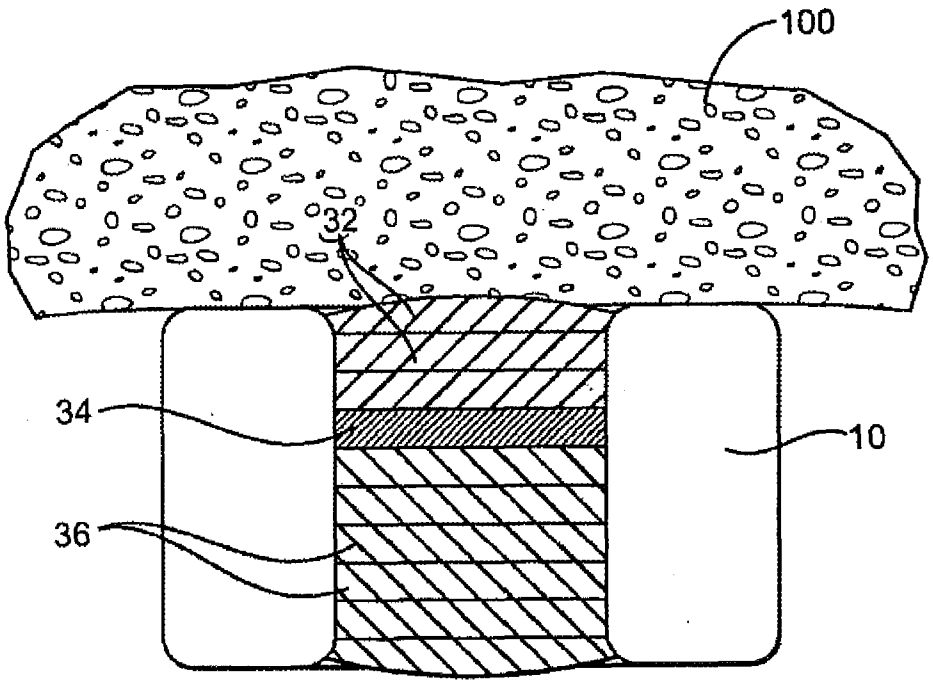


FIG. 5

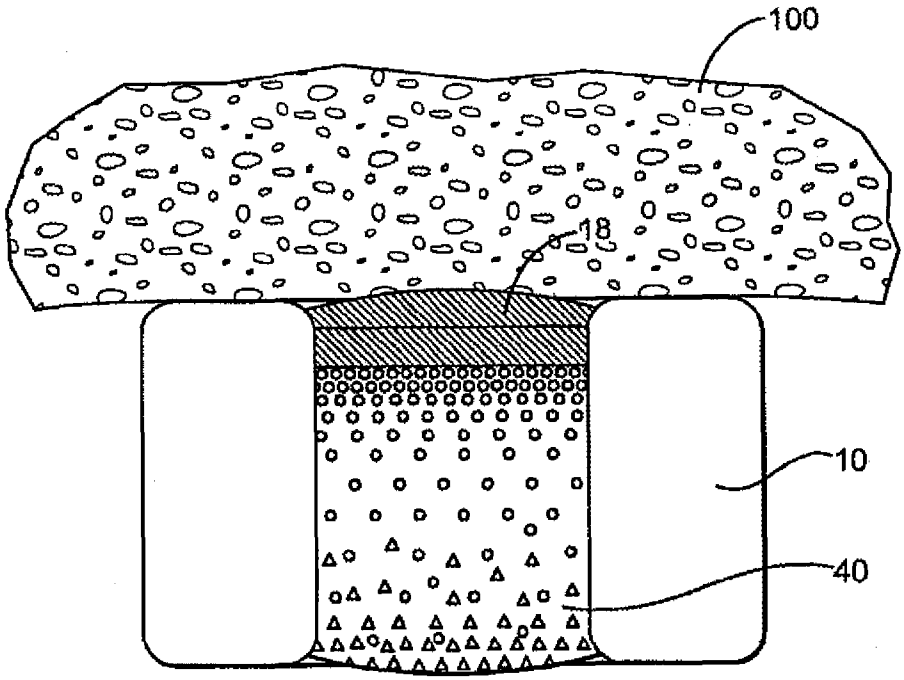


FIG. 6

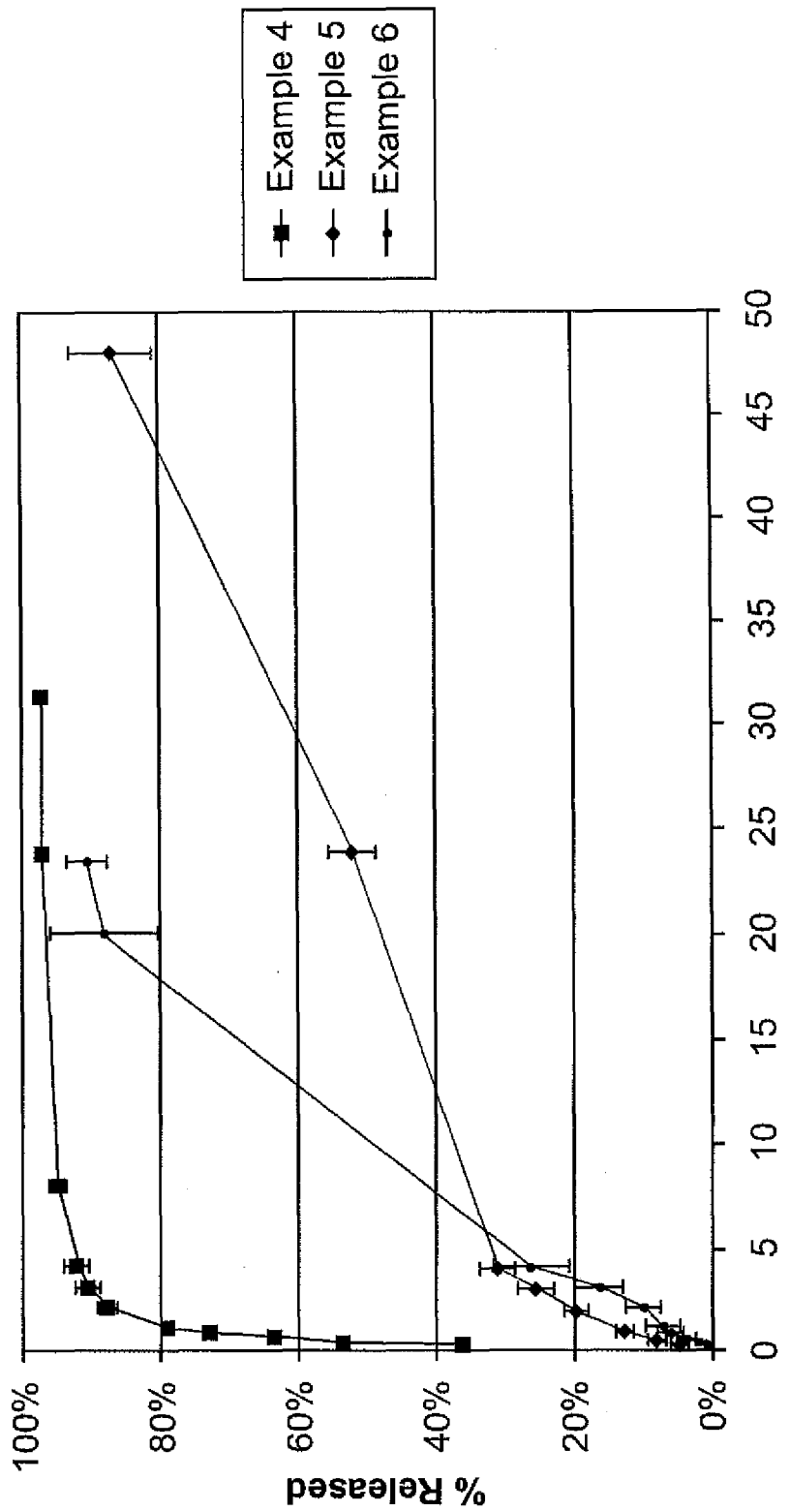

Example 4
Example 5
Example 6
% Released
100%
80%
60%
40%
20%
0%
0
5
10
15
20
25
30
35
40
45
50
Time (min)

FIG. 7