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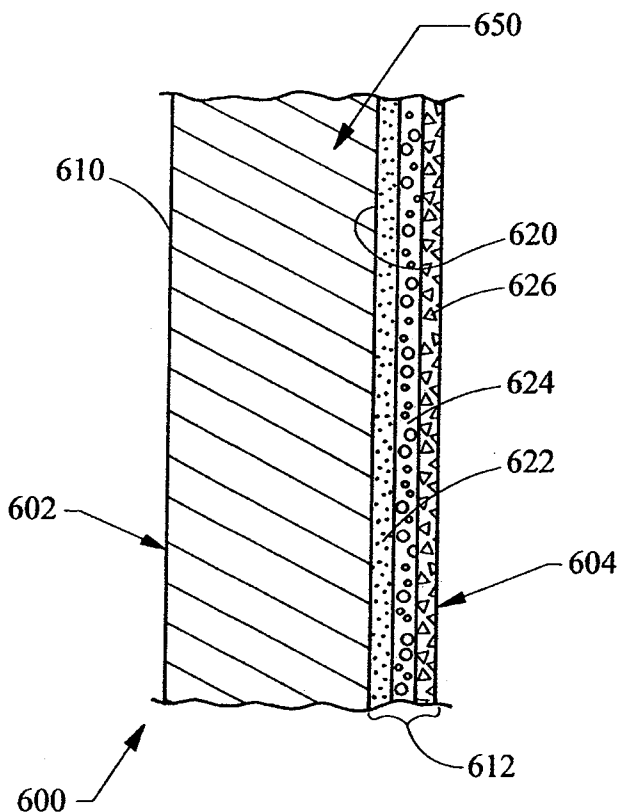
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(54) Title: TREATMENT OF AORTIC DISSECTION OR ANEURYSM



(57) Abstract: This application relates to methods for treating an aneurysm or an aortic dissection (230; 530). The methods include delivering a medical device (10; 100; 150; 200; 400) and a c-Jun N-terminal kinase (JNK) inhibitor compound to a body lumen at a point of treatment within a subject having the aneurysm or aortic dissection (230; 530), the medical device (10; 100; 150; 200; 400) being adapted to release the JNK inhibitor within the body lumen of the subject. This application also relates to medical devices (10; 100; 150; 200; 400) and JNK inhibitor compounds, where the medical device (10; 100; 150; 200; 400) is adapted to release the JNK inhibitor compound within a patient. Medical devices may include coated stents, grafts, stent grafts, balloons and catheters.

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TREATMENT OF AORTIC DISSECTION OR ANEURYSM

This invention relates generally to methods and medical devices for
5 treating an aneurysm and an aortic dissection. The medical devices incorporate
c-Jun *N*-terminal Kinase (JNK) inhibitor compounds. In particular, the invention
relates to local delivery of JNK inhibitor compounds. The invention also relates to
kits and to treating an aorta wall adjacent to an aortic aneurysm as a preventative
measure.

10 Diseases of the aorta are common in the general population and may
include endovascular disease, including aneurysms and aortic dissections.

Endovascular disease may be characterized by weakened vessels due to
elastin breakdown, which results in dilation of vessels and aneurysm. An
aneurysm is a sac formed by localized dilatation of the wall of an artery, a vein, or
15 the heart. Common areas where aneurysms occur and cause adverse medical
conditions include the coronary arteries, the carotid arteries, various cerebral
arteries, and the thoracic and abdominal aorta as well as iliac and femoral
arteries. When a local dilatation of a vessel occurs, irregular blood flow patterns
result in the lumen of the vessel, sometimes leading to clot formation. Typically,
20 the wall of the vessel also progressively dilates and weakens, often resulting in
vessel rupture. Vessel rupture, in turn, often causes dramatic negative
consequences such as a stroke, when a cerebral vessel ruptures, or even death,
when an abdominal aortic aneurysm (AAA) ruptures. Continued degeneration
can result in an increase in aneurysm size due to thinning of the medial
25 connective tissue of the aorta and loss of elastin.

Aortic dissections occur when the inner layer of the aorta's artery wall
splits open (dissects). The normal aorta contains collagen, elastin, and smooth
muscle cells that contribute to the intima, media, and adventitia, which are the
layers of the aorta. Hypertension with ageing is believed to contribute to
30 degenerative changes that may lead to breakdown of the collagen, elastin, and

smooth muscle cells and, ultimately, dissection of the aorta. Aortic dissection is more likely to occur where pressure on the artery wall from blood flow is high, such as the proximal aorta or the ascending aorta (the first segment of the aorta). When the aortic wall splits, the pulses of blood can penetrate the artery wall and its inner layer, causing the aorta to tear or split further. This tear usually continues distally (away from the heart) down the descending aorta and into its major branches. Less often, the tear may run proximally (back toward the heart). Aortic dissection can also start in the descending (distal) segment of the aorta.

In light of these consequences, improved devices and methods of treating and/or preventing aneurysms and aortic dissections are constantly being sought. Although the following discussion focuses on AAA treatment and prevention, it is equally applicable to endovascular disease in other locations, and aortic dissections.

Various implantable medical devices are advantageously inserted within various portions of the body. Minimally invasive techniques and instruments for placement of intraluminal medical devices have been developed to treat and repair undesirable conditions within body vessels including treatment of conditions that affect blood flow such as abdominal aortic aneurysm. Various percutaneous methods of implanting medical devices within the body using intraluminal transcatheter delivery systems can be used to treat a variety of such conditions. One or more intraluminal medical devices, such as tubular stent grafts, can be introduced to a point of treatment within a body vessel using a delivery catheter device passed through the vasculature communicating between a remote introductory location and the implantation site, and released from the delivery catheter device at the point of treatment within the body vessel.

Intraluminal medical devices can be deployed in a body vessel at a point of treatment and the delivery device subsequently withdrawn from the vessel, while the medical device is retained within the vessel to provide sustained improvement in valve function or to increase vessel patency. For example, an implanted stent graft can improve vessel function by permitting relatively less

turbulent fluid flow through the stent graft conduit bridging the site of an aneurysm.

There still, however, remains a great need for therapies useful for the prevention and treatment of aortic aneurysm and aortic dissections.

5 Researchers have hypothesized that the development, expansion and rupture of AAAs and aortic dissections are related to connective tissue destruction. For a discussion of this hypothesis, see for example, "Pharmacologic suppression of experimental abdominal aortic aneurysms" Curci J.A., et al., "A comparison of doxycycline and four chemically modified
10 tetracyclines," *Journal of Vascular Surgery* 28(6):1082-1093 (1998). Connective tissue destruction, in turn, has been linked to the presence of a number of enzymes which break down components of blood vessel wall connective tissues, such as elastin. Examples of such "elastolytic" enzymes include serine
15 proteinases and metalloproteinases (MMPs), particularly MMP-9 and MMP-2, which are derived from activated vascular cells and infiltrating inflammatory cells. It has been found that increased levels of some elastolytic enzymes, such as MMPs, are typically present in AAAs. MMPs have also been studied in
20 atherosclerotic and nonatherosclerotic thoracic aneurysms (Schmoker et al., "Matrix Metalloproteinase and Tissue Inhibitor Expression in Atherosclerotic and Nonatherosclerotic Aneurysms," *J Thorac Cardiovasc Surg*, 133:155-161 (2007)). It is believed that MMP production may be regulated, in part, by increased activation of JNK, since this kinase activates key transcription factors involved in
25 MMP gene expression (Han Z., et al., "c-Jun N-terminal Kinase is Required for Metalloproteinase Expression and Joint Destruction in Inflammatory Arthritis," *J. Clin. Invest.* 108:73-81 (2001)).

 Stimuli, including mechanical stress, oxidative stress, angiotensin II (AngII), tumor necrosis factor (TNF)- α , interleukin (IL) 1 β , IL-6 and interferon (IFN)- γ (reviewed in Curci JA, et al., *Pathogenesis of Abdominal Aortic Aneurysm. Current Therapy in Vascular Surgery* (eds. Ernst, C.B. & Stanley, J.C.) 199-206 (Elsevier, Philadelphia, 2001)) have been linked to AAA. Most, if
30 not all, of these stimuli activate JNK in vascular smooth muscle cells (VSMCs),

which synthesize extracellular matrix (ECM) and secrete MMPs, and macrophages, which secrete proinflammatory cytokines and MMPs. Because JNK is thought to be involved in a number of cellular stress responses, it may have an important role in AAA.

5 Also, several JNK isoforms, encoded by three genes phosphorylate specific sites (serine 63 and serine 73) on the amino-terminal transactivation domain of c-Jun after exposure to ultraviolet irradiation, growth factors, or cytokines (Devary Y., et al., "The Mammalian Ultraviolet Response is Triggered by Activation of Src Tyrosine Kinase," *Cell* 71:1081-1091 (1992); and Kallunki T.,
10 et al., "JNK2 Contains a Specificity-Determining Region Responsible for Efficient c-Jun Binding and Phosphorylation," *Genes Dev.* 8:2996-3007 (1994)). By phosphorylating these sites, the JNKs enhance the transcriptional activity of AP-1, a key regulator of MMP production.

 Yoshimura et al., for example, found that selective inhibition of JNK *in vivo*
15 not only prevented development of AAA but also caused regression of established AAA in mouse models (Yoshimura et al., "Regression of Abdominal Aortic Aneurysm by Inhibition of c-Jun N-terminal Kinase," *Nature Medicine*, 11(12):1330-1338 (2005)).

 U.S. Pub. No. 2007/0248944 A1 relates to prophylactic and therapeutic
20 agents for disorders of collagen and elastin metabolism.

 U.S. Pub. No. 2005/0019366 A1 relates to stents including an effective amount of JNK inhibitor, the stents being useful for treating or preventing a cardiovascular or renal disease.

 U.S. Pub. No. 2005/0181004 A1 relates to intravascular devices (stents,
25 stent grafts, covered stents, aneurysm coils, embolic agents, and drug delivery catheters and balloons) for use in combination with fibrosing agents in order to induce fibrosis or to promote fibrosis between the devices and host tissues.

 Pharmacological inhibition of JNK may be desirable to stop and/or prevent further progression and/or development of a vascular disease, such aneurysm,
30 and especially AAA, and aortic dissections and/or restore architecture of aortic tissues.

According to a first aspect of the present invention, there is provided a medical device for treating an aneurysm or an aortic dissection, the device including a c-Jun N-terminal kinase (JNK) inhibitor compound, the medical device being adapted to release the JNK inhibitor within a body lumen of a
 5 subject having the aneurysm or aortic dissection.

The JNK inhibitor compound may be 3-(4-fluorophenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole; 3-(3-(2-(piperidin-1-yl)ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole; 3-(4-fluorophenyl)-1H-indazole-5-carboxylic acid (3-morpholin-4-yl-propyl)-amide; 3-(3-(3-(piperidin-1-yl)propionylamino)phenyl)-1H-
 10 indazole-5-carboxylic acid amide; 3-(benzo[1,3]dioxol-5-yl)-5-(2H-tetrazol-5-yl)-1H-indazole; 3-(4-fluorophenyl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-indazole; N-tert-butyl-3-(5-(1H-1,2,4-triazol-3-yl)-1H-indazol-3-yl)-benzamide; 3-(3-(2-morpholin-4-yl-ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole; dimethyl-(2-(4-(5-(1H-1,2,4-triazol-3-yl)-1H-indazol-3-yl)-phenoxy)-ethyl)-amine; 5-(5(1,1-
 15 dimethyl-propyl)-1H-[1,2,4]triazol-3-yl)-3-(4-fluorophenyl)-1H-indazole; 3-(4-fluorophenyl)-5-(5-((pyrrolidin-1-yl)methyl)-1H-1,2,4-triazol-3-yl)-1H-indazole; 3-(6-methoxy-naphthalen-2-yl)-5-(5-(pyrrolidin-1-yl)methyl)-1H-[1,2,4]-triazol-3-yl)-1H-indazole; 3-(4-fluorophenyl)-1H-indazole-5-carboxylic acid amide; 4-(4-(4-chlorophenyl)pyrimidin-2-ylamino)benzamide; 4-(4-(4-chlorophenyl)pyrimidin-2-
 20 yl-amino)-N,N-dimethylbenzamide; 4-(4-(4-chlorophenyl)pyrimidin-2-ylamino)-N-(3-(piperidin-1-yl)propyl)benzamide; (4-(4-(4-chlorophenyl)pyrimidin-2-ylamino)phenyl)(piperazin-1-yl)methanone; 1-(4-(4-(4-(4-chlorophenyl)pyrimidin-2-ylamino)-benzoyl)-piperazin-1-yl)-ethanone; 1-(4-(4-(4-(4-(3-hydroxy-propyl)sulfanyl)-phenyl)-pyrimidin-2-ylamino)-benzoyl)-piperazin-1-yl)-ethanone;
 25 (4-(4-(4-chloro-phenyl)-pyrimidin-2-ylamino)-phenyl)-(4-(pyrrolidin-1-yl)-piperidin-1-yl)-methanone; 2H-dibenzo[cd,g]indazol-6-one; 7-chloro-2H-dibenzo[cd,g]indazol-6-one; 5-dimethylamino-2H-dibenzo[cd,g]indazol-6-one; 7-benzyloxy-H-dibenzo[cd,g]indazol-6-one; N-(6-oxo-2,6-dihydro-dibenzo[cd,g]indazol-6-one; 5-(2-piperdin-1-yl-ethylamino)-2H-
 30 dibenzo[cd,g]indazol-6-one; 5-amino-anthra[9,1-cd]isothiazol-6-one; N-(6-oxo-6H-anthra[9,1-cd]isothiazol-5-yl)-benzamide; 7-dimethylamine-anthra[9,1-

cd]isothiazol-6-one; or 2-oxa-1-azo-aceanthrylen-6-one; derivatives; or mixtures thereof. The JNK inhibitor compound may be compound 37, 38, 39, 40, 41, 42, 43, 44, 45, or 46, derivatives thereof, or mixtures thereof. Preferably, the JNK inhibitor compound is a 3,5 disubstituted indazole. The JNK inhibitor compound

5 may also be JNK Inhibitor 1 (L-stereoisomer) (SEQ ID NO: 1; GRKKRRQRRR-PP-RPKRPTTLNLFQVPRSQD-amide); JNK Inhibitor I, (L)-Form (SEQ ID NO 2: H-GRKKRRQRRRPPRPKRPTTLNLFQVPRSQDT-NH₂); Anthra[1,9-cd]pyrazol-6(2H)-one; JNK Inhibitor III (SEQ ID NO: 3: Ac-YGRKKRRQRRR-gaba-ILKQSMTLNLADPVGSLKPHLRANK-NH₂); JNK Inhibitor V (AS601245; 1,3-

10 Benzothiazol-2-yl-(2-((2-(3-pyridinyl)ethyl)amino)-4-pyrimidinyl)acetonitrile); benzothiazole acetonitrile derivatives; JNK Inhibitor VI (SEQ ID NO: 4: H₂N-RPKRPTTLNLF-NH₂); JNK Inhibitor VII, TAT-TI-JIP₁₅₃₋₁₆₃ (SEQ ID NO: 5: H₂N-YGRKKRRQRRR-RPKRPTTLNLF-NH₂); SB203580 (4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)1H-imidazole); Aloisine A (7-*n*-Butyl-6-(4-

15 hydroxyphenyl)[5H]pyrrolo[2,3-b]pyrazine); 4-Hydroxynoneal; and PD98059 (2'-amino-3'-methoxyflavone). Preferably, the medical device is a stent. The stent preferably includes a coating comprising the JNK inhibitor compound. The medical device may be a stent graft comprising a support frame attached to a flexible tubular covering, the JNK inhibitor compound releasably associated with

20 at least a portion of the stent graft. The medical device may be a graft. The method preferably further includes delivering a bioactive agent selected from the group consisting of matrix metalloproteinases' (MMPs) inhibitors, tetracycline, tetracycline-derivative compounds, beta blockers, cyclooxygenase-2 (COX-2) inhibitors, angiogenesis-converting enzyme (ACE) inhibitors, glucocorticoids,

25 nitric oxide synthase (NOS) inhibitors, anti-inflammatories, anti-oxidants, cellular adhesion molecules (CAMs), cathepsin inhibitors, and phenolic tannins, derivatives, and mixtures thereof.

According to a second aspect of the present invention, there is provided a medical device and a JNK inhibitor for treatment of abdominal aortic aneurysm or

30 an aortic dissection, the medical device being adapted to release the JNK inhibitor within a body lumen of a patient.

According to a third aspect of the present invention there is provided a method for treating an aneurysm or an aortic dissection including delivering a medical device and a c-Jun N-terminal kinase (JNK) inhibitor compound to a body lumen within a subject having the aneurysm or aortic dissection, the
5 medical device being adapted to release the JNK inhibitor within the body lumen of the subject.

According to a fourth aspect of the present invention there is provided a method for treating an aneurysm or an aortic dissection including delivering a medical device as described above to a body lumen within a subject having the
10 aneurysm or aortic dissection.

According to a fifth aspect of the present invention there is provided a method of treating an aneurysm or an aortic dissection comprising radially expanding a medical device in a lumen with a balloon catheter, wherein the balloon catheter releases a JNK inhibitor compound.

15 According to a sixth aspect of the present invention there is provided a method of treating an aneurysm or an aortic dissection comprising radially expanding a balloon catheter comprising a JNK inhibitor compound in a lumen, wherein the balloon catheter releases the JNK inhibitor compound within the lumen.

20 According to a seventh aspect of the present invention there is provided a kit including a medical device and a balloon catheter comprising a JNK inhibitor compound.

According to an eighth aspect of the present invention there is provided use of a JNK inhibitor in the manufacture of a medical device for treatment of
25 abdominal aortic aneurysm or an aortic dissection.

According to a ninth aspect of the present invention there is provided use of a JNK inhibitor in the manufacture of a medical device as claimed in any of claims 1 to 21 for treatment of abdominal aortic aneurysm or an aortic dissection.

30 Preferred embodiments of the present invention are described below with reference to the accompanying drawings, in which:

FIG. 1A is a side view of a coated expandable vascular stent endolumenal medical device;

FIG. 1B is a cross section of a strut of an implantable medical device comprising a single-layer coating configuration;

5 FIG. 1C is a cross section of a strut of an implantable medical device comprising a two-layer coating configuration;

FIG. 1D is a cross section of a strut of an implantable medical device comprising an alternate two-layer coating configuration;

10 FIG. 1E is a cross section of a strut of an implantable medical device comprising another alternate two-layer coating configuration;

FIG. 2A is a side view of a first stent graft implantable medical device;

FIG. 2B is a side view of a second stent graft implantable medical device;

FIG. 3 is a perspective view of a third stent graft implantable medical device comprising a two-layer graft material;

15 FIG. 4A is a partial, enlarged top view of a portion of a medical device;

FIG. 4B-4D are enlarged cross-sectional views along lines **B-B'** of the medical device of Figure 4A;

FIG. 5 is a medical device configured as a coated balloon;

20 FIG. 6 is a medical device configured as a flexible material in an annular configuration; and

FIG. 7 is a radial cross section of an exemplary medical device.

The present disclosure describes medical devices, which comprise inhibitors of c-Jun *N*-terminal Kinase (JNK; also known as stress-activated protein kinase), and methods of using these medical devices to stop or prevent
25 breakdown of host connective tissue and treat variety of diseases and conditions, including endovascular disease including aneurysms and aortic dissections. The medical device can be configured to provide a disease treatment by providing an effective amount of a JNK inhibitor compound proximate to a disease site within a body vessel. For example, the medical device can release or retain a JNK
30 inhibitor at a desired rate within a blood vessel upon placement proximate to an aneurysm or aortic dissection. By providing JNK inhibitors with the device, the

progression of local endovascular disease or aortic dissection may be mitigated, stopped and/or reversed, preventing further weakening and dilation of the vessel wall or splitting of the layers of aorta. These types of devices may preferably be used for treatment of aneurysms, especially aortic abdominal aneurysms and for
5 treatment or prevention of aortic dissections.

Definitions

The following detailed description and appended drawings describe and illustrate various exemplary embodiments of the invention. The description and
10 drawings serve to enable one skilled in the art to make and use the invention.

As used herein the terms "comprise(s)," "include(s)," "having," "has," "can," "contain(s)," and variants thereof, are intended to be open-ended transitional phrases, terms, or words that do not preclude the possibility of additional acts or structures. The present invention also contemplates other embodiments
15 "comprising," "consisting of" and "consisting essentially of," the embodiments or elements presented herein, whether explicitly set forth or not.

The recitation of "about" or "substantially" used with reference to a quantity, such as an angle, includes variations in the recited quantity that are equivalent to the quantity recited, for instance an amount that is insubstantially
20 different from a recited quantity for an intended purpose or function.

As used herein, the term "implantable" refers to an ability of a medical device to be positioned at a location within a body for any suitable period of time, such as within a body vessel. Furthermore, the terms "implantation" and "implanted" refer to the positioning of a medical device at a location within a
25 body, such as within a body vessel. Implantable medical devices can be configured for transient placement within a body vessel during a medical intervention (e.g., seconds, minutes, hours), or to remain in a body vessel for a prolonged period of time after an implantation procedure (e.g., weeks or months or years). Implantable medical devices can include devices configured for
30 bioabsorption within a body during a prolonged period of time.

As used herein, "endolumenal" or "translumenal" refer to a device adapted for placement within a body vessel by procedures wherein the prosthesis is advanced within and through the lumen of a body vessel from a remote location to a target site within the body vessel. In vascular procedures, a medical device
5 can typically be introduced "endovascularly" using a catheter over a guidewire under fluoroscopic guidance. The catheters and guidewires may be introduced through conventional access sites to the vascular system, such as through the femoral artery, or brachial and subclavian arteries, for access to the coronary arteries.

10 As used herein, the term "body vessel" means any body passage lumen that conducts fluid, including but not limited to blood vessels, oesophageal, intestinal, biliary, urethral and ureteral passages.

The term "bioabsorbable" is used herein to refer to materials selected to dissipate upon implantation within a body, independent of which mechanisms by
15 which dissipation can occur, such as dissolution, degradation, absorption and excretion. The terms "bioabsorbable," "bioresorbable," or "biodegradable" are used synonymously herein, unless otherwise specified, to refer to the ability of the material or its degradation products to be removed by biological events, such as by fluid transport away from the site of implantation or by cellular activity (e.g.,
20 phagocytosis). Only the term "bioabsorbable" will be used in the following description to encompass absorbable, absorbable, bioabsorbable, and biodegradable, without implying the exclusion of the other classes of materials.

As used herein, recitation of a "non-bioabsorbable" material refers to a material, such as a polymer or copolymer, which remains in the body without
25 substantial bioabsorption.

The term "alloy" refers to a substance composed of two or more metals or of a metal and a nonmetal intimately united, for example by chemical or physical interaction. Alloys can be formed by various methods, including being fused together and dissolving in each other when molten, although molten processing
30 is not a requirement for a material to be within the scope of the term "alloy." As

understood in the art, an alloy will typically have physical or chemical properties that are different from its components.

The term "mixture" refers to a combination of two or more substances in which each substance retains its own chemical identity and properties.

5 The terms "frame" and "support frame" are used interchangeably herein to refer to a structure that can be implanted, or adapted for implantation, within the lumen of a body vessel. Preferably, a frame functions as a stent. As used herein, a "stent" is any structure that is used to hold tissue in place within a body, including an interior portion of a blood vessel, lymph vessel, ureter, bile duct or
10 portion of the alimentary canal. A "stent graft," as used herein, refers to a support frame attached to a graft material.

The term "graft material" as used herein refers to a flexible material that can be attached to a support frame, for example to form a stent graft. A graft material can have any suitable shape, but preferably forms a tubular prosthetic
15 vessel. A graft material can be formed from any suitable material, including the biologically derived or synthetic materials described herein.

"JNK" means a protein or an isoform thereof expressed by a JNK 1, JNK 2, or JNK 3 gene (Gupta, S., Barrett, T., Whitmarsh, A. J., Cavanagh, J., Sluss, H. K., Derijard, B. and Davis, R. J. *The EMBO J* 15:2760-2770 (1996)).

20 As used herein, the term "JNK inhibitor" encompasses, but is not limited to, compounds disclosed herein. Without being limited by theory, specific JNK inhibitors are capable of inhibiting the activity of JNK *in vitro* or *in vivo*. The JNK inhibitor can be in the form of a pharmaceutically acceptable salt, free base, solvate, hydrate, stereoisomer, clathrate or prodrug thereof. Inhibitory activity of
25 JNK inhibitor may be determined by an assay or animal model well-known in the art. In one embodiment, the JNK inhibitor is a compound of structure (I)-(III) as shown below and/or compound SP600125.

As used herein, the term "pharmaceutically acceptable salt(s)" refers to a salt prepared from a pharmaceutically acceptable non-toxic acid or base
30 including an inorganic acid and base and an organic acid and base. Suitable pharmaceutically acceptable base addition salts of the JNK inhibitor include, but

are not limited to metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Suitable non-toxic acids include, but are not limited to, inorganic and organic acids such as acetic, alginic, anthranilic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, formic, fumaric, furoic, galacturonic, gluconic, glucuronic, glutamic, glycolic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phenylacetic, phosphoric, propionic, salicylic, stearic, succinic, sulfanilic, sulfuric, tartaric acid, and p-toluenesulfonic acid. Specific non-toxic acids include hydrochloric, hydrobromic, phosphoric, sulfuric, and methanesulfonic acids. Examples of specific salts thus include hydrochloride and mesylate salts. Others are well-known in the art, see for example, *Remington's Pharmaceutical Sciences*, 18th eds., Mack Publishing, Easton Pa. (1990) or *Remington: The Science and Practice of Pharmacy*, 19th eds., Mack Publishing, Easton Pa. (1995).

As used herein, the term "polymorph(s)" and related terms herein refer to solid forms of the JNK Inhibitor having different physical properties as a result of the order of the molecules in the crystal lattice. The differences in physical properties exhibited by solid forms affect pharmaceutical parameters such as storage stability, compressibility and density (important in formulation and product manufacturing), and dissolution rates (an important factor in determining bioavailability). Differences in stability may result from changes in chemical reactivity (e.g., differential oxidation, such that a dosage form discolors more rapidly when comprised of one solid form than when comprised of another solid form) or mechanical changes (e.g., tablets crumble on storage as a kinetically favored polymorph converts to thermodynamically more stable solid form) or both (e.g., tablets of one solid form are more susceptible to breakdown at high humidity). As a result of solubility/dissolution differences, in the extreme case, some solid form transitions may result in lack of potency or, at the other extreme, toxicity. In addition, the physical properties of the crystal may be important in

processing, for example, one solid form might be more likely to form solvates or might be difficult to filter and wash free of impurities (*i.e.*, particle shape and size distribution might be different between one solid form relative to the other).

As used herein and unless otherwise indicated, the term “clathrate” means
5 a JNK inhibitor, or a salt thereof, in the form of a crystal lattice that contains spaces (*e.g.*, channels) that have a guest molecule (*e.g.*, a solvent or water) trapped within.

As used herein and unless otherwise indicated, the term “hydrate” means
a JNK inhibitor, or a salt thereof, that further includes a stoichiometric or non-
10 stoichiometric amount of water bound by non-covalent intermolecular forces.

As used herein and unless otherwise indicated, the term “prodrug” means
a JNK inhibitor derivative that can hydrolyse, oxidize, or otherwise react under
biological conditions (*in vitro* or *in vivo*) to provide an active compound,
particularly a JNK inhibitor. Examples of prodrugs include, but are not limited to,
15 derivatives and metabolites of a JNK inhibitor that include biohydrolysable moieties such as biohydrolysable amides, biohydrolysable esters,
biohydrolysable carbamates, biohydrolysable carbonates, biohydrolysable ureides, and biohydrolysable phosphate analogues. Preferably, prodrugs of
compounds with carboxyl functional groups are the lower alkyl esters of the
20 carboxylic acid. The carboxylate esters are conveniently formed by esterifying
any of the carboxylic acid moieties present on the molecule. Prodrugs can
typically be prepared using well-known methods, such as those described by
Burger's Medicinal Chemistry and Drug Discovery 6th ed. (Donald J. Abraham
ed., 2001, Wiley) and *Design and Application of Prodrugs* (H. Bundgaard ed.,
25 1985, Harwood Academic Publishers Gmhf).

As used herein and unless otherwise indicated, the term “stereoisomer” or
“stereomerically pure” means one stereoisomer of a JNK inhibitor that is
substantially free of other stereoisomers of that compound. For example, a
stereomerically pure compound having one chiral center will be substantially free
30 of the opposite enantiomer of the compound. A stereomerically pure compound
having two chiral centers will be substantially free of other diastereomers of the

compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, more preferably greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, even more preferably greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, and most preferably greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound.

"Alkyl" means a saturated straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms. "Lower alkyl" means alkyl, as defined above, having from 1 to 4 carbon atoms. Representative saturated straight chain alkyls include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, -n-hexyl, -n-heptyl, -n-octyl, -n-nonyl and -n-decyl; while saturated branched alkyls include -isopropyl, -sec-butyl, -isobutyl, -tert-butyl, -isopentyl, 2-methylbutyl, 3-methylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylbutyl, 2,3-dimethylpentyl, 2,4-dimethylpentyl, 2,3-dimethylhexyl, 2,4-dimethylhexyl, 2,5-dimethylhexyl, 2,2-dimethylpentyl, 2,2-dimethylhexyl, 3,3-dimethylpentyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 2-ethylpentyl, 3-ethylpentyl, 2-ethylhexyl, 3-ethylhexyl, 4-ethylhexyl, 2-methyl-2-ethylpentyl, 2-methyl-3-ethylpentyl, 2-methyl-4-ethylpentyl, 2-methyl-2-ethylhexyl, 2-methyl-3-ethylhexyl, 2-methyl-4-ethylhexyl, 2,2-diethylpentyl, 3,3-diethylhexyl, 2,2-diethylhexyl, 3,3-diethylhexyl and the like.

An "alkenyl group" or "alkylidene" mean a straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and including at least one carbon-carbon double bond. Representative straight chain and branched (C₂-C₁₀) alkenyls include -vinyl, -allyl, -1-butenyl, -2-butenyl, -isobutylenyl, -1-pentenyl, -2-pentenyl, -3-methyl-1-butenyl, -2-methyl-2-butenyl, -2,3-dimethyl-2-butenyl, -1-hexenyl, -2-hexenyl, -3-hexenyl, -1-heptenyl, -2-heptenyl, -3-heptenyl, -1-octenyl, -2-octenyl, -3-octenyl, -1-nonenyl, -2-nonenyl, -3-nonenyl, -1-decenyl,

-2-decenyl, -3-decenyl and the like. An alkenyl group can be unsubstituted or substituted. A "cyclic alkylidene" is a ring having from 3 to 8 carbon atoms and including at least one carbon-carbon double bond, wherein the ring can have from 1 to 3 heteroatoms.

5 An "alkynyl group" means a straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and including at least one carbon-carbon triple bond. Representative straight chain and branched $-(C_2-C_{10})$ alkynyls include -acetylenyl, -propynyl, -1-butylnyl, -2-butylnyl, -1-pentylnyl, -2-pentylnyl, -3-methyl-1-butylnyl, -4-pentylnyl, -1-hexynyl, -2-hexynyl, -5-hexynyl, -1-heptynyl, -2-heptynyl, -6-heptynyl, -1-octynyl, -2-octynyl, -7-octynyl, -1-nonylnyl, -2-nonylnyl, -8-nonylnyl, -1-decynyl, -2-decynyl, -9-decynyl, and the like. An
10 alkynyl group can be unsubstituted or substituted.

The terms "halogen" and "halo" mean fluorine, chlorine, bromine or iodine.

"Haloalkyl" means an alkyl group, wherein alkyl is defined above, where
15 one or more hydrogen atoms are substituted with one or more halogen atoms, respectively.

"Keto" means a carbonyl group (*i.e.*, $C=O$).

"Acyl" means an $-C(O)$ alkyl group, wherein alkyl is defined above, including $-C(O)CH_3$, $-C(O)CH_2CH_3$, $-C(O)(CH_2)_2CH_3$, $-C(O)(CH_2)_3CH_3$, $-C(O)(CH_2)_4CH_3$, $-C(O)(CH_2)_5CH_3$, and the like.
20

"Acyloxy" means an $-OC(O)$ alkyl group, wherein alkyl is defined above, including $-OC(O)CH_3$, $-OC(O)CH_2CH_3$, $-OC(O)(CH_2)_2CH_3$, $-OC(O)(CH_2)_3CH_3$, $-OC(O)(CH_2)_4CH_3$, $-OC(O)(CH_2)_5CH_3$, and the like.

"Ester" means an $-C(O)O$ alkyl group, wherein alkyl is defined above, including $-C(O)OCH_3$, $-C(O)OCH_2CH_3$, $-C(O)O(CH_2)_2CH_3$, $-C(O)O(CH_2)_3CH_3$, $-C(O)O(CH_2)_4CH_3$, $-C(O)O(CH_2)_5CH_3$, and the like.
25

"Alkoxy" means $-O-(alkyl)$, wherein alkyl is defined above, including $-OCH_3$, $-OCH_2CH_3$, $-O(CH_2)_2CH_3$, $-O(CH_2)_3CH_3$, $-O(CH_2)_4CH_3$, $-O(CH_2)_5CH_3$, and the like. "Lower alkoxy" means $-O-(lower alkyl)$, wherein
30 lower alkyl is as described above.

“Alkoxyalkoxy” means —O-(alkyl)-O-(alkyl), wherein each alkyl is independently an alkyl group defined above, including —OCH₂OCH₃, —OCH₂CH₂OCH₃, —OCH₂CH₂OCH₂CH₃, and the like.

“Alkoxycarbonyl” means —C(=O)O-(alkyl), wherein alkyl is defined above, including —C(=O)O—CH₃, —C(=O)O—CH₂CH₃, —C(=O)O—(CH₂)₂CH₃, —C(=O)O—(CH₂)₃CH₃, —C(=O)O—(CH₂)₄CH₃, —C(=O)O—(CH₂)₅CH₃, and the like.

“Alkoxycarbonylalkyl” means -(alkyl)-C(=O)O-(alkyl), wherein each alkyl is independently defined above, including —CH₂—C(=O)O—CH₃, —CH₂—C(=O)O—CH₂CH₃, —CH₂—C(=O)O—(CH₂)₂CH₃, —CH₂—C(=O)O—(CH₂)₃CH₃, —CH₂—C(=O)O—(CH₂)₄CH₃, —CH₂—C(=O)O—(CH₂)₅CH₃, and the like.

“Alkoxyalkyl” means -(alkyl)-O-(alkyl), wherein each alkyl is independently an alkyl group defined above, including —CH₂OCH₃, —CH₂OCH₂CH₃, —(CH₂)₂OCH₂CH₃, —(CH₂)₂O(CH₂)₂CH₃, and the like.

“Aryl” means a carbocyclic aromatic group containing from 5 to 10 ring atoms. Representative examples include, but are not limited to, phenyl, tolyl, anthracenyl, fluorenyl, indenyl, azulenyl, pyridinyl and naphthyl, as well as benzo-fused carbocyclic moieties including 5,6,7,8-tetrahydronaphthyl. A carbocyclic aromatic group can be unsubstituted or substituted. In one embodiment, the carbocyclic aromatic group is a phenyl group.

“Aryloxy” means —O-aryl group, wherein aryl is as defined above. An aryloxy group can be unsubstituted or substituted. In one embodiment, the aryl ring of an aryloxy group is a phenyl group.

“Arylalkyl” means -(alkyl)-(aryl), wherein alkyl and aryl are as defined above, including —(CH₂)phenyl, —(CH₂)₂phenyl, —(CH₂)₃phenyl, —CH(phenyl)₂, —CH(phenyl)₃, —(CH₂)tolyl, —(CH₂)anthracenyl, —(CH₂)fluorenyl, —(CH₂)indenyl, —(CH₂)azulenyl, —(CH₂)pyridinyl, —(CH₂)naphthyl, and the like.

“Arylalkyloxy” means —O-(alkyl)-(aryl), wherein alkyl and aryl are defined above, including —O—(CH₂)₂phenyl, —O—(CH₂)₃phenyl, —O—CH(phenyl)₂, —O—CH(phenyl)₃, —O—(CH₂)tolyl, —O—(CH₂)anthracenyl, —O—(CH₂)fluorenyl,

—O—(CH₂)indenyl, —O—(CH₂)azulenyl, —O—(CH₂)pyridinyl, —O—(CH₂)naphthyl, and the like.

“Aryloxyalkyl” means -(alkyl)-O-(aryl), wherein alkyl and aryl are defined above, including —CH₂—O-(phenyl), —(CH₂)₂—O-phenyl, —(CH₂)₃—O-phenyl, —(CH₂)—O-tolyl, —(CH₂)—O-anthracenyl, —(CH₂)—O-fluorenyl, —(CH₂)—O-indenyl, —(CH₂)—O-azulenyl, —(CH₂)—O-pyridinyl, —(CH₂)—O-naphthyl, and the like.

“Cycloalkyl” means a monocyclic or polycyclic saturated ring having carbon and hydrogen atoms and having no carbon-carbon multiple bonds.

Examples of cycloalkyl groups include, but are not limited to, (C₃-C₇)cycloalkyl groups, including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, and saturated cyclic and bicyclic terpenes. A cycloalkyl group can be unsubstituted or substituted. In one embodiment, the cycloalkyl group is a monocyclic ring or bicyclic ring.

“Cycloalkyloxy” means —O-(cycloalkyl), wherein cycloalkyl is defined above, including —O-cyclopropyl, —O-cyclobutyl, —O-cyclopentyl, —O-cyclohexyl, —O-cycloheptyl and the like.

“Cycloalkylalkyloxy” means —O-(alkyl)-(cycloalkyl), wherein cycloalkyl and alkyl are defined above, including —O—CH₂-cyclopropyl, —O—(CH₂)₂-cyclopropyl, —O—(CH₂)₃-cyclopropyl, —O—(CH₂)₄-cyclopropyl, —O—CH₂-cyclobutyl, —O—CH₂-cyclopentyl, —O—CH₂-cyclohexyl, —O—CH₂-cycloheptyl, and the like.

“Aminoalkoxy” means —O-(alkyl)-NH₂, wherein alkyl is defined above, such as —O—CH₂-NH₂, —O—(CH₂)₂-NH₂, —O—(CH₂)₃-NH₂, —O—(CH₂)₄-NH₂, —O—(CH₂)₅-NH₂, and the like.

“Mono-alkylamino” means —NH(alkyl), wherein alkyl is defined above, such as —NHCH₃, —NHCH₂CH₃, —NH(CH₂)₂CH₃, —NH(CH₂)₃CH₃, —NH(CH₂)₄CH₃, —NH(CH₂)₅CH₃, and the like.

“Di-alkylamino” means —N(alkyl)(alkyl), wherein each alkyl is independently an alkyl group defined above, including —N(CH₃)₂, —N(CH₂CH₃)₂, —N((CH₂)₂CH₃)₂, —N(CH₃)(CH₂CH₃), and the like.

“Mono-alkylaminoalkoxy” means —O-(alkyl)-NH(alkyl), wherein each alkyl is independently an alkyl group defined above, including —O—(CH₂)—NHCH₃, —O—(CH₂)—NHCH₂CH₃, —O—(CH₂)—NH(CH₂)₂CH₃, —O—(CH₂)—NH(CH₂)₃CH₃, —O—(CH₂)—NH(CH₂)₄CH₃, —O—(CH₂)—NH(CH₂)₅CH₃, —O—(CH₂)₂—NHCH₃, and the like.

“Di-alkylaminoalkoxy” means —O-(alkyl)-N(alkyl)(alkyl), wherein each alkyl is independently an alkyl group defined above, including —O—(CH₂)—N(CH₃)₂, —O—(CH₂)—N(CH₂CH₃)₂, —O—(CH₂)—N((CH₂)₂CH₃)₂, —O—(CH₂)—N(CH₃)(CH₂CH₃), and the like.

“Arylamino” means —NH(aryl), wherein aryl is defined above, including —NH(phenyl), —NH(tolyl), —NH(anthracenyl), —NH(fluorenyl), —NH(indenyl), —NH(azulenyl), —NH(pyridinyl), —NH(naphthyl), and the like.

“Arylalkylamino” means —NH-(alkyl)-(aryl), wherein alkyl and aryl are defined above, including —NH—CH₂-(phenyl), —NH—CH₂-(tolyl), —NH—CH₂-(anthracenyl), —NH—CH₂-(fluorenyl), —NH—CH₂-(indenyl), —NH—CH₂-(azulenyl), —NH—CH₂-(pyridinyl), —NH—CH₂-(naphthyl), —NH—(CH₂)₂-(phenyl) and the like.

“Alkylamino” means mono-alkylamino or di-alkylamino as defined above, such as -N(alkyl)(alkyl), wherein each alkyl is independently an alkyl group defined above, including —N(CH₃)₂, —N(CH₂CH₃)₂, —N((CH₂)₂CH₃)₂, —N(CH₃)(CH₂CH₃) and —N(alkyl)(alkyl), wherein each alkyl is independently an alkyl group defined above, including —N(CH₃)₂, —N(CH₂CH₃)₂, —N((CH₂)₂CH₃)₂, —N(CH₃)(CH₂CH₃) and the like.

“Cycloalkylamino” means —NH-(cycloalkyl), wherein cycloalkyl is as defined above, including —NH-cyclopropyl, —NH-cyclobutyl, —NH-cyclopentyl, —NH-cyclohexyl, —NH-cycloheptyl, and the like.

“Carboxyl” and “carboxy” mean —COOH.

“Cycloalkylalkylamino” means —NH-(alkyl)-(cycloalkyl), wherein alkyl and cycloalkyl are defined above, including —NH—CH₂-cyclopropyl, —NH—CH₂-cyclobutyl, —NH—CH₂-cyclopentyl, —NH—CH₂-cyclohexyl, —NH—CH₂-cycloheptyl, —NH—(CH₂)₂-cyclopropyl and the like.

"Aminoalkyl" means $-(\text{alkyl})-\text{NH}_2$, wherein alkyl is defined above, including CH_2-NH_2 , $-(\text{CH}_2)_2-\text{NH}_2$, $-(\text{CH}_2)_3-\text{NH}_2$, $-(\text{CH}_2)_4-\text{NH}_2$, $-(\text{CH}_2)_5-\text{NH}_2$ and the like.

"Mono-alkylaminoalkyl" means $-(\text{alkyl})-\text{NH}(\text{alkyl})$, wherein each alkyl is independently an alkyl group defined above, including $-\text{CH}_2-\text{NH}-\text{CH}_3$, $-\text{CH}_2-\text{NHCH}_2\text{CH}_3$, $-\text{CH}_2-\text{NH}(\text{CH}_2)_2\text{CH}_3$, $-\text{CH}_2-\text{NH}(\text{CH}_2)_3\text{CH}_3$, $-\text{CH}_2-\text{NH}(\text{CH}_2)_4\text{CH}_3$, $-\text{CH}_2-\text{NH}(\text{CH}_2)_5\text{CH}_3$, $-(\text{CH}_2)_2-\text{NH}-\text{CH}_3$, and the like. "Di-alkylaminoalkyl" means $-(\text{alkyl})-\text{N}(\text{alkyl})(\text{alkyl})$, wherein each alkyl is independently an alkyl group defined above, including $-\text{CH}_2-\text{N}(\text{CH}_3)_2$, $-\text{CH}_2-\text{N}(\text{CH}_2\text{CH}_3)_2$, $-\text{CH}_2-\text{N}((\text{CH}_2)_2\text{CH}_3)_2$, $-\text{CH}_2-\text{N}(\text{CH}_3)(\text{CH}_2\text{CH}_3)$, $-(\text{CH}_2)_2-\text{N}(\text{CH}_3)_2$, and the like.

"Heteroaryl" means an aromatic heterocycle ring of 5 to 10 members and having at least one heteroatom selected from nitrogen, oxygen and sulphur, and containing at least one carbon atom, including both mono- and bicyclic ring systems. Representative heteroaryls are triazolyl, tetrazolyl, oxadiazolyl, pyridyl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinolinyl, pyrrolyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolinyl, phthalazinyl, quinazolinyl, pyrimidyl, oxetanyl, azepinyl, piperazinyl, morpholinyl, dioxanyl, thietanyl, and oxazolyl.

"Heteroarylalkyl" means $-(\text{alkyl})-(\text{heteroaryl})$, wherein alkyl and heteroaryl are defined above, including $-\text{CH}_2$ -triazolyl, $-\text{CH}_2$ -tetrazolyl, $-\text{CH}_2$ -oxadiazolyl, $-\text{CH}_2$ -pyridyl, $-\text{CH}_2$ -furyl, $-\text{CH}_2$ -benzofuranyl, $-\text{CH}_2$ -thiophenyl, $-\text{CH}_2$ -benzothiophenyl, $-\text{CH}_2$ -quinolinyl, $-\text{CH}_2$ -pyrrolyl, $-\text{CH}_2$ -indolyl, $-\text{CH}_2$ -oxazolyl, $-\text{CH}_2$ -benzoxazolyl, $-\text{CH}_2$ -imidazolyl, $-\text{CH}_2$ -benzimidazolyl, $-\text{CH}_2$ -thiazolyl, $-\text{CH}_2$ -benzothiazolyl, $-\text{CH}_2$ -isoxazolyl, $-\text{CH}_2$ -pyrazolyl, $-\text{CH}_2$ -isothiazolyl, $-\text{CH}_2$ -pyridazinyl, $-\text{CH}_2$ -pyrimidinyl, $-\text{CH}_2$ -pyrazinyl, $-\text{CH}_2$ -triazinyl, $-\text{CH}_2$ -cinnolinyl, $-\text{CH}_2$ -phthalazinyl, $-\text{CH}_2$ -quinazolinyl, $-\text{CH}_2$ -pyrimidyl, $-\text{CH}_2$ -oxetanyl, $-\text{CH}_2$ -azepinyl, $-\text{CH}_2$ -piperazinyl, $-\text{CH}_2$ -morpholinyl, $-\text{CH}_2$ -dioxanyl, $-\text{CH}_2$ -thietanyl, $-\text{CH}_2$ -oxazolyl, $-(\text{CH}_2)_2$ -triazolyl, and the like.

“Heterocycle” means a 5- to 7-membered monocyclic, or 7- to 10-membered bicyclic, heterocyclic ring which is either saturated, unsaturated, and which contains from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the nitrogen and sulfur heteroatoms can be optionally oxidized, and the nitrogen heteroatom can be optionally quaternized, including bicyclic rings in which any of the above heterocycles are fused to a benzene ring. The heterocycle can be attached via any heteroatom or carbon atom. Heterocycles include heteroaryls as defined above. Representative heterocycles include morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydroprimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

“Heterocycle fused to phenyl” means a heterocycle, wherein heterocycle is defined as above, that is attached to a phenyl ring at two adjacent carbon atoms of the phenyl ring.

“Heterocycloalkyl” means -(alkyl)-(heterocycle), wherein alkyl and heterocycle are defined above, including —CH₂-morpholinyl, —CH₂-pyrrolidinonyl, —CH₂-pyrrolidinyl, —CH₂-piperidinyl, —CH₂-hydantoinyl, —CH₂-valerolactamyl, —CH₂-oxiranyl, —CH₂-oxetanyl, —CH₂-tetrahydrofuranyl, —CH₂-tetrahydropyranyl, —CH₂-tetrahydropyridinyl, —CH₂-tetrahydroprimidinyl, —CH₂-tetrahydrothiophenyl, —CH₂-tetrahydrothiopyranyl, —CH₂-tetrahydropyrimidinyl, —CH₂-tetrahydrothiophenyl, —CH₂-tetrahydrothiopyranyl, and the like.

The term “substituted” as used herein means any of the above groups (*i.e.*, aryl, arylalkyl, heterocycle and heterocycloalkyl) wherein at least one hydrogen atom of the moiety being substituted is replaced with a substituent. In one embodiment, each carbon atom of the group being substituted is substituted with no more than two substituents. In another embodiment, each carbon atom of the group being substituted is substituted with no more than one substituent. In the case of a keto substituent, two hydrogen atoms are replaced with an oxygen, which is attached to the carbon via a double bond. Substituents may include

- halogen, hydroxyl, alkyl, haloalkyl, mono- or di-substituted aminoalkyl, alkyloxyalkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl, $\text{—NR}_a\text{R}_b$, $\text{—NR}_a\text{C(=O)R}_b$, $\text{—NR}_a\text{C(=O)NR}_a\text{R}_b$, $\text{—NR}_a\text{C(=O)OR}_b\text{—NR}_a\text{SO}_2\text{R}_b$, —OR_a , —C(=O)R_a , $\text{—C(=O)OR}_a\text{—C(=O)NR}_a\text{R}_b$, —OC(=O)R_a , —OC(=O)OR_a , $\text{—OC(=O)NR}_a\text{R}_b$, $\text{—NR}_a\text{SO}_2\text{R}_b$, or a radical of the formula —Y—Z—R_a where Y is alkanediyl, or a direct bond, Z is —O— , —S— , $\text{—N(R}_b\text{)—}$, —C(=O)— , —C(=O)O— , —OC(=O)— , $\text{—N(R}_b\text{)C(=O)—}$, $\text{—C(=O)N(R}_b\text{)—}$ or a direct bond, wherein R_a and R_b are the same or different and independently hydrogen, amino, alkyl, haloalkyl, aryl, arylalkyl, heterocycle, or heterocyclealkyl, or wherein R_a and R_b taken together with the nitrogen atom to which they are attached form a heterocycle.

“Haloalkyl” means alkyl, wherein alkyl is defined as above, having one or more hydrogen atoms replaced with halogen, wherein halogen is as defined above, including —CF_3 , —CHF_2 , $\text{—CH}_2\text{F}$, —CBr_3 , —CHBr_2 , $\text{—CH}_2\text{Br}$, —CCl_3 , —CHCl_2 , $\text{—CH}_2\text{Cl}$, —Cl_3 , —CHI_2 , $\text{—CH}_2\text{I}$, $\text{—CH}_2\text{—CF}_3$, $\text{—CH}_2\text{—CHF}_2$, $\text{—CH}_2\text{—CH}_2\text{F}$, $\text{—CH}_2\text{—CBr}_3$, $\text{—CH}_2\text{—CHBr}_2$, $\text{—CH}_2\text{—CH}_2\text{Br}$, $\text{—CH}_2\text{—CCl}_3$, $\text{—CH}_2\text{—CHCl}_2$, $\text{—CH}_2\text{—CH}_2\text{Cl}$, $\text{—CH}_2\text{—Cl}_3$, $\text{—CH}_2\text{—CHI}_2$, $\text{—CH}_2\text{—CH}_2\text{I}$, and the like.

- “Hydroxyalkyl” means alkyl, wherein alkyl is as defined above, having one or more hydrogen atoms replaced with hydroxy, including $\text{—CH}_2\text{OH}$, $\text{—CH}_2\text{CH}_2\text{OH}$, $\text{—(CH}_2\text{)}_2\text{CH}_2\text{OH}$, $\text{—(CH}_2\text{)}_3\text{CH}_2\text{OH}$, $\text{—(CH}_2\text{)}_4\text{CH}_2\text{OH}$, $\text{—(CH}_2\text{)}_5\text{CH}_2\text{OH}$, —CH(OH)—CH_3 , $\text{—CH}_2\text{CH(OH)CH}_3$, and the like.

“Hydroxy” means —OH .

“Sulfonyl” means $\text{—SO}_3\text{H}$.

- “Sulfonylalkyl” means $\text{—SO}_2\text{-(alkyl)}$, wherein alkyl is defined above, including $\text{—SO}_2\text{—CH}_3$, $\text{—SO}_2\text{—CH}_2\text{CH}_3$, $\text{—SO}_2\text{—(CH}_2\text{)}_2\text{CH}_3$, $\text{—SO}_2\text{—(CH}_2\text{)}_3\text{CH}_3$, $\text{—SO}_2\text{—(CH}_2\text{)}_4\text{CH}_3$, $\text{—SO}_2\text{—(CH}_2\text{)}_5\text{CH}_3$, and the like.

“Sulfinylalkyl” means —SO-(alkyl) , wherein alkyl is defined above, including —SO—CH_3 , $\text{—SO—CH}_2\text{CH}_3$, $\text{—SO—(CH}_2\text{)}_2\text{CH}_3$, $\text{—SO—(CH}_2\text{)}_3\text{CH}_3$, $\text{—SO—(CH}_2\text{)}_4\text{CH}_3$, $\text{—SO—(CH}_2\text{)}_5\text{CH}_3$, and the like.

“Sulfonamidoalkyl” means $\text{—NHSO}_2\text{—(alkyl)}$, wherein alkyl is defined above, including $\text{—NHSO}_2\text{—CH}_3$, $\text{—NHSO}_2\text{—CH}_2\text{CH}_3$, $\text{—NHSO}_2\text{—(CH}_2\text{)}_2\text{CH}_3$, $\text{—NHSO}_2\text{—(CH}_2\text{)}_3\text{CH}_3$, $\text{—NHSO}_2\text{—(CH}_2\text{)}_4\text{CH}_3$, $\text{—NHSO}_2\text{—(CH}_2\text{)}_5\text{CH}_3$, and the like.

“Thioalkyl” means —S—(alkyl) , wherein alkyl is defined above, including —S—CH_3 , $\text{—S—CH}_2\text{CH}_3$, $\text{—S—(CH}_2\text{)}_2\text{CH}_3$, $\text{—S—(CH}_2\text{)}_3\text{CH}_3$, $\text{—S—(CH}_2\text{)}_4\text{CH}_3$, $\text{—S—(CH}_2\text{)}_5\text{CH}_3$, and the like.

As used herein, a “stent” means any device useful for opening up blood vessels, such as for example, an artery, vein or capillary thereby improving blood flow; keeping an artery, vein or capillary open; sealing any tears or openings in an artery, vein or capillary; preventing an artery, vein or capillary wall from collapsing or closing off again; or preventing small pieces of plaque from breaking off. In one embodiment, the stent is a stent graft.

The term “graft material” as used herein refers to a flexible material that can be attached to a support frame, for example to form a stent graft. A graft material can have any suitable shape, but preferably forms a tubular prosthetic vessel. A graft material can be formed from any suitable material, including the biologically derived or synthetic materials described herein.

As used herein, a “stent graft” means any stent that is covered with a synthetic or natural (*i.e.*, biologically-derived) material to form a graft prosthesis. The term also encompasses grafted stents, wherein the stent is covered in its entirety with a natural or synthetic graft material (*e.g.*, Vanguard-graft stent, Palmaz-Impragraft stent or Corvita stent). In one embodiment, the stent graft is a prosthetic.

“Effective amount” or “therapeutically effective amount,” when used in connection with a JNK inhibitor, is an amount or dose of the JNK inhibitor that is useful for treating or preventing an aortic aneurysm and/or aortic dissection, but does not cause undesirable effects.

An “effective amount” when used in connection with another active agent is an amount of the other active agent that is useful for providing the agent's therapeutic or prophylactic effect while the JNK Inhibitor is exerting its therapeutic or prophylactic effect.

The term "coating," as used herein and unless otherwise indicated, refers generally to material attached to a medical device. A coating can include material covering any portion of a medical device, and can be configured as one or more coating layers. A coating can have a substantially constant or a varied thickness and composition. Coatings can be adhered to any portion of a medical device surface, including the luminal surface, the abluminal surface, or any portions or combinations thereof.

As used herein, the phrase "controlled release" refers to the release of a therapeutic compound at a predetermined rate. A controlled release may be characterized by a drug elution profile, which shows the measured rate that the material is removed from a material-coated device in a given solvent environment as a function of time. A controlled release does not preclude an initial burst release associated with the deployment of the medical device, because in some embodiments of the invention an initial burst, followed by a more gradual subsequent release, may be desirable. The release may be a gradient release in which the concentration of the therapeutic compound released varies over time or a steady state release in which the therapeutic compound is released in equal amounts over a certain period of time (with or without an initial burst release).

When coated, the coating may be present on any portion of a surface of the device. In one embodiment, the surface is the inner surface. In another embodiment, the surface is the outer surface. In one embodiment, the layer covers at least about 10% of the surface. In another embodiment, the layer covers at least about 20% of the surface. In another embodiment, the layer covers at least about 30% of the surface. In another embodiment, the layer covers at least about 40% of the surface. In another embodiment, the layer covers at least about 50% of the surface. In another embodiment, the layer covers at least about 60% of the surface. In another embodiment, the layer covers at least about 70% of the surface. In another embodiment, the layer covers at least about 80% of the surface. In another embodiment, the layer covers at least about 90% of the surface. In another embodiment, the layer covers about 100% of the surface.

As used herein, the term "preventing" includes inhibiting an aortic aneurysm and/or aortic dissection, in particular, abdominal aortic aneurysm and abdominal aortic dissection.

As used herein, the term "treating" includes eradicating an aortic aneurysm and/or aortic dissection, in particular, abdominal aortic aneurysm and abdominal aortic dissection. In one embodiment, "treating" refers to minimizing the spread or minimizing the worsening of a aortic aneurysm and/or aortic dissection, in particular, an abdominal aortic aneurysm and abdominal aortic dissection.

The term "pharmaceutically acceptable carrier" or "carrier" includes any material which, when combined with JNK inhibitor, allows the JNK inhibitor to retain biological activity, such as the ability to regulate MMPs production in the host connective tissue, and is non-reactive with the subject's immune system. Examples include, but are not limited to, any of the standard pharmaceutical carriers such as a phosphate buffered saline solution, water, emulsions such as oil/water emulsions, various polymer carrier materials, and various types of wetting agents. Compositions comprising such carriers are formulated by well known conventional methods (see, for example, Remington's Pharmaceutical Sciences, Chapter 43, 14th Ed., Mack Publishing Co., Easton, Pa.).

The term "biocompatible" refers to a material that is substantially non-toxic in the *in vivo* environment of its intended use, and that is not substantially rejected by the patient's physiological system (*i.e.*, is non-antigenic). This can be gauged by the ability of a material to pass the biocompatibility tests set forth in International Standards Organization (ISO) Standard No. 10993 and/or the U.S.

Pharmacopeia (USP) 23 and/or the U.S. Food and Drug Administration (FDA) blue book memorandum No. G95-1, entitled "Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation and Testing." Typically, these tests measure a material's toxicity, infectivity, pyrogenicity, irritation potential, reactivity, hemolytic activity, carcinogenicity and/or immunogenicity. A biocompatible structure or material, when introduced into a majority of patients, will not cause an undesirably adverse, long-lived or

escalating biological reaction or response, and is distinguished from a mild, transient inflammation which typically accompanies surgery or implantation of foreign objects into a living organism.

As used herein, the term "patient" means an animal (e.g., cow, horse,
5 sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit or guinea pig), preferably a mammal such as a non-primate or a primate (e.g., monkey or human), most preferably a human.

C-Jun N-terminal Kinase (JNK) Inhibitor Compounds

Preferred embodiments of the present invention provide local delivery of one or more JNK inhibitor compounds proximate to a site of treatment within a body vessel by a medical device. One or more JNK inhibitor compounds may be provided for release from the medical device.

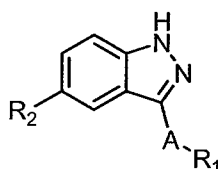
The JNK inhibitor compound(s) may, for example, be included as part of at least a portion of the base material of the medical device itself; be contained within a reservoir, a well or a groove; be within a carrier material deposited on at least a portion of the medical device, or as a separate layer deposited on at least a portion of the medical device (the layer may optionally be over coated with another layer) or on at least a portion of the medical device that has been coated with a primer layer for increased adhesion; or within the hollow walls of the device; or any combination of these. The JNK inhibitor compound may also be included in a separate carrier layer (or a multi-layered structure) that may be placed between elements of the medical device. For example, the separate layer may be placed between a stent and a graft material.

In certain embodiments, the release of the JNK inhibitor compound from the medical device depends, in part, upon the composition and configuration of the carrier material and/or the coating layer(s).

Illustrative JNK Inhibitor Compounds

As mentioned above, preferred embodiments of the present invention are directed to methods useful for treating or preventing an aortic aneurysm and/or aortic dissection, comprising implanting into a patient in need thereof a medical device (e.g., a stent comprising a therapeutically effective amount of a JNK Inhibitor). Illustrative JNK Inhibitors were previously described in U.S. Pub. No. 2005/0019366, disclosure of which is incorporated by reference in its entirety, and are set forth below. Examples of JNK inhibitors suitable for use in this invention are also provided below.

In another embodiment, the JNK inhibitor has the following structure (I):



(I)

5 wherein:

A is a direct bond, $-(CH_2)_a-$, $-(CH_2)_bCH=CH(CH_2)_c-$, or $-(CH_2)_bC\equiv C(CH_2)_c-$;

R_1 is aryl, heteroaryl or heterocycle fused to phenyl, each being optionally substituted with one to four substituents independently selected from R_3 ;

10 R_2 is $-R_3$, $-R_4$, $-(CH_2)_bC(=O)R_5$, $-(CH_2)_bC(=O)OR_5$, $-(CH_2)_bC(=O)NR_5R_6$, $-(CH_2)_bC(=O)NR_5(CH_2)_cC(=O)R_6$, $-(CH_2)_bNR_5C(=O)R_6$, $-(CH_2)_bNR_5C(=O)NR_6R_7$, $-(CH_2)_bNR_5R_6$, $-(CH_2)_bOR_5$, $-(CH_2)_bSO_dR_5$ or $-(CH_2)_bSO_2NR_5R_6$;

a is 1, 2, 3, 4, 5 or 6;

15 b and c are the same or different and at each occurrence independently selected from 0, 1, 2, 3 or 4;

d is at each occurrence 0, 1 or 2;

20 R_3 is at each occurrence independently halogen, hydroxy, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl, $-C(=O)OR_8$, $-OC(=O)R_8$, $-C(=O)NR_8R_9$, $-C(=O)NR_8OR_9$, $-SO_2NR_8R_9$, $-NR_8SO_2R_9$, $-CN$, $-NO_2$, $-NR_8R_9$, $-NR_8C(=O)R_9$, $-NR_8C(=O)(CH_2)_bOR_9$, $-NR_8C(=O)(CH_2)_bR_9$, $-O(CH_2)_bNR_8R_9$, or heterocycle fused to phenyl;

25 R_4 is alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl, each being optionally substituted with one to four substituents independently selected from R_3 , or R_4 is halogen or hydroxy;

R_5 , R_6 and R_7 are the same or different and at each occurrence independently hydrogen, alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl,

wherein each of R_5 , R_6 and R_7 are optionally substituted with one to four substituents independently selected from R_3 ; and

R_8 and R_9 are the same or different and at each occurrence independently hydrogen, alkyl, aryl, arylalkyl, heterocycle, or heterocycloalkyl, or R_8 and R_9 taken together with the atom or atoms to which they are bonded form a heterocycle, wherein each of R_8 , R_9 , and R_8 and R_9 taken together to form a heterocycle are optionally substituted with one to four substituents independently selected from R_3 .

In another embodiment, $-A-R_1$ is phenyl, optionally substituted with one to four substituents independently selected from halogen, alkoxy, $-NR_8C(=O)R_9$, $-C(=O)NR_8R_9$, and $-O(CH_2)_bNR_8R_9$, wherein b is 2 or 3 and wherein R_8 and R_9 are defined above.

In further embodiment, R_2 is $-R_4$, $-(CH_2)_bC(=O)R_5$, $-(CH_2)_bC(=O)OR_5$, $-(CH_2)_bC(=O)NR_5R_6$, $-(CH_2)_bC(=O)NR_5(CH_2)_cC(=O)R_6$, $-(CH_2)_bNR_5C(=O)R_6$, $-(CH_2)_bNR_5C(=O)NR_6R_7$, $-(CH_2)_bNR_5R_6$, $-(CH_2)_bOR_5$, $-(CH_2)_bSO_dR_5$ or $-(CH_2)_bSO_2NR_5R_6$, and b is an integer ranging from 0-4.

In another embodiment, R_2 is $-(CH_2)_bC(=O)NR_5R_6$, $-(CH_2)_bNR_5C(=O)R_6$, 3-triazolyl or 5-tetrazolyl, wherein b is 0 and wherein R_8 and R_9 are defined above.

In another embodiment, R_2 is 3-triazolyl or 5-tetrazolyl.

In another embodiment:

(a) $-A-R_1$ is phenyl, optionally substituted with one to four substituents independently selected from halogen, alkoxy, $-NR_8C(=O)R_9$, $-C(=O)NR_8R_9$, and $-O(CH_2)_bNR_8R_9$, wherein b is 2 or 3; and

(b) R_2 is $-(CH_2)_bC(=O)NR_5R_6$, $-(CH_2)_bNR_5C(=O)R_6$, 3-triazolyl or 5-tetrazolyl, wherein b is 0 and wherein R_8 and R_9 are defined above.

In another embodiment:

(a) $-A-R_1$ is phenyl, optionally substituted with one to four substituents independently selected from halogen, alkoxy, $-NR_8C(=O)R_9$, $-C(=O)NR_8R_9$, and $-O(CH_2)_bNR_8R_9$, wherein b is 2 or 3; and

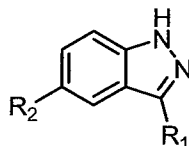
(b) R_2 is 3-triazolyl or 5-tetrazolyl.

In another embodiment, R_2 is R_4 , and R_4 is 3-triazolyl, optionally substituted at its 5-position with:

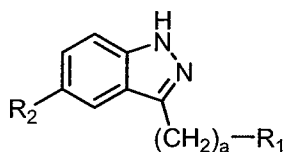
- (a) a C_1 - C_4 straight or branched chain alkyl group optionally substituted with a hydroxyl, methylamino, dimethylamino or 1-pyrrolidinyl group; or
 5 (b) a 2-pyrrolidinyl group.

In another embodiment, R_2 is R_4 , and R_4 is 3-triazolyl, optionally substituted at its 5-position with: methyl, n-propyl, isopropyl, 1-hydroxyethyl, 3-hydroxypropyl, methylaminomethyl, dimethylaminomethyl, 1-(dimethylamino)ethyl, 1-pyrrolidinylmethyl or 2-pyrrolidinyl.

- 10 In another embodiment, the compounds of structure (I) have structure (IA) when A is a direct bond, or have structure (IB) when A is $-(CH_2)_a-$:

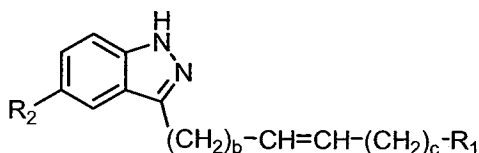


(IA)

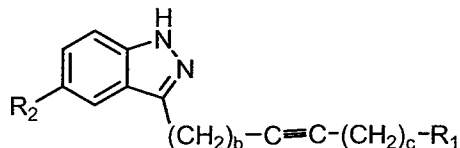


(IB)

15 In other embodiments, the compounds of structure (I) have structure (IC) when A is a $-(CH_2)_bCH=CH(CH_2)_c-$, and have structure (ID) when A is $-(CH_2)_bC\equiv C(CH_2)_c-$:

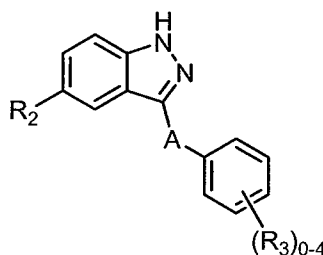


(IC)



(ID)

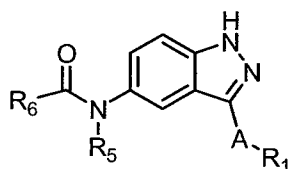
In further embodiments of this invention, R_1 of structure (I) is aryl or substituted aryl, such as phenyl or substituted phenyl as represented by the following structure (IE):



5

(IE)

In another embodiment, R_2 of structure (I) is $-(CH_2)_bNR_4(C=O)R_5$. In one aspect of this embodiment, $b=0$ and the compounds have the following structure (IF):



10

(IF)

Representative R_2 groups of the compounds of structure (I) include alkyl (such as methyl and ethyl), halo (such as chloro and fluoro), haloalkyl (such as trifluoromethyl), hydroxy, alkoxy (such as methoxy and ethoxy), amino, arylalkyloxy (such as benzyloxy), mono- or di-alkylamine (such as $-NHCH_3$, $-N(CH_3)_2$ and $-NHCH_2CH_3$), $-NHC(=O)R_6$ wherein R_6 is a substituted or unsubstituted phenyl or heteroaryl (such as phenyl or heteroaryl substituted with hydroxy, carboxy, amino, ester, alkoxy, alkyl, aryl, haloalkyl, halo, $-CONH_2$ and $-CONH$ alkyl), $-NH$ (heteroarylalkyl) (such as $-NHCH_2$ (3-pyridyl), $-NHCH_2$ (4-pyridyl)), heteroaryl (such as pyrazolo, triazolo and tetrazolo), $-C(=O)NHR_6$ wherein R_6 is hydrogen, alkyl, or as defined above (such as $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)NH$ (H-carboxyphenyl), $-C(=O)N(CH_3)_2$), arylalkenyl (such as phenylvinyl, 3-nitrophenylvinyl, 4-carboxyphenylvinyl), heteroarylalkenyl (such as 2-pyridylvinyl, 4-pyridylvinyl).

15

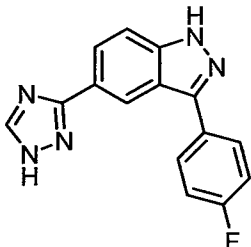
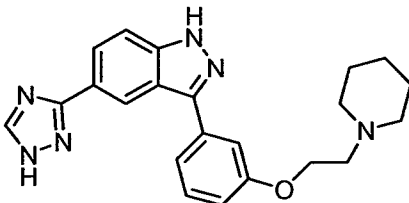
20

Representative R_3 groups of the compounds of structure (I) include halogen (such as chloro and fluoro), alkyl (such as methyl, ethyl and isopropyl), haloalkyl (such as trifluoromethyl), hydroxy, alkoxy (such as methoxy, ethoxy, n-propyloxy and isobutyloxy), amino, mono- or di-alkylamino (such as dimethylamine), aryl (such as phenyl), carboxy, nitro, cyano, sulfinylalkyl (such as methylsulfinyl), sulfonylalkyl (such as methylsulfonyl), sulfonamidoalkyl (such as $-\text{NHSO}_2\text{CH}_3$), $-\text{NR}_8\text{C}(=\text{O})(\text{CH}_2)_b\text{OR}_9$ (such as $\text{NHC}(=\text{O})\text{CH}_2\text{OCH}_3$), $\text{NHC}(=\text{O})\text{R}_9$ (such as $-\text{NHC}(=\text{O})\text{CH}_3$, $-\text{NHC}(=\text{O})\text{CH}_2\text{C}_6\text{H}_5$, $-\text{NHC}(=\text{O})(2\text{-furyl})$), and $-\text{O}(\text{CH}_2)_b\text{NR}_8\text{R}_9$ (such as $-\text{O}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$).

The compounds of structure (I) can be made using organic synthesis techniques known to those skilled in the art, as well as by the methods described in International Publication No. WO 02/10137 (particularly in Examples 1-430, at page 35, line 1 to page 396, line 12), published Feb. 7, 2002, which is incorporated herein by reference in its entirety. Further, specific examples of these compounds are found in this publication.

Illustrative examples of JNK Inhibitors of structure (I) are shown in Table A:

Table A:

Compound	Chemical Name	Structure
1	3-(4-fluorophenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole	
2	3-(3-(2-(piperidin-1-yl)ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole	

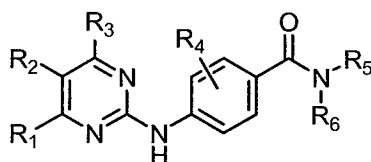
3	3-(4-fluorophenyl)-1H-indazole-5-carboxylic acid (3-morpholin-4-yl-propyl)-amide	
4	3-(3-(3-(piperidin-1-yl)propionylamino)phenyl)-1H-indazole-5-carboxylic acid amide	
5	3-(benzo[1,3]dioxol-5-yl)-5-(2H-tetrazol-5-yl)-1H-indazole	
6	3-(4-fluorophenyl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-indazole	
7	N-tert-buty-3-(5-(1H-1,2,4-triazol-3-yl)-1H-indazol-3-yl)-benzamide	
8	3-(3-(2-morpholin-4-ylethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole	

9	Dimethyl-(2-(4-(5-(1H-1,2,4-triazol-3-yl)-1H-indazol-3-yl)-phenoxy)-ethyl)-amine	
10	5-(5(1,1-dimethyl-propyl)-1H-[1,2,4]triazol-3-yl)-3-(4-fluorophenyl)-1H-indazole	
11	3-(4-fluorophenyl)-5-(5-((pyrrolidin-1-yl)methyl)-1H-1,2,4-triazol-3-yl)-1H-indazole	
12	3-(6-methoxy-naphthalen-2-yl)-5-(5-(pyrrolidin-1-ylmethyl)-1H-[1,2,4]-triazol-3-yl)-1H-indazole	
13	3-(4-fluorophenyl)-1H-indazole-5-carboxylic acid amide	

and pharmaceutically acceptable salts thereof.

In another embodiment, the JNK inhibitor has the following structure (II):

34



(II)

wherein:

R₁ is aryl or heteroaryl optionally substituted with one to four substituents

5 independently selected from R₇;

R₂ is hydrogen;

R₃ is hydrogen or lower alkyl;

R₄ represents one to four optional substituents, wherein each substituent
is the same or different and independently selected from halogen, hydroxy, lower
10 alkyl and lower alkoxy;

R₅ and R₆ are the same or different and independently —R₈, —

(CH₂)_aC(=O)R₉, —(CH₂)_aC(=O)OR₉, —(CH₂)_aC(=O)NR₉R₁₀, —

(CH₂)_aC(=O)NR₉(CH₂)_bC(=O)R₁₀, —(CH₂)_aNR₉C(=O)R₁₀,

(CH₂)_aNR₁₁C(=O)NR₉R₁₀, —(CH₂)_aNR₉R₁₀, —(CH₂)_aOR₉, —(CH₂)_aSO_cR₉ or —

15 (CH₂)_aSO₂NR₉R₁₀;

or R₅ and R₆ taken together with the nitrogen atom to which they are
attached to form a heterocycle or substituted heterocycle;

R₇ is at each occurrence independently halogen, hydroxy, cyano, nitro,
carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl,

20 hydroxyalkyl, aryl, arylalkyl, heterocycle, substituted heterocycle,

heterocycloalkyl, —C(=O)OR₈, —OC(=O)R₈, —C(=O)NR₈R₉, —C(=O)NR₈OR₉,

—SO_cR₈, —SO_cNR₈R₉, —NR₈SO_cR₉, —NR₈R₉, —NR₈C(=O)R₉, —

NR₈C(=O)(CH₂)_bOR₉, —NR₈C(=O)(CH₂)_bR₉, —O(CH₂)_bNR₈R₉, or heterocycle

fused to phenyl;

25 R₈, R₉, R₁₀ and R₁₁ are the same or different and at each occurrence

independently hydrogen, alkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl;

or R₈ and R₉ taken together with the atom or atoms to which they are attached to
form a heterocycle;

a and b are the same or different and at each occurrence independently selected from 0, 1, 2, 3 or 4; and

c is at each occurrence 0, 1 or 2.

In one embodiment, R_1 is a substituted or unsubstituted aryl or heteroaryl.

- 5 When R_1 is substituted, it is substituted with one or more substituents defined below. In one embodiment, when substituted, R_1 is substituted with a halogen, — SO_2R_8 or — $SO_2NR_8R_9$.

In another embodiment, R_1 is substituted or unsubstituted aryl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinolinyl, pyrrolyl, indolyl, oxazolyl, 10 benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolinyl, phthalazinyl or quinazolinyl.

In another embodiment R_1 is substituted or unsubstituted aryl or heteroaryl. When R_1 is substituted, it is substituted with one or more substituents 15 defined below. In one embodiment, when substituted, R_1 is substituted with a halogen, — SO_2R_8 or — $SO_2R_8R_9$.

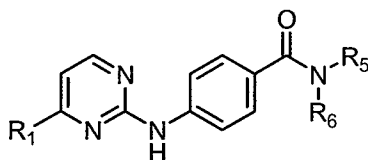
In another embodiment, R_1 is substituted or unsubstituted aryl, preferably phenyl. When R_1 is a substituted aryl, the substituents are defined below. In one 20 embodiment, when substituted, R_1 is substituted with a halogen, — SO_2R_8 or — $SO_2NR_8R_9$.

In another embodiment, R_5 and R_6 , taken together with the nitrogen atom to which they are attached form a substituted or unsubstituted nitrogen-containing non-aromatic heterocycle, in one embodiment, piperazinyl, piperidinyl or morpholinyl.

25 When R_5 and R_6 , taken together with the nitrogen atom to which they are attached form substituted piperazinyl, piperadinyl or morpholinyl, the piperazinyl, piperadinyl or morpholinyl is substituted with one or more substituents defined below. In one embodiment, when substituted, the substituent is alkyl, amino, alkylamino, alkoxyalkyl, acyl, pyrrolidinyl or piperidinyl.

30 In one embodiment, R_3 is hydrogen and R_4 is not present, and the JNK inhibitor has the following structure (IIA):

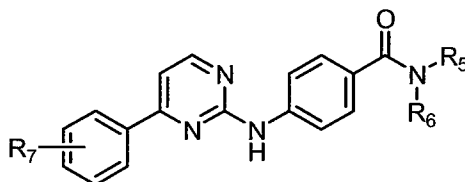
36



(IIA)

and pharmaceutically acceptable salts thereof.

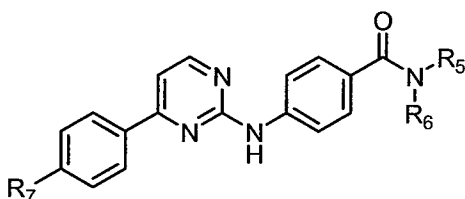
In a more specific embodiment, R₁ is phenyl optionally substituted with R₇,
5 and having the following structure (IIB):



(IIB)

and pharmaceutically acceptable salts thereof.

In still a further embodiment, R₇ is at the para position of the phenyl group
10 relative to the pyrimidine, as represented by the following structure (IIC):



(IIC)

and pharmaceutically acceptable salts thereof.

The JNK inhibitors of structure (II) can be made using organic synthesis
15 techniques known to those skilled in the art, as well as by the methods described
in International Publication No. WO 02/46170 (particularly Examples 1-27 at page
23, line 5 to page 183, line 25), published Jun. 13, 2002, which is hereby
incorporated by reference in its entirety. Further, specific examples of these
compounds are found in the publication.

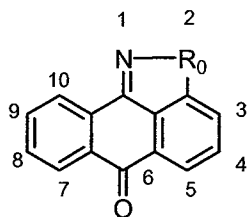
20 Illustrative examples of JNK inhibitors of structure (II) are shown in Table
B:

Table B.

Compound	Chemical name	Structure
14	4-(4-(4-chlorophenyl)pyrimidin-2-ylamino)benzamide	
15	4-(4-(4-chlorophenyl)pyrimidin-2-ylamino)-N,N-dimethylbenzamide	
16	4-(4-(4-chlorophenyl)pyrimidin-2-ylamino)-N-(3-(piperidin-1-yl)propyl)benzamide	
17	(4-(4-(4-chlorophenyl)pyrimidin-2-ylamino)phenyl)(piperazin-1-yl)methanone	
18	1-(4-(4-(4-(4-chlorophenyl)pyrimidin-2-ylamino)-benzoyl)-piperazin-1-yl)-ethanone	
19	1-(4-(4-(4-(4-(3-hydroxypropylsulfanyl)-phenyl)-pyrimidin-2-ylamino)-benzoyl)-piperazin-1-yl)-ethanone	
20	(4-(4-(4-chloro-phenyl)-pyrimidin-2-ylamino)-phenyl)-(4-(pyrrolidin-1-yl)-piperidin-1-yl)-methanone	

and pharmaceutically acceptable salts thereof.

In another embodiment, the JNK inhibitor has the following structure (III):

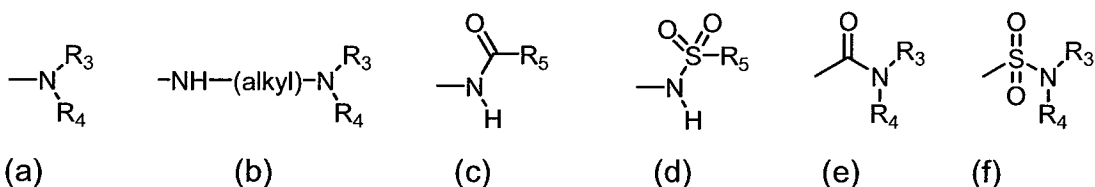


(III)

5 wherein R_0 is $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, NH or $-\text{CH}_2-$;

the compound of structure (II) being: (i) unsubstituted, (ii) monosubstituted and having a first substituent, or (iii) disubstituted and having a first substituent and a second substituent;

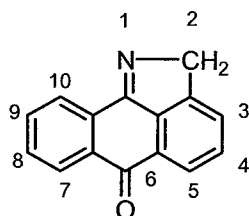
10 the first or second substituent, when present, is at the 3, 4, 5, 7, 8, 9, or 10 position, wherein the first and second substituent, when present, are independently alkyl, hydroxy, halogen, nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxy, carbonyl, alkoxy, aryl, aryloxy, arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono-alkylaminoalkoxy, di-alkylaminoalkoxy, or a group represented by structure (a), (b), (c), (d), (e), or (f):



20 wherein R_3 and R_4 are taken together and represent alkylidene or a heteroatom-containing cyclic alkylidene or R_3 and R_4 are independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl; and

25 R_5 is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, amino, mono-alkylamino, di-alkylamino, arylamino, arylalkylamino, cycloalkylamino, cycloalkylalkylamino, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl.

In another embodiment, the JNK inhibitor has the following structure (IIIA):



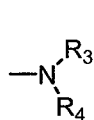
(IIIA)

2H-Dibenzo[cd,g]indol-6-one

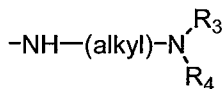
- 5 being: (i) unsubstituted, (ii) monosubstituted and having a first substituent, or (iii) disubstituted and having a first substituent and a second substituent;

the first or second substituent, when present, is at the 3, 4, 5, 7, 8, 9, or 10 position;

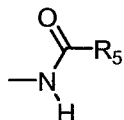
- 10 wherein the first and second substituent, when present, are independently alkyl, hydroxy, halogen, nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxycarbonyl, alkoxy, aryl, aryloxy, arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono-alkylaminoalkoxy, di-alkylaminoalkoxy, or a group represented by structure (a), (b), (c), (d), (e), or (f):



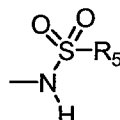
(a)



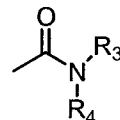
(b)



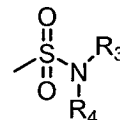
(c)



(d)



(e)



(f)

- 15 wherein R_3 and R_4 are taken together and represent alkylidene or a heteroatom-containing cyclic alkylidene or R_3 and R_4 are independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl; and

20 R_5 is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy, alkoxyalkyl, alkoxycarbonylalkyl, amino, mono-alkylamino, di-alkylamino, arylamino, arylalkylamino, cycloalkylamino, cycloalkylalkylamino, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl.

A subclass of the compounds of structure (IIIA) is that wherein the first or second substituent is present at the 5, 7, or 9 position. In one embodiment, the first or second substituent is present at the 5 or 7 position.

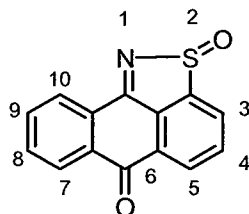
A second subclass of compounds of structure (IIIA) is that wherein the first or second substituent is present at the 5, 7, or 9 position;

the first or second substituent is independently alkoxy, aryloxy, aminoalkyl, mono-alkylaminoalkyl, di-alkylaminoalkyl, or a group represented by the structure (a), (c), (d), (e), or (f);

R_3 and R_4 are independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, or cycloalkylalkyl; and

R_5 is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, or cycloalkylalkyl.

In another embodiment, the JNK Inhibitor has the following structure (IIIB):



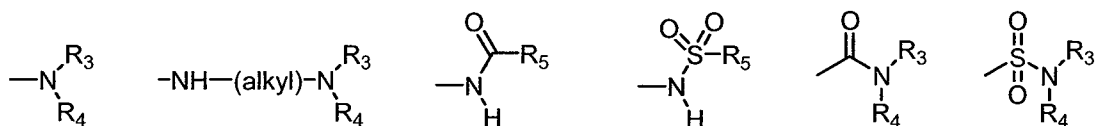
(IIIB)

2-Oxo-2H2I4-anthra[9,1-cd]isothiazol-6-one (Compound 21)

being (i) unsubstituted, (ii) monosubstituted and having a first substituent, or (ii) disubstituted and having a first substituent and a second substituent;

the first or second substituent, when present, is at the 3, 4, 5, 7, 8, 9, or 10 position;

wherein the first and second substituent, when present, are independently alkyl, halogen, hydroxy, nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono-alkylaminoalkoxy, di-alkylaminoalkoxy, or a group represented by structure (a), (b) (c), (d), (e), or (f):



(a) (b) (c) (d) (e) (f)

wherein R_3 and R_4 are taken together and represent alkylidene or a heteroatom-containing cyclic alkylidene or R_3 and R_4 are independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl; and

R_5 is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy, alkoxyalkyl, alkoxycarbonylalkyl, amino, mono-alkylamino, di-alkylamino, arylamino, arylalkylamino, cycloalkylamino, cycloalkylalkylamino, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl.

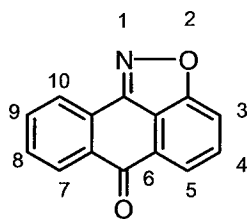
A subclass of the compounds of structure (IIIB) is that wherein the first or second substituent is present at the 5, 7, or 9 position. In one embodiment, the first or second substituent is present at the 5 or 7 position.

A second subclass of the compounds of structure (IIIB) is that wherein the first or second substituent is independently alkoxy, aryloxy, or a group represented by the structure (a), (c), (d), (e), or (f);

R_3 and R_4 are independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, or cycloalkylalkyl; and

R_5 is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, or cycloalkylalkyl.

In another embodiment, the JNK inhibitor has the following structure (IIIC):



(IIIC)

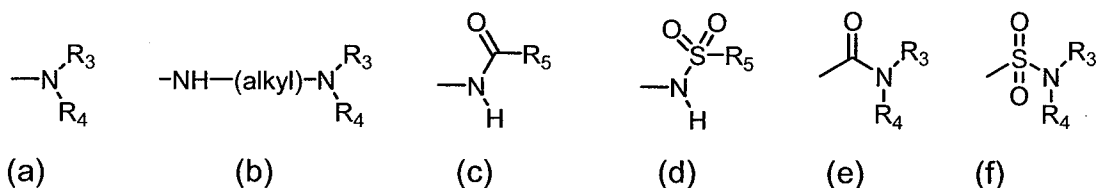
2-Oxa-1-aza-aceanthrylen-6-one (Compound 22)

being (i) monosubstituted and having a first substituent or (ii) disubstituted and having a first substituent and a second substituent;

the first or second substituent, when present, is at the 3, 4, 5, 7, 8, 9, or 10 position;

wherein the first and second substituent, when present, are independently alkyl, halogen, hydroxy, nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono-alkylaminoalkoxy, di-

5 alkylaminoalkoxy, or a group represented by structure (a), (b), (c) (d), (e), or (f):



wherein R_3 and R_4 are taken together and represent alkylidene or a
 10 heteroatom-containing cyclic alkylidene or R_3 and R_4 are independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl; and

R_5 is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy, alkoxyalkyl, alkoxyalkoxyalkyl, amino, mono-alkylamino, di-alkylamino,
 15 arylamino, arylalkylamino, cycloalkylamino, cycloalkylalkylamino, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl.

A subclass of the compounds of structure (IIIC) is that wherein the first or second substituent is present at the 5, 7, or 9 position. In one embodiment, the first or second substituent is present at the 5 or 7 position.

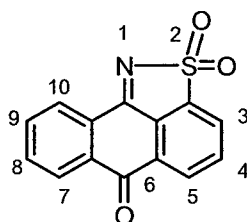
20 A second subclass of the compounds of structure (IIIC) is that wherein the first or second substituent is independently alkoxy, aryloxy, aminoalkyl, mono-alkylaminoalkyl, di-alkylaminoalkyl, or a group represented by the structure (a), (c), (d), (e), or (f);

R_3 and R_4 are independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, or
 25 cycloalkylalkyl; and

R_5 is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, or cycloalkylalkyl.

In another embodiment, the JNK inhibitor has the following structure (IIID):

43



(IIID)

2,2-Dioxo-2Hl⁶-anthra[9,1-cd]
isothiazol-6-one (Compound 23)

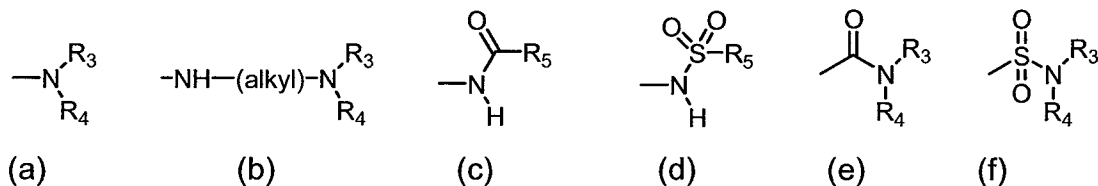
5

being (i) monosubstituted and having a first substituent present at the 5, 7, or 9 position, (ii) disubstituted and having a first substituent present at the 5 position and a second substituent present at the 7 position, (iii) disubstituted and having a first substituent present at the 5 position and a second substituent present at the 9 position, or (iv) disubstituted and having a first substituent present at the 7 position and a second substituent present at the 9 position;

10

wherein the first and second substituent, when present, are independently alkyl, halogen, hydroxy, nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxycarbonyl, alkoxy, aryl, aryloxy, arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono-alkylaminoalkoxy, di-alkylaminoalkoxy, or a group represented by structure (a), (b), (c), (d), (e), or (f):

15



20

wherein R₃ and R₄ are taken together and represent alkylidene or a heteroatom-containing cyclic alkylidene or R₃ and R₄ are independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl; and

25

R₅ is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy, alkoxyalkyl, alkoxycarbonylalkyl, amino, mono-alkylamino, di-alkylamino,

arylamino, arylalkylamino, cycloalkylamino, cycloalkylalkylamino, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl.

A subclass of the compounds of structure (IIID) is that wherein the first or second substituent is present at the 5 or 7 position.

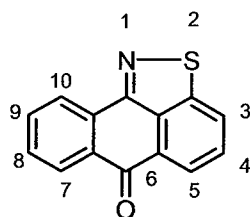
- 5 A second subclass of the compounds of structure (IIID) is that wherein the first or second substituent is independently alkyl, trifluoromethyl, sulfonyl, carboxyl, alkoxycarbonyl, alkoxy, aryl, aryloxy, arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono-alkylaminoalkoxy, di-alkylaminoalkoxy, or a group represented by structure (a),
 10 (c), (d), (e), or (f).

Another subclass of the compounds of structure (IID) is that wherein the first and second substituent are independently alkoxy, aryloxy, or a group represented by the structure (a), (c), (d), (e), or (f);

- R_3 and R_4 are independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, or
 15 cycloalkylalkyl; and

R_5 is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, alkoxycarbonyl, or cycloalkylalkyl.

In another embodiment, the JNK Inhibitor has the following structure (IIIE):

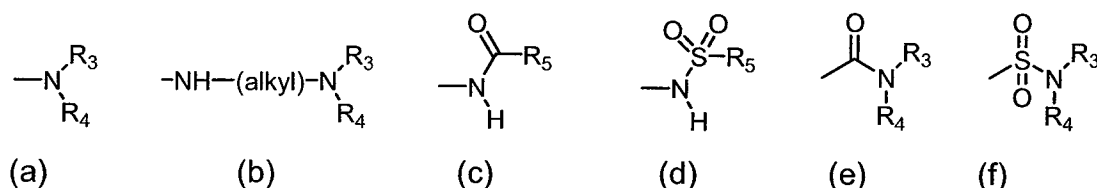


(IIIE)

Anthra[9,1-cd]isothiazol-6-one (Compound 24)

- being (i) monosubstituted and having a first substituent present at the 5, 7, or 9 position, (ii) disubstituted and having a first substituent present at the 5 position and a second substituent present at the 9 position, (iii) disubstituted and
 25 having a first substituent present at the 7 position and a second substituent present at the 9 position, or (iv) disubstituted and having a first substituent present at the 5 position and a second substituent present at the 7 position;

wherein the first and second substituent, when present, are independently alkyl, halogen, hydroxy, nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono-alkylaminoalkoxy, di-alkylaminoalkoxy, or a group represented by structure (a), (b), (c), (d), (e), or (f):



wherein R₃ and R₄ are taken together and represent alkylidene or a heteroatom-containing cyclic alkylidene or R₃ and R₄ are independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl; and

R₅ is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy, alkoxyalkyl, alkoxyalkoxyalkyl, amino, mono-alkylamino, di-alkylamino, arylamino, arylalkylamino, cycloalkylamino, cycloalkylalkylamino, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl.

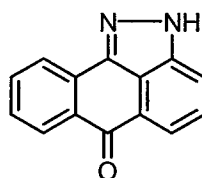
A subclass of the compounds of structure (IIIE) is that wherein the first or second substituent is present at the 5 or 7 position.

A second subclass of the compounds of structure (IIIE) is that wherein the compound of structure (IIIE) is disubstituted and at least one of the substituents is a group represented by the structure (d) or (f).

Another subclass of the compounds of structure (IIIE) is that wherein the compounds are monosubstituted. Yet another subclass of compounds is that wherein the compounds are monosubstituted at the 5 or 7 position with a group represented by the structure (e) or (f).

Preferably, the JNK inhibitor is a compound, anthra[1,9-cd]pyrazol-6(2H)-one (SP600125; A.G. Scientific, Inc.) (Han et al., "c-Jun N-terminal Kinase is Required for Metalloproteinase Expression and Joint Destruction in Inflammatory Arthritis," *The Journal of Clinical Investigation* 2001, 108(1):73-81) of formula IIIF:

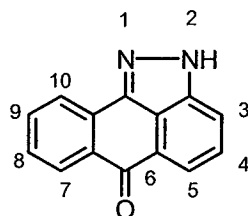
46



SP600125

Compound 25

In another embodiment, the JNK inhibitor has the following structure (IIIG):



(IIIG)

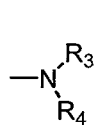
2H-Dibenzo[cd,g]indazol-6-one

(Compound 26)

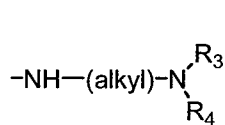
being (i) unsubstituted, (ii) monosubstituted and having a first substituent,
or (iii) disubstituted and having a first substituent and a second substituent;

the first or second substituent, when present, is at the 3, 4, 5, 7, 8, 9, or 10 position;

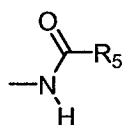
wherein the first and second substituent, when present, are independently alkyl, hydroxy, halogen, nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono-alkylaminoalkoxy, di-alkylaminoalkoxy, or a group represented by structure (a), (b), (c), (d), (e), or (f):



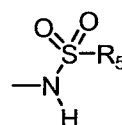
(a)



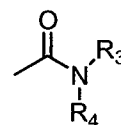
(b)



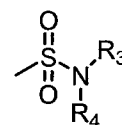
(c)



(d)



(e)



(f)

wherein R₃ and R₄ are taken together and represent alkylidene or a heteroatom-containing cyclic alkylidene or R₃ and R₄ are independently hydrogen,

alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl; and

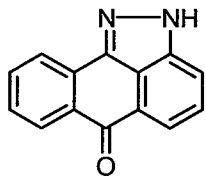
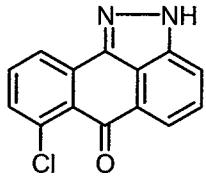
- R_5 is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy, alkoxyalkyl, alkoxycarbonylalkyl, amino, mono-alkylamino, di-alkylamino, arylamino, arylalkylamino, cycloalkylamino, cycloalkylalkylamino, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl.

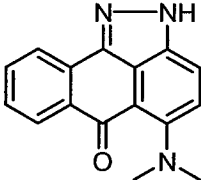
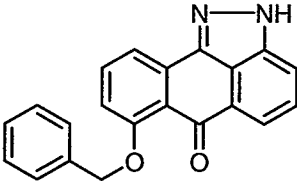
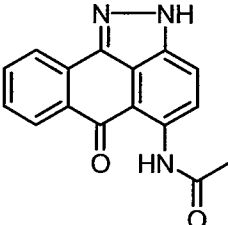
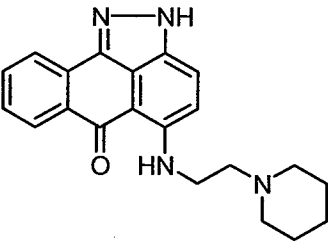
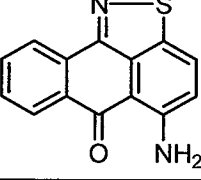
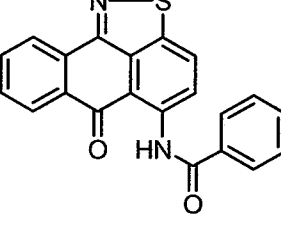
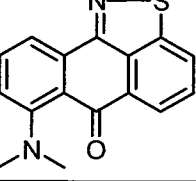
In one embodiment, the compound of structure (IIIG), or a pharmaceutically acceptable salt thereof is unsubstituted at the 3, 4, 5, 7, 8, 9, or 10 position.

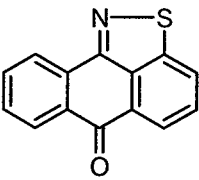
- The JNK inhibitors of structure (III) can be made using organic synthesis techniques known to those skilled in the art, as well as by the methods described in International Publication No. WO 01/12609 (particularly Examples 1-7 at page 24, line 6 to page 49, line 16), published Feb. 22, 2001, as well as International Publication No. WO 02/066450 (particularly compounds AA-HG at pages 59-108), published Aug. 29, 2002, each of which is hereby incorporated by reference in its entirety. Further, specific examples of these compounds can be found in the publications.

Illustrative examples of JNK inhibitors of structure (III) are shown in Table C:

Table C.

Compound	Name	Structure
27	2H-dibenzo[cd,g]indazol-6-one	
28	7-chloro-2H-dibenzo[cd,g]indazol-6-one	

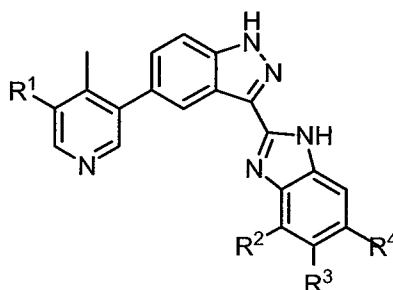
29	5-dimethylamino-2H-dibenzo[cd,g]indazol-6-one	
30	7-benzyloxy-H-dibenzo[cd,g]indazol-6-one	
31	N-(6-oxo-2,6-dihydro-dibenzo[cd,g]indazol-6-one	
32	5-(2-piperdin-1-yl-ethylamino)-2H-dibenzo[cd,g]indazol-6-one	
33	5-amino-anthra[9,1-cd]isothiazol-6-one	
34	N-(6-oxo-6H-anthra[9,1-cd]isothiazol-5-yl)-benzamide	
35	7-dimethylamine-anthra[9,1-cd]isothiazol-6-one	

36	2-oxa-1-azo-aceanthrylen-6-one	
----	--------------------------------	--

and pharmaceutically acceptable salts thereof.

Other examples of JNK inhibitors include 3,5 disubstituted indazole compounds, which were previously described in U.S. Pat. Nos. 7,008,953 and 6,555,539, disclosures of which are incorporated by reference in their entirety.

5 Further JNK inhibitor may be a compound of structure IV:



(IV)

wherein R^1 , R^2 , R^3 and R^4 are selected from the group consisting of H, halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, hydroxy, C_{1-6} alkoxy, C_{1-10} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-C(O)R^5$, $-C(O)OR^5$, $-OC(O)R^5$, $-NR^5C(O)R^6$, $-C(O)NR^5R^6$, $-(CR^5R^6)NR^7R^8$, $-CR^5R^6NR^7R^8$, $-NR^5OR^6$, $-SO_2NR^5R^6$, $-S(O)_j(C_{1-6} \text{ alkyl})$ wherein j is an integer from 0 to 2, $-(CR^5R^6)_t(C_{6-10} \text{ aryl})$, $-(CR^5R^6)_t(C_{3-10} \text{ cycloalkyl})$, $-(CR^5R^6)_t(4-10 \text{ membered heterocyclic})$, $-(CR^5R^6)_qC(O)(CR^7R^8)_t(C_{6-10} \text{ aryl})$, $-(CR^5R^6)_qC(O)(CR^7R^8)_t(C_{3-10} \text{ cycloalkyl})$, $-(CR^5R^6)_qC(O)(CR^7R^8)_t(4-10 \text{ membered heterocyclic})$, $-(CR^5R^6)_tO(CR^7R^8)_q(C_{6-10} \text{ aryl})$, $-(CR^5R^6)_tO(CR^7R^8)_q(C_{3-10} \text{ cycloalkyl})$, $-(CR^5R^6)_tO(CR^7R^8)_q(4-10 \text{ membered heterocyclic})$, $-(CR^5R^6)_qSO_2(CR^7R^8)_t(C_{6-10} \text{ aryl})$, $-(CR^5R^6)_qSO_2(CR^7R^8)_t(C_{3-10} \text{ cycloalkyl})$ and $-(CR^5R^6)_qSO_2(CR^7R^8)_t(4-10 \text{ membered heterocyclic})$, wherein q and t are each independently an integer from 0 to 5, 1 or 2 ring carbon atoms of the cycloalkyl or heterocyclic moieties of the foregoing R^1 , R^2 , R^3 or R^4 groups are optionally substituted with an oxo ($=O$) moiety, each R^5 , R^6 , R^7 and R^8 is independently selected from H, C_{1-6} alkyl; and, wherein R^1 , R^2 , R^3 and R^4 are not H at the same time.

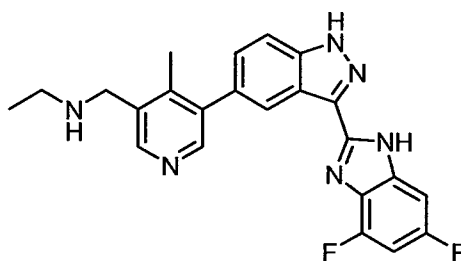
In one embodiment R^1 is $-(CR^5R^6)NR^7R^8$, and R^2 , R^3 and R^4 are independently selected from H or F.

In one embodiment R^1 is ethylaminomethyl, R^3 is H, and R^2 and R^4 are F.

In another embodiment R^1 is ethylaminomethyl, R^2 and R^4 are H, and R^3 is

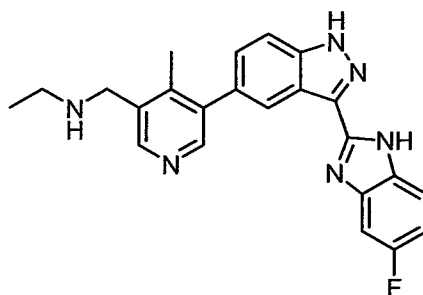
5 F.

In a further embodiment, the JNK inhibitor may selected from compounds 37 and 38 shown below:



Compound 37

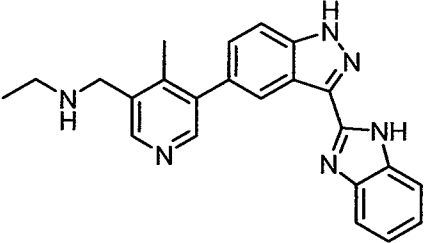
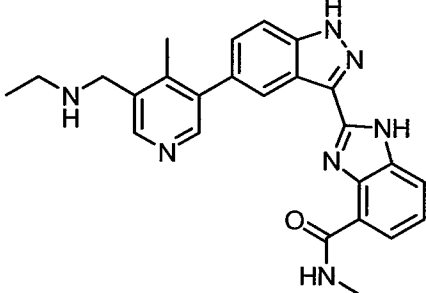
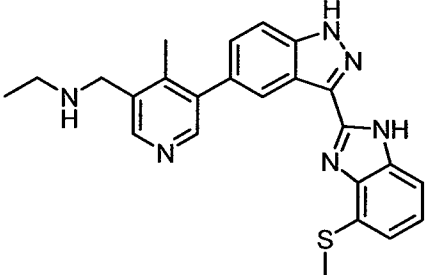
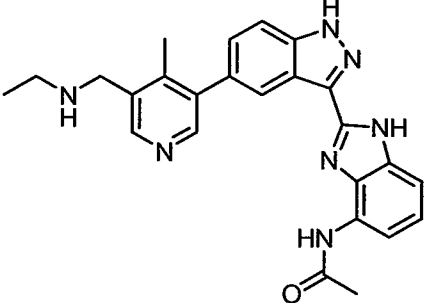
10



Compound 38

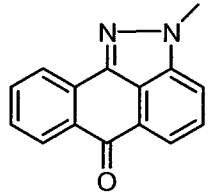
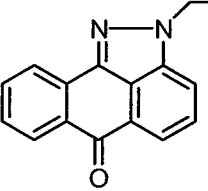
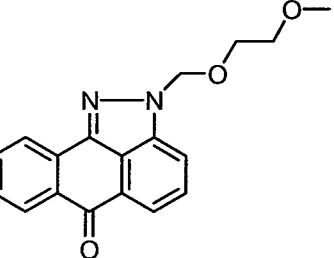
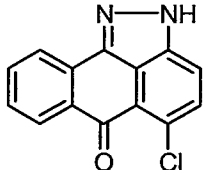
Additional examples of 3,5 disubstituted indazole compounds are shown in Table D.

Table D.

Compound	Structure
39	
40	
41	
42	

Further examples of JNK inhibitors include compounds in Table E
 (Bennett B.L., et al., "SP600125, an anthrapyrazolone inhibitor of Jun N-terminal
 5 kinase" *PNAS* 98(24):13681-13686 (2001));

Table E.

Compound	Structure
43	
44	
45	
46	

Other JNK inhibitors include, but are not limited to, those disclosed in International Publication No. WO 00/39101, (particularly at page 2, line 10 to page 6, line 12); International Publication No. WO 01/14375 (particularly at page 2, line 4 to page 4, line 4); International Publication No. WO 00/56738 (particularly at page 3, line 25 to page 6, line 13); International Publication No. WO 01/27089 (particularly at page 3, line 7 to page 5, line 29); International Publication No. WO 00/12468 (particularly at page 2, line 10 to page 4, line 14); European Patent Publication 1 110 957 (particularly at page 19, line 52 to page 21, line 9); International Publication No. WO 00/75118 (particularly at page 8, line 10 to page 11, line 26); International Publication No. WO 01/12621 (particularly at page 8, line 10 to page 10, line 7); International Publication No. WO 00/64872 (particularly at page 9, line 1 to page, 106, line 2); International Publication No.

WO 01/23378 (particularly at page 90, line 1 to page 91, line 11); International Publication No. WO 02/16359 (particularly at page 163, line 1 to page 164, line 25); U.S. Pat. No. 6,288,089 (particularly at column 22, line 25 to column 25, line 35); U.S. Pat. No. 6,307,056 (particularly at column 63, line 29 to column 66, line 12); International Publication No. WO 00/35921 (particularly at page 23, line 5 to page 26, line 14); International Publication No. WO 01/91749 (particularly at page 29, lines 1-22); International Publication No. WO 01/56993 (particularly in at page 43 to page 45); and International Publication No. WO 01/58448 (particularly in at page 39), each of which is incorporated by reference herein in its entirety.

- 10 In addition, JNK inhibitors include commercially available JNK inhibitors, including (a) JNK Inhibitor 1 (L-stereoisomer) (SEQ ID NO: 1; GRKKRRQRRR-PP-RPKRPTTLNLFQVPRSQD-amide; Alexis Biochemicals, San Diego, CA); (b) JNK Inhibitor I, (L)-Form ((L)-HIV-TAT₄₈₋₅₇-PP-JBD₂₀; ((L)-JNKI1; c-Jun NH₂-terminal kinase; SEQ ID NO 2: H-
- 15 GRKKRRQRRRPPRPKRPTTLNLFQVPRSQDT-NH₂; SAPK Inhibitor I; from Calbiochem); (c) JNK Inhibitor II (SP600125; Anthra[1,9-*cd*]pyrazol-6(2*H*)-one; 1,9-pyrazoloanthrone; SAPK Inhibitor II; from Calbiochem or Biosource); (d) JNK Inhibitor III (SEQ ID NO: 3: Ac-YGRKKRRQRRR-gaba-ILKQSM TNLNADPVGSLKPHLRAKN-NH₂; HIV- TAT₄₇₋₅₇-gaba-c-Jun δ ₃₃₋₅₇; SAPK
- 20 Inhibitor III; Calbiochem); (e) JNK Inhibitor V (AS601245; 1,3-Benzothiazol-2-yl-(2-((2-(3-pyridinyl)ethyl)amino)-4-pyrimidinyl)acetonitrile; SAPK Inhibitor V; from Calbiochem or AXXORA Platform) (Carboni S., et al., "AS601245 (1,3-Benzothiazol-2-yl (2-[[2-(3-pyridinyl) ethyl] amino}-4 pyrimidinyl) Acetonitrile): A c-Jun NH₂-Terminal Protein Kinase Inhibitor with Neuroprotective Properties" *J Pharm Exp Therap* 310(1):25-31 (2004)) and other benzothiazole acetonitrile derivatives; (f) JNK Inhibitor VI, TI-JIP₁₅₃₋₁₆₃ (SEQ ID NO: 4: H₂N-RPKRPTTLNLF-NH₂; Truncated inhibitor based on JNK-Interacting Protein 1; Calbiochem); (g) JNK Inhibitor VII, TAT-TI-JIP₁₅₃₋₁₆₃ (SEQ ID NO: 5: H₂N-YGRKKRRQRRR-RPKRPTTLNLF-NH₂; TAT₃₈₋₄₈-Truncated Inhibitor based on
- 30 JNK-Interacting Protein 1; Calbiochem); (h) SB203580 (4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)1*H*-imidazole; Calbiochem); (i) Aloisine A (7-*n*-

Butyl-6-(4-hydroxyphenyl)[5H]pyrrolo[2,3-b]pyrazine; Calbiochem); (j) 4-Hydroxynoneal (HNE; 4-hydroxy-2-nonenal; Calbiochem); (k) PD98059 (2'-amino-3'-methoxyflavone; from Biosource); (l) ALX-159-600-R100 and ALX-159-600-R200 (SEQ ID NO: 6: GRKKRRQRRR-PP-RPKRPTTLNLFQVPRSQD-
 5 amide; from AXXORA Platform).

Additional examples of JNK inhibitors include: CEP1347 (K252a derivative; from Aegera Therapeutics, Inc.); peptide: TI-JIP=RPKRPTTLNLF (SEQ ID NO: 7; from Crystal Genomics;); Drug-2193 (from Crystal Genomics); Kinase interaction motif sequence, (K/R)₂₋₃-X₁₋₆-(L/I)-X-(L/I) (Barr R.K, et al., "The Critical
 10 Features and the Mechanism of Inhibition of a Kinase Interaction Motif-Based Peptide Inhibitor of JNK," *J Biol Chem.* 2004 Aug 27;279(35):36327-38. Epub 2004 Jun 18); and CC-401 (from Celgene; Uehara T et al., *J Hepatol.*, 2005 Jun;42(6):850-9. Epub 2005 Apr 7). Yet another example of a JNK inhibitor is Calbiochem product no. 420133, which has an alternate name similar to peptide
 15 TI-JIP (H-Arg-Pro-Lys-Arg-Pro-Thr-Thr-Leu-Asn-Leu-Phe-NH₂; SEQ ID NO: 8) that may specifically inhibit JNK activity without inhibiting ERK or p38.

Pharmaceutical compositions including dosage forms of preferred embodiments of the invention, which comprise a therapeutically effective amount of a JNK inhibitor, may be used in the preferred methods of the invention.

20 All the JNK inhibitors described above may be used in accordance with preferred this invention. Other suitable JNK inhibitors, derivatives, or mixtures thereof, will be known to those of ordinary skill in the art and are also included.

In one example, JNK inhibitors may be, for example, admixed with excipients or carriers suitable for either enteral or parenteral application. In one
 25 embodiment, JNK inhibitors may be admixed with a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; and/or if desired c) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures. These compositions may be
 30 sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure

and/or buffers. In addition, they may also contain other therapeutically valuable substances. The JNK inhibitor compositions may be prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1 to 95%, more preferably 0.1 to 75%, and most preferably about 1 to 50%, of the JNK inhibitor.

Methods of Treatment

In one embodiment, the present invention provides a method for treating a patient having an aneurysm, and especially abdominal aortic aneurysm, the method comprising a step of delivering a medical device of preferred embodiments of this invention and as described below to a point of treatment within the patient having the aneurysm. The medical device is adapted to release the JNK inhibitor at the point of treatment within the body lumen of the patient.

In another embodiment, the present invention provides a method for treating a patient having an aortic dissection, the method comprising the step of delivering a medical device and JNK inhibitor compound of this invention and as described below to the patient at a point of treatment within the patient having the aortic dissection. The medical device is adapted to release the JNK inhibitor at or near the point of treatment within the body lumen of the patient.

For example, the medical device can release or retain a JNK inhibitor at a desired rate within a blood vessel upon placement proximate to an aneurysm or aortic dissection. By providing JNK inhibitors with the device, the progression of local endovascular disease or aortic dissection may be mitigated, stopped and/or reversed, preventing further weakening and dilation of the vessel wall or splitting of the layers of aorta.

In another embodiment, the present invention provides a method of treating an aneurysm or an aortic dissection comprising radially expanding a medical device and JNK inhibitor compound of this invention and as described below, in a lumen with a balloon catheter, wherein the balloon catheter releases a JNK inhibitor compound.

In yet another embodiment, the present invention is a method of treating an aneurysm or an aortic dissection comprising radially expanding a balloon catheter comprising a JNK inhibitor compound in a lumen, wherein the balloon catheter releases the JNK inhibitor compound within the lumen.

5

Medical Devices Comprising JNK Inhibitor Compounds

In another embodiment, the invention provides a medical device and one or more JNK inhibitor compounds. Preferably, the medical device is an implantable device.

10 Preferably, a therapeutically effective concentration of JNK inhibitor compound(s) can be incorporated in the medical device. The concentration of the JNK inhibitor per unit of abluminal surface area of the medical device may be selected to achieve a desired tissue concentration upon implantation of the medical device. A therapeutically effective amount of JNK inhibitor may be
15 selected based on considerations such as the material of the medical device surface, the design of the medical device, the coating configuration and the molecular structure of the JNK inhibitor, all of which can determine the rate of elution of the JNK inhibitor within a particular body vessel. Other factors include the weight and condition of the patient. It is to be understood that preferred
20 embodiments of the present invention have application for both human and veterinary use.

 Preferably, the JNK inhibitor(s) is coated on the abluminal surface of the medical device in an amount effective to inhibit production of MMPs. Most preferably, JNK inhibitor(s) can be coated on the abluminal surface at
25 concentrations sufficient to deliver a desired amount of the JNK inhibitor to modulate production of MMPs at a body vessel site adjacent to degradation. For instance, a JNK inhibitor may be included on the abluminal surface of a medical device at a concentration effective to deliver from about 0.01 mg to about 5000 mg of a therapeutically effective amount of a JNK inhibitor to adjoining body
30 vessel wall tissue upon placement of the medical device within the body vessel lumen. In another embodiment, the device will comprise about 0.1 mg to about

4500 mg of a therapeutically effective amount of a JNK inhibitor. In another embodiment, the device will comprise about 1 mg to about 4000 mg of a therapeutically effective amount of a JNK inhibitor. In another embodiment, the device will comprise about 25 mg to about 4000 mg of a therapeutically effective amount of a JNK inhibitor. In another embodiment, the device will comprise about 50 mg to about 3000 mg of a therapeutically effective amount of a JNK inhibitor. In another embodiment, the device will comprise about 100 mg to about 2000 mg of a therapeutically effective amount of a JNK inhibitor. In another embodiment, the device will comprise about 250 mg to about 1500 mg of a therapeutically effective amount of a JNK inhibitor. In another embodiment, the device will comprise about 500 mg to about 1000 mg of a therapeutically effective amount of a JNK inhibitor. In another embodiment, the device will comprise about 250 mg to about 500 mg of a therapeutically effective amount of a JNK inhibitor. Other concentrations of JNK inhibitor are also contemplated.

The medical device can be adapted to release a JNK inhibitor at a predetermined location within body of a patient. The medical device can have any suitable configuration. In one embodiment, the medical device may be an implantable medical device, such as graft, stent, and stent graft. Preferably the implantable medical device is an endolumenal medical device, which may be placed inside a lumen of a patient. For example, a stent graft may be placed inside a body vessel. Alternatively, an implantable device may be a medical device, which may be placed on the outside of a body lumen during an open surgery. For example, a vascular wrap comprising a JNK inhibitor may be placed on the outside of the vessel. In yet another embodiment, the medical device may be a delivery device, such as a balloon catheter. Exemplary medical devices are described below. Other configurations are also contemplated.

In one embodiment, the medical device may be a stent **10**. The stent may have any configuration adapted to maintain the lumen of a body vessel at a desired degree of patency. FIG. 1A shows a side view of a stent **10** configured as a radially-expandable frame **12** formed from a plurality of interconnected struts **16** and bends **14** forming a pair of longitudinally joined hoop members.

Alternatively, a stent may include one or a plurality of radially-expanding stents such as Z-STENTS®, which are available from Cook, Incorporated (Bloomington, IN). The frame **12** defines a tubular lumen **18** and defines a plurality of openings **19** between the lumen **18** and the exterior surface of the frame.

5 The frame **12** can be formed from any suitable biocompatible material providing properties suited for an intended application, such as desired rigidity or flexibility. Stent **10** is capable of providing circumferential support while, at the same time, being axially flexible. The stent frame **12** may be formed by forming the desired pattern directly out of a tube, *e.g.* by laser cutting or chemical etching.
10 Alternatively, the desired pattern may be formed out of a flat sheet, *e.g.* by laser cutting or chemical etching, and then rolling that flat sheet into a tube and joining the edges, *e.g.* by welding. Any other suitable manufacturing method known in the art may be employed for manufacturing a stent in accordance with the invention. Furthermore, stents may be formed by etching a pattern into a
15 material or mould and depositing stent material in the pattern, such as by chemical vapour deposition or the like. Such stents may be formed of plastic, metal or other materials and may exhibit a multitude of configurations. The metals from which such stents are formed may include stainless steels, titanium, Nitinol, and tantalum among others.

20 The frame **12** can be configured in any suitable pattern providing desired hoop strength and flexibility within a body vessel. The stent **10** may be moveable from a radially compressed state to the radially expanded state shown in FIG. 1A. In the radially compressed state, the stent **10** may be symmetrically radially compressed about the longitudinal axis within the center of the tubular lumen **18**,
25 and loaded into a suitable catheter-based endolumenal delivery system. The stent **10** can be positioned at a point of treatment within a body vessel using the delivery system, and radially expanded by any suitable means to the radially expanded deployed state shown in FIG. 1A. Means for expanding the stent **10** can include inflation of a balloon within the tubular lumen **18** of the stent, or self-
30 expansion of the stent **10** upon removal of a means for radially constraining the

stent in the radially compressed state. The frame may be configured and formed from materials that provide balloon-expandable or radially-expanding structures.

The frame **12** may be a frame configured for treatment or prevention of aortic dissections. Specifically, the frame for treatment of aortic dissection is preferably configured to provide a radially outward force against the surface of an aorta upon implantation, providing a therapeutically effective radial force directed against the intima so as to compress the intimal, medial and/or adventitial layers of the aorta against one another, thereby preventing or mitigating aortic dissection. A self-expanding frame may be selected to have a self-expanded radius greater than the radius of the site of implantation within the aorta. The site of the frame may be selected based on medically appropriate criteria to provide a desired amount of radial force against the intimal wall of the aorta to treat or prevent aortic dissection. The frame may be formed from a self-expanding material, such as the nickel-titanium alloy NITINOL®, and may have any suitable configuration of struts and bends. For example, the frame can be configured as a stent **10** as shown in FIG. 1A. Optionally, one or more frames having the configuration of stent **10** can be joined longitudinally to form an elongated prosthesis of a desired length. The stent **10** can form a repeating unit cell of the elongated prosthesis, and multiple stent **10** unit cells may be joined end to end in a manner that imparts a desired amount of lateral and tortional flexibility to the elongated prosthesis. Alternatively, a single elongated prosthesis may be formed as a single unit, for example by laser cutting a cannula of a nickel-titanium alloy to form a self-expanding stent comprising a plurality of unit cells with the configuration of stent **10**. Balloon-expandable materials, such as stainless steel or cobalt-chromium alloys, may also be used to form prosthetic stents for treatment of aortic dissection. Inflation of a PTA balloon may be used to place the prosthesis within the aorta, and inflation of the balloon may be regulated to provide a desired radial force against the wall of the aorta.

Preferably, the stent **10** or elongated prosthesis comprising a plurality of stent **10** unit cells may be coated with a releasable JNK inhibitor in a manner that provides for the therapeutically effective release of the JNK inhibitor into the

intimal wall of the aorta. An elongated prosthesis may be delivered or implanted at any medically appropriate site within the aorta, including the proximal or distal segment of the aorta. The elongated prosthesis may have any suitable configuration of struts, bends, and openings. One example of an elongated
5 prosthesis is a self-expanding stainless steel stent for percutaneous implantation sold under the tradename ZENITH®, commercially available from Cook, Incorporated (Bloomington, IN). Other examples include a Wallstent variety stent, Cook-Z® Stent or Zilver Stent. Some exemplary stents are disclosed in U.S. Pat. Nos. 5,292,331; 6,090,127; 5,133,732; 4,739,762; and 5,421,955.

10 In one embodiment, the JNK inhibitor(s) may be contained within a reservoir incorporated with the medical device.

In one embodiment, the medical device may contain apertures, holes, wells, slots and the like occurring within the surface of the device for containing the JNK inhibitor compound and optionally containing other materials, such as a
15 biodegradable polymer, mixed with or positioned in additional layers adjoining the JNK inhibitor compound. For example, the JNK inhibitor may be contained within a hole in a strut **16** or bend **14**. In an alternative embodiment, the JNK inhibitor may be contained within wells formed in the strut **16** and/or a bend **14** portion of the frame **12**. The wells may also be configured as slots or grooves in the
20 surface of the frame **12**. Placement of the releasable JNK inhibitor within a hole or well in the frame may provide the advantage of controlling the total amount of the JNK inhibitor released from the medical device **10**, as well as the rate of release. Referring to FIG. 4A, the abluminal surface **324** of an arcuate frame portion **310** of a medical device frame comprises a plurality of wells **326**
25 containing a JNK inhibitor. The well **326** may contain a coating comprising the JNK inhibitor alone, a mixture of the JNK inhibitor with suitable polymers or a coating comprising multiple layers. FIGS. 4B-4E show cross sectional views of various well configurations along line B-B' of frame **310**. The holes or wells may have any suitable shape or size, including a concave well formed by removing a
30 portion of the frame **310** (FIG. 4B) or formed by re-shaping a portion of the frame (FIG. 4C), a V-shape well (FIG. 4D) or a square shaped well (FIG. 4E). The

holes, wells, slots, grooves and the like, described above, may be formed in the surface of the release system of the medical device **10** by any suitable technique. For example, such techniques include drilling or cutting by utilizing lasers, electron-beam machining and the like or employing photoresist procedures and etching the desired apertures.

In one embodiment, the medical device may include hollow members that are adapted to contain the JNK inhibitor. Nearby, *in vivo* reservoirs may attach to these hollow members to supply the JNK inhibitor. Medical devices and methods for delivery of therapeutic agents using hollow members adapted to contain a drug were previously described in US 2007/0265699, contents of which are incorporated herein in its entirety.

The stent may be balloon expandable or radially-expanding, including elastically self-expanding and thermally self-expanding. The balloon expandable stents are typically made of a ductile material, such as stainless steel tube, which has been machined to form a pattern of openings separated by stent elements. Radial expansion can be achieved by applying a radially outwardly directed force to the lumen of a balloon expandable stent and deforming the stent beyond its elastic limit from a smaller initial diameter to an enlarged final diameter. In this process the slots deform into "diamond shapes." Balloon expandable stents are typically radially and longitudinally rigid and have limited recoil after expansion. These stents have superior hoop strength against compressive forces but should this strength be overcome, the devices will deform and not recover. Balloon-expandable frame **12** structures may be preferably formed from cobalt-chromium alloys or stainless steel materials. Self-expanding stents, on the other hand, may be fabricated from either spring metal or shape memory alloy wire, which has been woven, wound or formed into a stent having interstices separated with wire stent elements. When compared to balloon-expandable stents, these devices have less hoop strength but their inherent resiliency allows them to recover once a compressive force that results in deformation is removed. Other suitable frame materials include thermoformable polymers, such as polyethylene and polyurethane, and bioabsorbable polymer materials.

several bioabsorbable, biocompatible polymers have been developed for use in medical devices, and have been approved for use by the U.S. Food and Drug Administration (FDA). These FDA-approved materials include polyglycolic acid (PGA), polylactic acid (PLA), Polyglactin 910 (comprising a 9:1 ratio of glycolide per lactide unit, and known also as VICRYL™), polyglyconate (comprising a 9:1 ratio of glycolide per trimethylene carbonate unit, and known also as MAXON™), and polydioxanone (PDS). In general, these materials biodegrade *in vivo* in a matter of months, although some more crystalline forms can biodegrade more slowly. Biodegradable polymers that can be used to form the support frame of a medical device, or can be coated on a frame, include a wide variety of materials. Examples of such materials include polyesters, polycarbonates, polyanhydrides, poly(amino acids), polyimines, polyphosphazenes and various naturally occurring biomolecular polymers, as well as co-polymers and derivatives thereof. Certain hydrogels, which are cross-linked polymers, can also be made to be biodegradable. These include, but are not necessarily limited to, polyesters, poly(amino acids), copoly(ether-esters), polyalkylenes oxalates, polyamides, poly(iminocarbonates), polyorthoesters, polyoxaesters, polyamidoesters, polyoxaesters containing amido groups, poly(anhydrides), polyphosphazenes, poly-alpha-hydroxy acids, trimethylene carbonate, poly-beta-hydroxy acids, polyorganophosphazines, polyanhydrides, polyesteramides, polyethylene oxide, polyester-ethers, polyphosphoester, polyphosphoester urethane, cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), polyalkylene oxalates, polyvinylpyrrolidone, polyvinyl alcohol, poly-N-(2-hydroxypropyl)-methacrylamide, polyglycols, aliphatic polyesters, poly(orthoesters), poly(ester-amides), polyanhydrides, modified polysaccharides and modified proteins. Some specific examples of bioabsorbable materials include poly(epsilon-caprolactone), poly(dimethyl glycolic acid), poly(hydroxy butyrate), poly(p-dioxanone), polydioxanone, PEO/PLA, poly(lactide-co-glycolide), poly(hydroxybutyrate-co-valerate), poly(glycolic acid-co-trimethylene carbonate), poly(epsilon-caprolactone-co-p-dioxanone), poly-L-glutamic acid or poly-L-lysine, polylactic acid, polylactide,

polyglycolic acid, polyglycolide, poly(D,L-lactic acid), L-poly(lactic acid), poly(glycolic acid), polyhydroxyvalerate, cellulose, chitin, dextran, fibrin, casein, fibrinogen, starch, and hyaluronic acid.

At least a portion of the medical device frame **12** may be coated with one or more JNK inhibitors. The JNK inhibitor may be releasably associated with the frame **12** in any suitable manner, preferably providing for the release of a therapeutically effective amount of the JNK inhibitor from the device upon placement of the frame **12** within a body vessel. For example, the JNK inhibitor may be adhered to a surface of the frame **12**. Referring to FIG. 1A, the frame **12** comprises a luminal surface **22** defining the lumen **18** and an abluminal surface **24** positioned opposite the luminal surface **22**. FIG. 1B shows a cross section **20** view of a coated portion of the frame **12** along the line marked **2B-2B** in FIG. 1A. The coating **26a** comprises a JNK inhibitor and can have any suitable composition or configuration that provides for a therapeutically effective release of the JNK inhibitor within a body vessel. For example, the coating can optionally comprise a polymer matrix, such as a biodegradable polymer or a porous biostable polymer mixed with the JNK inhibitor. The coating **26a** in FIG. 1B may be applied to the abluminal surface **24** of the frame portion **12a**, however, the coating **26a** could be applied to the luminal surface **22** in addition to, or instead of, application to the abluminal surface **24**.

The coating may optionally comprise multiple layers. As such, these multiple layers may include varying amounts of JNK inhibitor(s) creating a drug gradient. Two, three, four or more layers including the JNK inhibitor(s) are contemplated. For example, FIG. 1C shows an alternative cross section **20'** view of a coated portion of frame **12** along the line marked **2B-2B** in FIG. 1A. The coating comprises two layers: a first layer **26b** comprising a JNK inhibitor positioned on the abluminal side **24** of frame portion **12b**, and a second layer **28** positioned over the luminal side **22** and the abluminal side **24** of the first layer **26b**. The second layer **28** can provide for a slower rate of release of the JNK inhibitor, for example by providing a porous diffusion barrier. The second layer **28** can comprise a biodegradable elastomer, such as poly(lactic acid), or a

porous biostable material, such as parylene or a poly(alkyl)methacrylate (e.g., poly(butyl)methacrylate). FIG. 1D shows an alternative cross section **20''** view of a coated portion of frame **12** along the line marked **2B-2B** in FIG. 1A. The coating comprises two layers: a first layer **29** positioned over the luminal side **22** and the abluminal side **24** of frame portion **12c**, and a second layer **26c** positioned over the abluminal side **24** of the first layer. The second layer **26c** comprises JNK inhibitor, and optionally comprises other materials such as biodegradable or biostable polymer matrix-forming components. The first layer **29** can provide for a slower rate of release of the JNK inhibitor from the second layer **26c**, for example by exerting an attractive force toward the second layer **26c** (e.g., electrostatic or van der Waals forces). The second layer **28** may comprise a biodegradable elastomer, such as poly(lactic acid), or a porous biostable material, such as parylene or a poly(alkyl)methacrylate (e.g., poly(butyl)methacrylate). In other configurations, JNK inhibitor may be linked to the surface of the frame without the need for a coating by means of detachable bonds and release with time. In yet other configurations, JNK inhibitor(s) may be included as a separate layer (separate carrier layer that includes JNK inhibitor(s)) that may be attached or placed near the frame **12**. These JNK inhibitors may be removed by active mechanical or chemical processes, or may be in a permanently immobilized form that presents the inhibitors at the implantation site. Multiple layers of JNK inhibitor(s), or mixtures of carrier material/JNK inhibitor(s), separated by polymer layers may be present to form a multilayer coating on a medical device. As discussed above, these layers may include varying amounts of the JNK inhibitor(s). In certain embodiments, different JNK inhibitors may be present in the different layers. For example, different bioactive agents, may be present in different layers. In another embodiment, bioactive agents different from JNK inhibitors may also be included in addition to the JNK inhibitors in the same layers or different layers. Examples of other suitable bioactive agents are described below.

In one embodiment, the coating may also be confined to the abluminal surface. Referring to FIG. 1E, an alternative cross section **20** view of a coated

portion of frame **12** along the line marked **2B-2B** in FIG. 1A comprises a two-layer coating: a first layer **29** positioned over the abluminal side **24** of frame portion **12d**, and a second layer **26d** positioned over the first layer. The second layer **26d** comprises a JNK inhibitor, and optionally comprises other materials
5 such as biodegradable or biostable polymer matrix-forming components. The coating does not cover the luminal side **22** of the frame.

The JNK inhibitor(s) may be incorporated into the medical device in any suitable manner. The term "incorporated" means that JNK inhibitors may be coated, adsorbed, placed, deposited, attached, impregnated, mixed, or otherwise
10 incorporated into the device and the layers described herein by methods known in the art. Coating layers may be applied in sequential fashion by placing the layers near the medical device and/or spraying a solution comprising a volatile solvent and a JNK inhibitor to the surface of the medical device. A coating layer comprising a JNK inhibitor is preferably adhered to the surface of the using an
15 ultrasonic nozzle spray coating technique employing ultrasound to atomize a spray solution comprising the JNK inhibitor in suitable solvent, to provide a smooth and uniform coating. Optionally, the spray solution can further comprise a soluble polymer, such as a biodegradable polymer. In general, high frequency ultrasonic nozzles are smaller, create smaller drops, and consequently have
20 smaller maximum flow capacity than nozzles that operate at lower frequencies. The ultrasonic nozzle can be operated at any suitable frequency, including 24 kHz, 35kHz, 48 kHz, 60 kHz, 120 kHz or higher. Preferably, a frequency of 60-120 kHz or higher is used to atomize the solution comprising the JNK inhibitor. The nozzle power can be set at any suitable level, but is preferably about 0.9–1.2
25 W and more preferably about 1.0-1.1 W. The maximum flow rate and median drop diameter corresponding to particular nozzle designs can be selected as design parameters by one skilled in the art. Preferably, the flow rate is between about 0.01–2.00 mL/min.

In another embodiment, the medical device may be a stent graft **100**, as
30 shown in FIG. 2A. The stent graft **100** may be formed from a graft material **130** and a frame **112**. The frame **112** may comprise a plurality of longitudinally

aligned hoops **110** attached to the tubular graft material **130** so as to define a cylindrical lumen **118**. A distal frame hoop **111a** may be flared radially outward to secure the stent graft **100** within a body vessel upon implantation. A first group of three frame hoops **111b** may be positioned on the luminal side **122** of the graft material **130** between a second group of frame hoops **111c** positioned on the abluminal **124** side of the graft material **130**. A cross sectional view of a portion of a first frame hoop **111b** is shown in detail view **102**; a cross sectional view of a portion of a second frame hoop **111c** is shown in detail view **104**. The stent graft **100** may be moveable from a radially compressed state to the radially expanded state shown in FIG. 2A, for example, by expansion of a balloon within the lumen **118**, or by self expansion of the frame **112** within a body vessel. Medical devices are preferably packable in a compressed state within an endovascular delivery system having an outer diameter of from about 0.06 inches (5 French) to about 0.27 inches (20 French); preferably from about 0.10 inches (8 French) to about 0.22 inches (17 French); and most preferably from about 0.13 inches (5 French) to about 0.19 inches (14 French).

Resiliently compressible, self-expanding frames **112**, such as self-expanding stent materials discussed above, are preferred in order to seal with the body lumen. PCT Publication WO 98/53761, hereby incorporated by reference in its entirety, discloses a number of details concerning stents, stent grafts, and a method for implanting stent grafts into the human body.

The graft material **130** may be any suitable material for an intended use. The graft material **130** may be a woven or non-woven fabric, such as Dacron®, or may be a polymeric material such as expanded polytetrafluoroethylene (ePTFE), or may be a reconstituted or naturally derived collagenous material, including extracellular matrix material, such as small intestine submucosa (SIS). Other materials suitable for use as the graft material are also contemplated.

The graft material **130** is preferably selected and adapted to retain a therapeutically effective amount of a JNK inhibitor. Preferably, the graft material is selected from the group consisting of polyester, polyurethane (THORALON (THORATEC, Pleasanton, CA)), polyethylene, polypropylene and

polytetrafluoroethylene. The graft material may alternatively be made from a reconstituted or naturally-derived collagenous material. Suitable bioremodelable materials may be provided by collagenous extracellular matrix materials (ECMs) possessing biotropic properties, including in certain forms angiogenic

5 collagenous ECMs. For example, suitable collagenous materials include ECMs such as submucosa, renal capsule membrane, dermal collagen, dura mater, pericardium, fascia lata, serosa, peritoneum or basement membrane layers, including liver basement membrane. Suitable submucosa materials for these purposes include, for instance, intestinal submucosa, including small intestinal
10 submucosa, stomach submucosa, urinary bladder submucosa, and uterine submucosa.

As prepared, the submucosa material and any other ECM may optionally retain growth factors or other bioactive components native to the source tissue.

For example, the submucosa or other ECM may include one or more growth

15 factors such as basic fibroblast growth factor (FGF-2), transforming growth factor beta (TGF-beta), epidermal growth factor (EGF), and/or platelet derived growth factor (PDGF). As well, submucosa or other ECM may include other biological materials such as heparin, heparin sulfate, hyaluronic acid, fibronectin and the like.

20 Submucosa or other ECM materials may be derived from any suitable organ or other tissue source that usually contains connective tissues. The ECM materials processed for use as the graft material will typically include abundant collagen, most commonly being constituted at least about 80% by weight collagen on a dry weight basis. Such naturally-derived ECM materials will for the
25 most part include collagen fibres that are non-randomly oriented, for instance occurring as generally uniaxial or multi-axial but regularly oriented fibres. When processed to retain native bioactive factors, the ECM material can retain these factors interspersed as solids between, upon and/or within the collagen fibres.

Particularly desirable naturally-derived ECM materials for use in preferred

30 embodiments of the invention will include significant amounts of such interspersed, non-collagenous solids that are readily ascertainable under light

microscopic examination with specific staining. Such non-collagenous solids can constitute a significant percentage of the dry weight of the ECM material in certain embodiments, for example at least about 1%, at least about 3%, and at least about 5% by weight in various embodiments of the invention.

5 The submucosa or other ECM material used as the graft material may also exhibit an angiogenic character and thus be effective to induce angiogenesis in a host engrafted with the material. In this regard, angiogenesis is the process through which the body makes new blood vessels to generate increased blood supply to tissues. Thus, angiogenic materials, when contacted with host tissues,
10 promote or encourage the infiltration of new blood vessels. Methods for measuring *in vivo* angiogenesis in response to biomaterial implantation have recently been developed. For example, one such method uses a subcutaneous implant model to determine the angiogenic character of a material. See, C. Heeschen et al., Nature Medicine 7 (2001), No. 7, 833-839. When combined
15 with a fluorescence microangiography technique, this model can provide both quantitative and qualitative measures of angiogenesis into biomaterials. C. Johnson et al., Circulation Research 94 (2004), No. 2, 262-268.

 Submucosa or other ECM tissue used in the invention is preferably highly purified, for example, as described in U.S. Patent No. 6,206,931. Thus, preferred
20 ECM material will exhibit an endotoxin level of less than about 12 endotoxin units (EU) per gram, more preferably less than about 5 EU per gram, and most preferably less than about 1 EU per gram. As additional preferences, the submucosa or other ECM material may have a bioburden of less than about 1 colony forming units (CFU) per gram, more preferably less than about 0.5 CFU
25 per gram. Fungus levels are desirably similarly low, for example less than about 1 CFU per gram, more preferably less than about 0.5 CFU per gram. Nucleic acid levels are preferably less than about 5 µg/mg, more preferably less than about 2 µg/mg, and virus levels are preferably less than about 50 plaque forming units (PFU) per gram, more preferably less than about 5 PFU per gram. These
30 and additional properties of submucosa or other ECM tissue taught in U.S. Patent No. 6,206,931 may be characteristic of the submucosa tissue used as the

graft material in the present invention. Other collagen sources may be used in order to provide a desired amount of various collagen types including type I, III, IV and VI (Murata, et al., Atherosclerosis, 1986 Jun;60(3):251-62).

5 The preferred type of submucosa for use as a graft material in embodiments of this invention is derived from the intestines, more preferably the small intestine, of a warm blooded vertebrate; *i.e.*, SIS. SIS is commercially available from Cook Biotech, West Lafayette, IN.

10 The graft material **130** may be attached to the frame **112** by any suitable method, including suturing, cross linking of the graft material **130** to the frame **112**, the application of adhesive compositions to join the frame **112** to the graft material **130** or by heat or by ultrasonic bonding.

Any portion of the stent graft may be coated with or include the JNK inhibitor.

15 In one embodiment, a JNK inhibitor may be coated or positioned within or on the graft material **130**. One or more JNK inhibitor(s) may be incorporated in or coated on a graft material **130** by any suitable method. Various methods of coating, impregnating, or lining the graft material with the bioactive compounds may be utilized and are known in the art. For example, the JNK inhibitor(s) may be deposited onto the graft material by spraying, dipping, pouring, pumping,
20 brushing, wiping, vacuum deposition, vapour deposition, plasma deposition, electrostatic deposition, epitaxial growth, or any other method known to those skilled in the art. The type of coating or vehicle utilized to immobilize the JNK inhibitor to the graft material may vary depending on a number of factors, including the type of the medical device, including the graft material, the type of
25 JNK inhibitor, and the rate of release thereof. JNK inhibitor(s) may be incorporated into or mixed with the graft material during the formation of the graft material. The JNK inhibitor may be present in a liquid, a finely divided solid, or any other appropriate physical form when the graft material solidifies from a solution. In another embodiment, JNK inhibitor(s) may be incorporated into a
30 solid form of the graft material, for example by spraying or dipping. Optionally, the graft material, or a coating applied thereto, may include one or more

additives, for example, auxiliary substances, such as diluents, carriers, excipients, stabilizers, or the like. Optionally, an adhesion-promoting coating layer may be applied to the graft material prior to coating it with the JNK inhibitor. The adhesion promoting layer can be configured to provide a durable coating of the inhibitor compound adhered to the graft material. Examples of suitable adhesion promoting materials include silane and parylene polymers. The amount of JNK inhibitor will be dependent upon a particular JNK inhibitor employed and medical condition to be treated. The JNK inhibitor preferably remains on the graft material during the delivery and implantation of the medical device. Accordingly, various materials may be utilized as surface modifications to prevent the JNK inhibitor(s) from coming off prematurely. These materials are known and commonly used in the art.

One particular method of coating or impregnating a graft involves impregnating the graft with the JNK inhibitor(s) by applying pressure to force the inhibitor(s) into the interstices of the graft. Pressure or force can be applied using a number of mechanical means for impregnating a solution of the JNK inhibitor(s) into the graft material. Once coated, the grafts are allowed to dry and then may be subjected to sterilizing conditions prior to introduction into the body.

In one aspect, a dry, finely subdivided JNK inhibitor(s) may be blended with a wet or fluid material, such as ePTFE, used to form the graft material before the material solidifies. Alternatively, air pressure or other suitable means may be employed to disperse the JNK inhibitor substantially evenly within the pores of the solidified graft material **130**. In situations where the JNK inhibitor is insoluble in the wet or fluid graft material, the inhibitor compound may be finely subdivided as by grinding with a mortar and pestle or by other means. Preferably, the JNK inhibitor is micronized, e.g., a product wherein some or all particles are the size of about 5 microns or less. The finely subdivided JNK inhibitor can then be distributed desirably substantially evenly throughout the bulk of the wet or fluid ePTFE layer before cross-linking or cure solidifies the layer. Alternatively, a JNK inhibitor may be incorporated into the graft material **130** by mixing a crystalline, particulate material (e.g., salt or sugar) that is not soluble in a solvent into an

extrudate used to make the graft material to form the extrudate; casting the extrudate solution with particulate material; and then applying a second solvent, such as water, to dissolve and remove the particulate material, thereby leaving a porous graft material 130. The graft material 130 may then be placed into a solution containing JNK inhibitor(s) in order to fill the pores. Preferably, the stent graft would be exposed to a vacuum during solution impregnation to insure that the JNK inhibitor applied to it is received into the pores. Alternatively, the JNK inhibitor may be coated on the outside surface of the graft material. The drug may be applied to the outside surface of the graft material such as by dipping, spraying, or painting.

Optionally, the JNK inhibitor may be contained within a reservoir, such as encapsulated in microparticles, such as microspheres, microfibres or microfibrils, which can then be incorporated into a graft material. Various methods are known for encapsulating bioactives within microparticles or microfibres (see Patrick B. Deasy, Microencapsulation and Related Drug Processes, Marel Dekker, Inc., New York, 1984). For example, a suitable microsphere for incorporation would have a diameter of about 10 microns or less. The microsphere could be contained within the mesh of fine fibrils connecting the matrix of nodes in the graft material. The microparticles containing the drug may be incorporated within a zone by adhesively positioning them onto the material or by mixing the microparticles with a fluid or gel and flowing them into the graft material. The fluid or gel mixed with the microparticles could, for example, be a carrier agent designed to improve the cellular uptake of the JNK inhibitor incorporated into the graft material. Moreover, it is well within the contemplation of the present invention that carrier agents, which may include hyaluronic acid, may be incorporated within each of the embodiments of the present invention so as to enhance cellular uptake of the JNK inhibitor associated with the device. The microparticles embedded in the graft material may have a polymeric wall surrounding the JNK inhibitor or a matrix containing the JNK inhibitor and optional carrier agents. Moreover, microfibers or microfibrils, which may be JNK inhibitor loaded by extrusion, can be adhesively layered or woven into the graft

material. Alternatively, the JNK inhibitor may be coated on the outside surface of the graft material. The inhibitor may be applied to the outside surface of the graft material by, for example, dipping, spraying, or painting.

Alternatively, the graft material may further include a coating posited over
5 the graft material. The coating may include, for example, a biocompatible hydrophilic material, such as hydrophilic polymer. Hydrophilic polymers that may be suitable for use as a coating for the graft fabric material are readily and commercially available from, for example, Biosearch Medical Products, Sommerville, N.J.; Hydromer Inc. Branchburg, N.J.; Surmodics, Eden Prairie,
10 Wis.; and STS Biopolymers, Inc., Henrietta, N.Y. For example, hydrophilic polymer may include, but not be limited to, polyethylene oxide, polyvinyl pyrrolidone, polyethylene glycol, carboxymethyl cellulose, hydroxymethyl cellulose, and other suitable hydrophilic polymers, or a combination thereof.

The medical device may also be configured as an elongated stent graft for
15 treatment of aortic dissections as described in U.S. Publication No. 2004/0176832 A1, published on September 9, 2004, which is incorporated by reference in its entirety. For example, FIG. 2B shows an elongated stent graft **150** in a radially expanded configuration. The elongated stent graft **150** comprises an elongated frame **152** and a biocompatible graft material cover **156**
20 around a first end **159** of the elongated stent graft **150** to form a covered portion **155** and an uncovered frame portion **160**. The elongated frame **152** is formed from a plurality of longitudinally connected hoop members **151** joined by flexible links **157**. Each hoop member **151** is formed from a sinusoidal member comprising an interconnected array of struts and bends. The flexible links **157**
25 enable each hoop member **151** to radially expand separately. The elongated stent graft **150** may have a total length of from 100 to 300 mm and a diameter when expanded of 22 to 45 mm. The covered portion **156** may have a length of from 50 to 150 mm and a diameter when expanded of 22 to 45 mm. The length of the elongated stent graft **150** may be selected based on various factors,
30 including the nature of the aortic aneurysm or dissection, the length of aorta at the site of treatment, and the dimensions of the aneurysm or the rupture in the

wall of the aorta. Optionally, the elongated stent graft **150** may include barbs at the first end **159** of the elongated stent graft **150**. The elongated frame **152** may be in the form of a mesh and formed from a biocompatible and biodegradable mesh material to permit dissipation of the elongated frame **152** after a desired
5 period of time within a blood vessel.

Referring to FIG. 3, a stent graft **200**, may comprise a multilayered graft material construct including a frame **212** positioned between an inner tubular graft material **230** defining the lumen **218** and an outer tubular graft material **232** defining the outer surface of the stent graft **200**. The frame **212** and the nested
10 tubular graft materials **230**, **232** can be joined by a plurality of sutures **240** at each end of the stent graft **200**. One or more JNK inhibitors can be incorporated in each of the tubular graft materials **230**, **232**. For example, a JNK inhibitor may be included within the outer tubular graft material **232**, and a second JNK
15 JNK inhibitor can be selected for retention or release into fluid flowing through the lumen **218**.

A medical device may be preferably compressible into a radially compressed delivery configuration being configured for implantation from a suitably small delivery system. The delivery system preferably has sufficient
20 pushability, trackability and lateral flexibility. The device may be delivered to the treatment site by endovascular insertion. Preferably, the endovascular delivery system is sufficiently rigid to enable the health practitioner performing the implantation procedure to push the delivery system deep into the vascular tree of a patient, but not so rigid as to cause vascular damage during the implantation
25 procedure. Furthermore, preferably the delivery system would have enough lateral flexibility to allow tracking of the path of any one of the blood vessels leading to the implantation site. A delivery system, or introducer, typically comprises a cannula or a catheter, having a variety of shapes according to the intended clinical application and implantation site. The medical device may be
30 radially collapsed and inserted into the catheter or cannula using conventional methods. In addition to the cannula or catheter, various other components may

need to be provided in order to obtain a delivery system that is optimally suited for its intended purpose. These include and are not limited to various outer sheaths, pushers, stoppers, guidewires, sensors, etc. Once the device is deployed within a vessel, it expands and it can remain in place indefinitely, acting
5 as a substitute vessel for the flow of blood or other fluids. Alternatively, if the device may be intended for temporary treatment, it can be removed after a desired period of time (hours, days, months, or years) from within the patient by conventional means.

In yet another embodiment, a medical device may be configured as a
10 medical device delivery system comprising a JNK inhibitor. The delivery system may include a structure, such as a balloon catheter, configured to deliver the medical device to a predetermined location within a body lumen of a patient and release a JNK inhibitor before, during or after deployment of the medical device. Examples of balloons used for drug delivery were described in U.S. Publication
15 No. 2004/0073190 A1, published on Apr. 15, 2004, and U.S. Publication No. 2005/0278021 A1, published on Dec. 15, 2005, the disclosures of which are incorporated by reference in their entirety.

FIG. 5 shows a portion of a distal portion of a catheter device **400** coated with the JNK inhibitor. The catheter **410** may include an inflatable balloon **420**
20 proximate to the distal end **404** of the catheter **410**. Inflation of the coated balloon **420** within a body vessel **402** may place the JNK inhibitor in contact with the wall **406** of the body vessel **402**. The balloon **420** may be inflated to a controlled pressure (e.g., up to 1 to 20 atm) to fill the cross-section of the body lumen **408** and press the coated balloon surface **440** against the wall **406** of the
25 body vessel lumen **408**. The coated balloon surface **440** is configured to release the JNK inhibitor from the surface of the balloon **420** during compression of the inflated balloon against the wall **406** of the body vessel lumen **408**.

Optionally, at least a portion of the coating **440** of the expandable balloon may include the JNK inhibitor mixed with, or layered with, a swellable hydrogel
30 polymer. The coating **440** may preferably have a thickness in the range of about 10 to 50 microns in the swelled state. The hydrogel polymer may be selected

from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, and polyethylene oxides. In general, when dry, the hydrogel coating is preferably on the order of about 1 to 10 microns thick. Typically, the hydrogel coating

5 thickness may swell by about a factor of 6 to 10 or more when the hydrogel coating is hydrated. For example, a 1 to 3 microns thick hydrogel coating, when dry, may swell to about 10 to 30 microns thickness when hydrated. For example, a hydrogel coating on an angioplasty balloon may be coated on the surface of a balloon catheter (e.g., polyethylene) by applying a solution of 4,4'

10 diphenylmethane diisocyanate (MDI) in methylethylketone to the surface of the balloon. After drying in an air oven at 85° C for 30 minutes, the balloon may be dipped in a solution of poly(acrylic acid) in dimethylformamide (DMF) and tertiarybutyl alcohol. The balloon may be oven dried to remove solvent from the coating. The surface of the balloon becomes instantly lubricous upon exposure

15 to water. The formation of the hydrogel is further described in U.S. Pat. No. 5,091,205. The JNK inhibitor may be incorporated within the hydrogel polymer coating by, for example, dipping a hydrogel coated balloon in an aqueous solution of the JNK inhibitor.

The medical device may be a balloon catheter configured to deliver the

20 JNK inhibitor and to deploy a second medical device, such as a radially-expandable stent crimped around the balloon portion of the catheter. For example, referring again to FIG. 5, a second medical device, such as a stent **430**, can be crimped over a balloon coated with the JNK inhibitor. Expansion of the coated balloon portion **440** of the catheter **410** can function to radially expand

25 and deploy a stent **430**, while simultaneously releasing the JNK inhibitor onto the luminal surface of the stent **430** and/or the wall **406** of the body vessel **402**. The JNK inhibitor may be coated on at least a portion of the inflatable balloon **420**, for instance at the proximal region **424** and distal region **422** that extend

30 longitudinally beyond a crimped stent **430**. Inflation of the balloon **420** typically leads to inflation of the distal region **422** and proximal region **424** of the balloon **420** (also referred to as the “dogbone” inflation pattern). Preferably, the JNK

inhibitor may be coated on the distal region **422** and the proximal region **420** of the balloon **420** that are not enclosed by the stent **430**. During delivery of a stent **430** by balloon inflation, the proximal region **424** and distal region **422** may radially expand before the portion of the balloon **420** enclosed by the stent **430**,
5 thereby delivering the JNK inhibitor to the wall of the body vessel before the stent is fully expanded.

The medical device may be an infusion catheter comprising one or more drug delivery channels from the central lumen of the catheter to the outer surface of the catheter. For example, a JNK inhibitor may be locally delivered in liquid
10 form from the catheter near a point of treatment within an aorta. Optionally, the infusion catheter medical device may include one or more balloons. In one embodiment, the infusion catheter includes a pair of balloons spaced longitudinally along the catheter, and one or more channels in communication with the outside surface of the catheter between the balloons. The balloons may
15 be inflated prior to or during delivery of the JNK inhibitor, localizing the JNK inhibitor within an isolated segment of the body vessel between the two balloons.

The infusion catheter may also include a balloon segment with one or more pores permitting delivery of the JNK inhibitor across the balloon membrane. The balloon may be inflated with air or with a solution of the JNK inhibitor that is
20 released through the balloon pores at a desired rate. The size of the pores, the viscosity and concentration of the solution comprising the JNK inhibitor, as well as the inflation pressure of the balloon, may be selected to provide a desired rate of delivery of the JNK inhibitor to a vessel wall upon inflation of the balloon.

A catheter may also be utilized to deliver a plurality of delivery capsules,
25 including a JNK inhibitor, which may be initially disposed over an exterior surface of an inflatable balloon. By inflating the balloon, the JNK inhibitor capsules may become implanted into the interior wall of the aneurysm. Catheter may then be removed, leaving the capsules in place. The capsules may be any of a variety of conventional controlled drug delivery structures intended to release the desired
30 drug into the aneurysmal wall or dissected aortic wall over time at a controlled

rate. Optionally, the capsules may comprise hooks or other similar anchors for holding the capsules in the wall.

The JNK inhibitor may also be placed on the balloon in a form of microencapsulated spheres, which may be disposed on the exterior of or
5 extruded within the wall of a balloon associated with a balloon catheter. The balloon catheter and balloon are conventional and well known in the art. The microcapsules may be fabricated in accordance with any of the known methods for preparing microcapsules. See U.S. Pat. Nos. 4,897,268; 4,675,189;
4,542,025; 4,530,840; 4,389,330; 4,622,244; 4,464,317; and 4,943,449, the
10 disclosures of which are incorporated herein by reference. The microcapsule spheres may be configured to release the JNK inhibitor when the balloon is inflated. As the balloon inflates, microencapsulated spheres containing the JNK inhibitor can detach from the expanding balloon coating. For example, a typical dilatation catheter balloon may expand in circumference by 500% which stresses
15 the attachment points to the microencapsulated spheres. Other examples of suitable balloons using microencapsulated spheres were previously described in U.S. Pat. No. 6,129,705, disclosure of which is incorporated by reference herein in its entirety.

In one embodiment, a photodynamic therapy (PDT) balloon catheter may
20 be used when a JNK inhibitor is formulated to be taken up at the treatment site, then infrared, UV or visible light (of wavelength of 200 nm up to 1200 nm) may be used to activate the drug. PDT balloon catheters were previously described in U.S. Pat. Nos. 5,797,868; 5,709,653; and 5,728,068, disclosures of which are incorporated by reference herein in their entirety. Two methods for
25 photodynamic therapy (PDT) treatment of blood vessels including use of a balloon are disclosed in the U.S. Pat. Nos. 5,169,395 and 5,298,018, which are also incorporated by reference herein in their entirety. The elastin-based biomaterials that may be used to for photodynamic therapy were described in U.S. Pat. No. 6,372,228, which is incorporated herein by reference in its entirety.

30 In yet another embodiment, the medical device may be configured as a flexible graft material comprising a JNK inhibitor. The flexible graft material may

have any suitable configuration, including a patch, sheet, tube, etc. Some specific examples include a tubular vascular graft, a flow-modifying device or an occluding device adapted for implantation within a body vessel or aneurysmal sac. The flexible graft material may be formed from any suitable material,

5 including those described above with reference to the graft material for use with a stent graft. Exemplary materials include polyester, polyurethane, polyethylene, polypropylene, polytetrafluoroethylene (including ePTFE), reconstituted or naturally-derived collagenous material (e.g., ECM materials possessing biotrophic properties, including in certain forms angiogenic collagenous ECMs). The JNK

10 inhibitor may be coated on or impregnated into a graft material in any suitable manner, including the methods for attaching the JNK inhibitor to a graft material. FIG. 6 shows a flexible graft material **510** configured as a ring of an ECM material impregnated with a therapeutically-effective amount of a JNK inhibitor. The flexible graft material **510** may be placed around a balloon **520** portion of a

15 delivery catheter **522** within a body vessel **502** comprising an aneurysm **530**. The flexible graft material **510** may be delivered via delivery catheter **522** placing the flexible graft material **510** around the balloon **520**, placing the balloon **520** at a desired implantation site within a body vessel lumen, and expanding the

20 balloon **520** within the body vessel to bring the flexible graft material **510** into contact with the wall of the body vessel in a manner that permits adhesion of the flexible graft material **510** to the body vessel. Optionally, the balloon **520** may be coated with a JNK inhibitor in addition to, or instead of, providing a flexible graft material **510** comprising a JNK inhibitor. The site of implantation may be

25 positioned at a therapeutically effective distance **550** from an aneurysm **530**. The abluminal surface of the flexible material **510** can be configured to permit adhesive contact with the internal wall of a body vessel. For example, the abluminal surface of the flexible graft material **510** may have a corrugated or porous morphology or may include an adhesive substance. Preferably, the

30 JNK inhibitor releasably attached to the surface.

In one embodiment, a JNK inhibitor-loaded film may be pre-mounted upon a deflated balloon catheter. The balloon catheter may be maneuvered into the desired arterial or venous location using standard techniques. The balloon may then be inflated, compressing the stent (film material) against the vessel wall and
5 then the balloon may be deflated and removed leaving the JNK inhibitor-loaded film in place. A protective sleeve (e.g., of plastic) may be used to protect the stent during its passage to the vessel and then withdrawn once the film is in the desired location.

In one embodiment, methods are provided for treating endovascular
10 disease, such as aneurysm, and more specifically, an abdominal aortic aneurysm. The methods comprise delivering a medical device and a JNK inhibitor to a point of treatment in a patient having the aneurysm. The JNK inhibitor may be releasably incorporated into the medical device.

In another embodiment, methods are provided for preventing or treating
15 an aortic dissection. The methods comprise delivering a medical device and a JNK inhibitor to a point of treatment in a patient having the aortic dissection, or presenting symptoms thereof. The JNK inhibitor may be releasably incorporated into the medical device.

In some embodiments, the JNK inhibitor may be releasably coated on one
20 or more surfaces of the medical device. For example, FIG. 7 is a radial cross section **600** of a medical device formed from a medical device material **610** having a luminal surface **610** facing the luminal side **602** of the medical device and an abluminal surface **620** facing toward the abluminal side **604** of the medical device. The medical device material **610** represents a portion of any
25 implantable medical device, including a stent frame, a graft material, a balloon portion or a catheter portion.

The medical device may include one or more coating or other layers that include JNK inhibitor(s). For example, the medical device shown in FIG. 7 includes a three-layer coating positioned on the abluminal surface **620**, a first
30 coating layer **622**, a second coating layer **624**, and a third coating layer **626**. However, coatings may have any suitable number of layers, including 1, 2, 3, 4,

5, and 6-layer coatings applied to the luminal surface **610** and/or the abluminal surface **622**. At least one or more separate sheet layers that include JNK inhibitors embedded or otherwise included in the carrier material, which may be placed near the medical device or between the elements of the device, are also contemplated.

In one aspect, the coating **612** may form a concentration gradient of a JNK inhibitor. For example, in FIG. 7, the coating **610** comprises a first coating layer **622** having a first concentration of the JNK inhibitor in a carrier material, a second coating layer **624** having a second concentration of the JNK inhibitor in a carrier material and a third coating layer **626** having a third concentration of the JNK inhibitor in a carrier material. The carrier material may include, for example, a bioabsorbable polymer and/or a porous biostable polymer. Alternatively, the one or more coating layers may be positioned on the luminal surface **610** instead, or in addition to, positioning coating layers on the abluminal surface **620**. The layers may optionally include the JNK inhibitor in combination with other bioactive agents, and/or carrier compositions.

In another aspect, the coating **612** may include one or more layers having different compositions. For example, the first coating layer **622** may be an adhesion-promoting layer comprising a material such as parylene or silane that promotes the adhesion of the second coating layer **624** to the coated medical device surface (e.g., the luminal surface **610** or the abluminal surface **620**). The second coating layer **624** may include the JNK inhibitor and optionally comprise a carrier material such as a bioabsorbable polymer. The third coating layer **626** may include a porous material through which the JNK inhibitor in the second coating layer **624** may diffuse. Optionally, the third coating layer **626** may include a soluble material impregnated within an insoluble porous material, such that dissolution of the soluble material upon implantation of the medical device results in the formation of pores in the third coating layer **626**. This or other layers may also contain adhesive material(s) that cause the layer(s) to adhere to the aorta wall.

Illustrative embodiments of the present invention have been described in considerable detail for the purpose of disclosing a practical, operative structure whereby the invention may be practiced advantageously. The embodiments described herein are intended to be exemplary only. The invention encompasses
5 embodiments both comprising and consisting of the elements described herein with reference to the illustrative embodiments.

Combination Therapy

In one embodiment, the invention provides a medical device comprising
10 one or more JNK inhibitor(s) and one or more other bioactive agents. Preferably, therapeutically effective amounts of the JNK inhibitor and bioactive agents are provided. Examples of suitable JNK inhibitors were described above.

Other bioactive agents may be incorporated with the medical device using the methods which were described above in connection with incorporating the
15 JNK inhibitor(s) with the medical device of this invention.

Other bioactive agents that may be incorporated with the medical device of this invention include MMPs inhibitors, including endogenous inhibitors, such as tissue inhibitors of MMPs (TIMPs) and α -macroglobulins, and synthetic inhibitors, such as chelating agents (e.g., EDTA and 1,10-phenanthroline),
20 peptides, antibodies, and the like. Agents that would enhance function of TIMPs may also be used.

Any suitable tetracycline, including tetracycline per se, or tetracycline-derivative compounds, preferably doxycycline hydrate, doxycycline aureomycin and chloromycin may be included. Preferred tetracycline compounds include
25 CMTs (CMT that lack the dimethylamino group at position 4 of the ring structure of tetracycline, including 4-dedimethylaminotetracycline (CMT-1), 4-dedimethylamino-5-oxytetracycline, 4-dedimethylamino-7-chlorotetracycline (CMT-4), 4-hydroxy-4-dedimethylaminotetracycline (CMT-6), 5 a,6-anhydro-4-hydroxy-4-dedimethylaminotetracycline, 6-demethyl-6-deoxy-4-
30 dedimethylaminotetracycline (CMT-3; COL-3), 4-dedimethylamino-12a-deoxytetracycline (CMT-7), and 6- α -deoxy-5-hydroxy-4-

dedimethylaminotetracycline (CMT-8); tetracyclines modified at the 2 carbon position to produce a nitrile, e.g., tetracyclinonitrile; 6- α -benzylthiomethylenetetracycline, the mono-N-alkylated amide of tetracycline, 6-fluoro-6-demethyltetracycline, and 11 α -chlorotetracycline).

5 In another embodiment beta blockers may be included. Beta blockers include acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, esmolol, labetolol, metoprolol, nadolol, penbutolol, pindolol, propranolol, and timolol.

Other bioactive agents useful in embodiments of this invention include cyclooxygenase-2 (COX-2) inhibitors; angiotensin-converting enzyme (ACE)
10 inhibitors; glucocorticoids; nitric acid synthase (NOS) inhibitors; other anti-inflammatories; anti-oxidants; and cellular adhesion molecules (CAMs).

COX-2 inhibitors include Celecoxib, Rofecoxib, Valdecoxib, Etoricoxib, Parecoxib, all of which are available in pharmacological preparations. Additionally, COX-2 inhibition has been demonstrated from herbs, such as green
15 tea, ginger, turmeric, chamomile, Chinese gold-thread, barberry, baikal skullcap, Japanese knotweed, rosemary, hops, feverfew, and oregano; and other agents, such as piroxicam, mefenamic acid, meloxicam, nimesulide, diclofenac, MF-tricyclide, raldecoxide, nambumetone, naproxen, herbimycin-A, and diaryl hydroxyfuranones.

20 NSAIDs that may be used in embodiments according to the present invention include ketoralac tromethamine (Toradol), indomethacin, ketorolac, ibuprofen and aspirin among others. Additionally, steroidal based anti-inflammatories, such as methylprednisolone, dexamethasone or sulfasalazine may be provided. Other suitable anti-inflammatory agents include cyclosporine A
25 and azathioprine.

Another type of suitable bioactive agents are anti-oxidants, such as curcumin, vitamins, and vitamin constituents, such as α -tocopherol and β -carotene.

Yet other bioactive agents include ACE inhibitors, such as captopril,
30 enalapril, losartan and lisinopril and the active forms of several ACE inhibitor prodrugs on the market.

Another group of bioactive agents that may be used include cathepsin inhibitors. Cathepsin inhibitors may be classified as cysteine proteinase inhibitors, aspartic proteinase inhibitors, or serine proteinase inhibitors. For a comprehensive review of cathepsin inhibitors see Kim W. and Kang K, "Recent
5 developments of cathepsin inhibitors and their selectivity," Expert Opin. Ther. Patents (2002) 12(3), pp 419-432. The medical devices comprising cathepsin inhibitors were previously described in US 2007/0293937, which is incorporated herein by reference in its entirety.

Other bioactive agents, such as the NOS inhibitors, including
10 aminoguanidine are also useful in combination with the JNK inhibitors of preferred embodiments of the present invention.

Elastin-stabilizing compounds, such as phenolic tannin compounds, may also be included with the JNK inhibitors. Phenolic tannin compounds were previously described in WO 2007/133479, which is incorporated herein in its
15 entirety.

Preferred embodiments of the invention also provide medical device coatings comprising the JNK inhibitor(s) in combination with one or more bioactive agents described in U.S. Patent No. 5,834,449; U.S. Publication Nos. 2005/0266043 A1, published on Dec. 1, 2005, and 2006/0004441 A1, published
20 on Jan. 5, 2006, which are incorporated herein by reference.

Additional Embodiments:

In one embodiment, a method for treating an aneurysm or an aortic dissection comprises delivering a medical device and a c-Jun N-terminal kinase (JNK) inhibitor compound to a body lumen within a subject having the aneurysm
25 or aortic dissection, the medical device being adapted to release the JNK inhibitor within the body lumen of the subject. In the method, the JNK inhibitor compound may be selected from the group consisting of 3-(4-fluorophenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole; 3-(3-(2-(piperidin-1-yl)ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole; 3-(4-fluorophenyl)-1H-indazole-5-carboxylic acid
30 (3-morpholin-4-yl-propyl)-amide; 3-(3-(3-(piperidin-1-yl)propionylamino)phenyl)-1H-indazole-5-carboxylic acid amide; 3-(benzo[1,3]dioxol-5-yl)-5-(2H-tetrazol-5-

yl)-1H-indazole; 3-(4-fluorophenyl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-indazole;
 N-tert-buty-3-(5-(1H-1,2,4-triazol-3-yl)-1H-indazol-3-yl)-benzamide; 3-(3-(2-
 morpholin-4-yl-ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole; dimethyl-(2-
 (4-(5-(1H-1,2,4-triazol-3-yl)-1H-indazol-3-yl)-phenoxy)-ethyl)-amine; 5-(5(1,1-
 5 dimethyl-propyl)-1H-[1,2,4]triazol-3-yl)-3-(4-fluorophenyl)-1H-indazole; 3-(4-
 fluorophenyl)-5-(5-((pyrrolidin-1-yl)methyl)-1H-1,2,4-triazol-3-yl)-1H-indazole; 3-
 (6-methoxy-naphthalen-2-yl)-5-(5-(pyrrolidin-1-ylmethyl)-1H-[1,2,4]-triazol-3-yl)-
 1H-indazole; 3-(4-fluorophenyl)-1H-indazole-5-carboxylic acid amide; 4-(4-(4-
 chlorophenyl)pyrimidin-2-ylamino)benzamide; 4-(4-(4-chlorophenyl)pyrimidin-2-
 10 ylamino)-N,N-dimethylbenzamide; 4-(4-(4-chlorophenyl)pyrimidin-2-ylamino)-N-
 (3-(piperidin-1-yl)propyl)benzamide; (4-(4-(4-chlorophenyl)pyrimidin-2-
 ylamino)phenyl)(piperazin-1-yl)methanone; 1-(4-(4-(4-(4-chlorophenyl)pyrimidin-
 2-ylamino)-benzoyl)-piperazin-1-yl)-ethanone; 1-(4-(4-(4-(4-(3-hydroxy-
 propylsulfanyl)-phenyl)-pyrimidin-2-ylamino)-benzoyl)-piperazin-1-yl)-ethanone;
 15 (4-(4-(4-chloro-phenyl)-pyrimidin-2-ylamino)-phenyl)-(4-(pyrrolidin-1-yl)-piperidin-
 1-yl)-methanone; 2H-dibenzo[cd,g]indazol-6-one; 7-chloro-2H-
 dibenzo[cd,g]indazol-6-one; 5-dimethylamino-2H-dibenzo[cd,g]indazol-6-one; 7-
 benzyloxy-H-dibenzo[cd,g]indazol-6-one; N-(6-oxo-2,6-dihydro-
 dibenzo[cd,g]indazol-6-one; 5-(2-piperdin-1-yl-ethylamino)-2H-
 20 dibenzo[cd,g]indazol-6-one; 5-amino-anthra[9,1-cd]isothiazo-6-one; N-(6-oxo-6H-
 anthra[9,1-cd]isothiazol-5-yl)-benzamide; 7-dimethylamine-anthra[9,1-
 cd]isothiazol-6-one; and 2-oxa-1-azo-aceanthrylen-6-one; derivatives; and
 mixtures thereof. In the method, the JNK inhibitor compound may be selected
 from the group consisting of compounds 37, 38, 39, 40, 41, 42, 43, 44, 45, and
 25 46, derivatives thereof, and mixtures thereof. In the method, the JNK inhibitor
 compound may be a 3,5 disubstituted indazole. In the method, the JNK inhibitor
 compound may be selected from the group consisting of JNK Inhibitor 1 (L-
 stereoisomer) (SEQ ID NO: 1; GRKKRRQRRR-PP-RPKRPTTLNLFQVPRSQD-
 amide); JNK Inhibitor I, (L)-Form (SEQ ID NO 2: H-
 30 GRKKRRQRRRPPRPKRPTTLNLFQVPRSQDT-NH₂); Anthra[1,9-cd]pyrazol-
 6(2H)-one; JNK Inhibitor III (SEQ ID NO: 3: Ac-YGRKKRRQRRR-gaba-

ILKQSMTLNLADPVGSLKPHLRAKN-NH₂); JNK Inhibitor V (AS601245; 1,3-Benzothiazol-2-yl-(2-((2-(3-pyridinyl)ethyl)amino)-4-pyrimidinyl)acetonitrile); benzothiazole acetonitrile derivatives; JNK Inhibitor VI (SEQ ID NO: 4: H₂N-RPKRPTTLNLF-NH₂); JNK Inhibitor VII, TAT-TI-JIP₁₅₃₋₁₆₃ (SEQ ID NO: 5: H₂N-YGRKKRRQRRR-RPKRPTTLNLF-NH₂); SB203580 (4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)1H-imidazole); Aloisine A (7-*n*-Butyl-6-(4-hydroxyphenyl)[5H]pyrrolo[2,3-*b*]pyrazine); 4-Hydroxynoneal; and PD98059 (2'-amino-3'-methoxyflavone). In the method, the medical device may be a stent. In the method, the stent may comprise a plurality on interconnected struts and bends and the JNK inhibitor compound may be releasably associated with the struts, bends, or a combination thereof. In the method, the stent may alternatively comprise a plurality of Z-stents. In the method, the stent may further comprise a coating comprising the JNK inhibitor compound. In the method, the coating may comprise one or more layers comprising the JNK inhibitor compound and a bioabsorbable polymer. In the method, the medical device may be a stent graft comprising a support frame attached to a flexible tubular covering, the JNK inhibitor compound releasably associated with at least a portion of the stent graft. In the method, the medical device may comprise at least one surface adapted for contact with a body vessel wall and the JNK inhibitor compound coated on at least a portion of the at least one surface. In the method, the medical device may comprise an elongated member having (i) an abluminal surface and (ii) a luminal surface defining a cylindrical lumen extending longitudinally along the length of the elongated member, wherein the JNK inhibitor compound may be releasably associated with at least one surface of the elongated member. In the method, the medical device may be a stent graft wherein the elongated member may be configured as a flexible tubular covering, and further comprising a radially expandable support frame comprising a plurality of hoops attached to the elongated member, the cylindrical lumen forming a fluid conduit defined by the luminal surface, wherein the JNK inhibitor compound may be releasably associated with the abluminal surface of the elongated member. In the method, the medical device may be a stent graft wherein the elongated member may be

configured as a flexible tubular covering, wherein the flexible tubular covering comprises ePTFE or PTFE and the radially expandable support frame comprises a plurality of radially-expandable members each comprising a plurality of interconnecting struts and bends. In the method, the flexible tubular covering
5 may comprise a covering selected from the group consisting of polyesters, polyurethanes, polyethylenes, polyethylene terephthalates, polypropylenes, polytetrafluoroethylenes, reconstituted or naturally-derived collagenous materials, and small intestine submucosa. In the method, the medical device may be a balloon catheter comprising an expandable surface, and a coating on the
10 expandable surface, wherein the coating comprises the JNK inhibitor compound. In the method, the medical device may be a graft. In the method, the JNK inhibitor compound may be contained within a reservoir associated with the medical device. In the method, the JNK inhibitor compound may be contained within a well or a groove on a surface of the medical device. In the method, the
15 JNK inhibitor compound may be in or disposed on at least one separate carrier layer on a surface of the medical device. The method may further comprise a step of delivering a bioactive agent selected from the group consisting of matrix metalloproteinases' inhibitors, tetracycline, tetracycline-derivative compounds, beta blockers, cyclooxygenase-2 (COX-2) inhibitors, angiogenesis-converting
20 enzyme (ACE) inhibitors, glucocorticoids, nitric acid synthase (NOS) inhibitors, anti-inflammatories, anti-oxidants, cellular adhesion molecules (CAMs), cathepsin inhibitors, and phenolic tannins, derivatives, and mixtures thereof. In the method, the medical device may be adapted to release the bioactive agent.

In another embodiment, the invention is a method of treating an aneurysm
25 or an aortic dissection comprising radially expanding a medical device in a lumen with a balloon catheter, wherein the balloon catheter releases a JNK inhibitor compound.

In yet another embodiment, the invention is a method of treating an aneurysm or an aortic dissection comprising radially expanding a balloon
30 catheter comprising a JNK inhibitor compound in a lumen, wherein the balloon catheter releases the JNK inhibitor compound within the lumen.

In still another embodiment, the invention is a medical device and a c-Jun N-terminal kinase (JNK) inhibitor for treatment of abdominal aortic aneurysm or an aortic dissection, the medical device being adapted to release the JNK inhibitor within a body lumen of a patient. The JNK inhibitor may be selected

5 from the group consisting of 3-(4-fluorophenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole; 3-(3-(2-(piperidin-1-yl)ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole; 3-(4-fluorophenyl)-1H-indazole-5-carboxylic acid (3-morpholin-4-yl-propyl)-amide; 3-(3-(3-(piperidin-1-yl)propionylamino)phenyl)-1H-indazole-5-carboxylic acid amide; 3-(benzo[1,3]dioxol-5-yl)-5-(2H-tetrazol-5-yl)-1H-indazole;

10 3-(4-fluorophenyl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-indazole; N-tert-butyl-3-(5-(1H-1,2,4-triazol-3-yl)-1H-indazol-3-yl)-benzamide; 3-(3-(2-morpholin-4-ylethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole; dimethyl-(2-(4-(5-(1H-1,2,4-triazol-3-yl)-1H-indazol-3-yl)-phenoxy)-ethyl)-amine; 5-(5(1,1-dimethyl-propyl)-1H-[1,2,4]triazol-3-yl)-3-(4-fluorophenyl)-1H-indazole; 3-(4-fluorophenyl)-5-(5-

15 ((pyrrolidin-1-yl)methyl)-1H-1,2,4-triazol-3-yl)-1H-indazole; 3-(6-methoxynaphthalen-2-yl)-5-(5-(pyrrolidin-1-ylmethyl)-1H-[1,2,4]triazol-3-yl)-1H-indazole; 3-(4-fluorophenyl)-1H-indazole-5-carboxylic acid amide; 4-(4-(4-chlorophenyl)pyrimidin-2-ylamino)benzamide; 4-(4-(4-chlorophenyl)pyrimidin-2-ylamino)-N,N-dimethylbenzamide; 4-(4-(4-chlorophenyl)pyrimidin-2-ylamino)-N-

20 (3-(piperidin-1-yl)propyl)benzamide; (4-(4-(4-chlorophenyl)pyrimidin-2-ylamino)phenyl)(piperazin-1-yl)methanone; 1-(4-(4-(4-(4-chlorophenyl)pyrimidin-2-ylamino)-benzoyl)-piperazin-1-yl)-ethanone; 1-(4-(4-(4-(4-(3-hydroxypropylsulfanyl)-phenyl)-pyrimidin-2-ylamino)-benzoyl)-piperazin-1-yl)-ethanone; (4-(4-(4-chlorophenyl)-pyrimidin-2-ylamino)-phenyl)-(4-(pyrrolidin-1-yl)-piperidin-

25 1-yl)-methanone; 2H-dibenzo[cd,g]indazol-6-one; 7-chloro-2H-dibenzo[cd,g]indazol-6-one; 5-dimethylamino-2H-dibenzo[cd,g]indazol-6-one; 7-benzyloxy-H-dibenzo[cd,g]indazol-6-one; N-(6-oxo-2,6-dihydro-dibenzo[cd,g]indazol-6-one; 5-(2-piperdin-1-yl-ethylamino)-2H-dibenzo[cd,g]indazol-6-one; 5-amino-anthra[9,1-cd]isothiazo-6-one; N-(6-oxo-6H-

30 anthra[9,1-cd]isothiazol-5-yl)-benzamide; 7-dimethylamine-anthra[9,1-cd]isothiazol-6-one; and 2-oxa-1-azo-aceanthrylen-6-one; derivatives; and

mixtures thereof. The JNK inhibitor compound may be selected from the group consisting of compounds 37, 38, 39, 40, 41, 42, 43, 44, 45, and 46, derivatives thereof, and mixtures thereof. The JNK inhibitor may be a 3,5 disubstituted indazole. The JNK inhibitor may be selected from the group consisting of JNK

5 Inhibitor I (L-stereoisomer) (SEQ ID NO: 1; GRKKRRQRRR-PP-RPKRPTTLNLFQVPRSQD-amide); JNK Inhibitor I, (L)-Form (SEQ ID NO 2: H-GRKKRRQRRRPPRPKRPTTLNLFQVPRSQDT-NH₂); Anthra[1,9-*cd*]pyrazol-6(2*H*)-one; JNK Inhibitor III (SEQ ID NO: 3: Ac-YGRKKRRQRRR-gaba-ILKQSMTLNLADPVGSLKPHLRAKN-NH₂); JNK Inhibitor V (AS601245; 1,3-

10 Benzothiazol-2-yl-(2-((2-(3-pyridinyl)ethyl)amino)-4-pyrimidinyl)acetonitrile); benzothiazole acetonitrile derivatives; JNK Inhibitor VI (SEQ ID NO: 4: H₂N-RPKRPTTLNLF-NH₂); JNK Inhibitor VII, TAT-TI-JIP₁₅₃₋₁₆₃ (SEQ ID NO: 5: H₂N-YGRKKRRQRRR-RPKRPTTLNLF-NH₂); SB203580 (4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)1*H*-imidazole); Aloisine A (7-*n*-Butyl-6-(4-

15 hydroxyphenyl)[5*H*]pyrrolo[2,3-*b*]pyrazine); 4-Hydroxynoneal; and PD98059 (2'-amino-3'-methoxyflavone). The medical device may be a stent. The stent may

comprise a plurality of interconnected struts and bends and the JNK inhibitor may be releasably associated with the struts, bends, or a combination thereof. The

stent may comprise a plurality of Z-stents. The stent may further comprise a

20 coating comprising the JNK inhibitor. The coating may comprise one or more layers comprising the JNK inhibitor and a bioabsorbable polymer. The medical

device may be a stent graft comprising a support frame attached to a flexible tubular covering, the JNK inhibitor releasably associated with at least a portion of the stent graft. The medical device may comprise at least one surface adapted

25 for contact with a body vessel wall and the JNK inhibitor coated on at least a portion of at least one surface. Th medical device may comprise an elongated member having (i) an abluminal surface and (ii) a luminal surface defining a cylindrical lumen extending longitudinally along the length of the elongated

member, wherein the JNK inhibitor may be releasably associated with at least

30 one surface of the elongated member. The medical device may be a stent graft wherein the elongated member may be configured as a flexible tubular covering,

and further may comprise a radially expandable support frame comprising a plurality of hoops attached to the elongated member, the cylindrical lumen forming a fluid conduit defined by the luminal surface, wherein the JNK inhibitor may be releasably associated with the abluminal surface of the elongated member. The medical device may be a stent graft wherein the elongated member may be configured as a flexible tubular covering, wherein the flexible tubular covering may comprise ePTFE or PTFE and the radially expandable support frame may comprise a plurality of radially-expandable members each comprising a plurality of interconnecting struts and bends. The flexible tubular covering may comprise a covering selected from the group consisting of polyesters, polyurethanes, polyethylenes, polyethylene terephthalates, polypropylenes, polytetrafluoroethylenes, reconstituted or naturally-derived collagenous materials, and small intestine submucosa. The medical device may be a balloon catheter comprising an expandable surface, and a coating on the expandable surface, wherein the coating comprises the JNK inhibitor. The device may be a graft. The JNK inhibitor may be contained within a reservoir associated with the medical device. The JNK inhibitor may be contained within a well or a groove on a surface of the medical device. The JNK inhibitor may be in or disposed on at least one separate carrier layer on a surface of the medical device. The device may further comprise a bioactive agent selected from the group consisting of matrix metalloproteinases' inhibitors, tetracycline, tetracycline-derivative compounds, beta blockers, cyclooxygenase-2 (COX-2) inhibitors, angiogenesis-converting enzyme (ACE) inhibitors, glucocorticoids, nitric acid synthase (NOS) inhibitors, anti-inflammatories, anti-oxidants, cellular adhesion molecules (CAMs), cathepsin inhibitors, and phenolic tannins, derivatives, and mixtures thereof. The medical device may be adapted to release the bioactive agent.

In yet another embodiment a kit comprises a medical device; and a balloon catheter comprising a JNK inhibitor compound.

In addition to the embodiments described above, embodiments of the invention includes combinations of the preferred embodiments discussed above, and variations of all embodiments.

5 The disclosures in United States patent application no. 60/881,879, from which this application claims priority, and in the abstract accompanying this application are incorporated herein by reference.

SEQUENCE LISTING

<110> Grewe, David D.
 Biggs, David P.
 Ragheb, Anthony O.
 Ruane, Patrick H.

 <120> METHODS AND MEDICAL DEVICES FOR TREATING AN ANEURYSM AND AN
 AORTIC DISSECTION BY LOCAL DELIVERY OF JNK INHIBITOR COMPOUNDS

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CLAIMS

1. A medical device (10; 100; 150; 200; 400) for treating an aneurysm or an aortic dissection (230; 530), the device including a c-Jun N-terminal kinase (JNK) inhibitor compound, the medical device being adapted to release the JNK inhibitor within a body lumen of a subject having the aneurysm or aortic dissection.
5
2. A device as claimed in claim 1, wherein the JNK inhibitor compound is a 3,5 disubstituted indazole.
3. A device as claimed in claim 1 or 2, wherein the medical device is a
10 stent (10; 430).
4. A device as claimed in claim 3, wherein the stent includes a plurality of interconnected struts (16) and bends (14) and the JNK inhibitor compound is releasably associated with the struts, bends, or a combination thereof.
- 15 5. A device as claimed in claim 3, wherein the stent (10; 430) includes a plurality of Z-stents.
6. A device as claimed in claim 3, 4 or 5, wherein the stent (10, 430) includes a coating (26) including the JNK inhibitor compound.
7. A device as claimed in claim 6, wherein the coating (26) includes
20 one or more layers (26, 29) including the JNK inhibitor compound and a bioabsorbable polymer.
8. A device as claimed in any preceding claim, wherein the medical device is a stent graft (100; 150; 200) including a support frame attached to a flexible tubular covering, the JNK inhibitor compound releasably associated with
25 at least a portion of the stent graft.
9. A device as claimed in any preceding claim, wherein the medical device (10; 100; 150; 200; 400) includes at least one surface (24) arranged to contact a body vessel wall (406; 502) and the JNK inhibitor compound is coated on at least a portion of the wall-contacting surface.

10. A device as claimed in any preceding claim, wherein the medical device (10; 100; 150; 200; 400) includes an elongated member having (i) an abluminal surface (124) and (ii) a luminal surface (122) defining a lumen (118) extending longitudinally along the length of the elongated member, wherein the JNK inhibitor compound is releasably associated with at least one surface (22, 24) of the elongated member.

11. A device as claimed in claim 10, wherein the medical device is a stent graft (100; 150; 200) wherein the elongated member is configured as a flexible tubular covering (130), and including a radially expandable support frame (112) comprising a plurality of hoops (110) attached to the elongated member, the lumen (118) forming a fluid conduit defined by the luminal surface (122), wherein the JNK inhibitor compound is releasably associated with the abluminal surface (124) of the elongated member.

12. A device as claimed in claim 10 or 11, wherein the medical device is a stent graft (100; 150; 200) wherein the elongated member is configured as a flexible tubular covering (130), wherein the flexible tubular covering comprises ePTFE or PTFE and the radially expandable support frame (112) comprises a plurality of radially-expandable members each comprising a plurality of interconnecting struts and bends.

13. A device as claimed in any preceding claim, wherein the device includes a flexible tubular covering (130) comprising polyester, polyurethane, polyethylene, polyethylene terephthalate, polypropylene, polytetrafluoroethylene, reconstituted or naturally-derived collagenous material, and/or small intestine submucosa.

14. A device as claimed in any preceding claim, wherein the medical device is a balloon catheter (410) including an expandable surface (440), and a coating on the expandable surface, wherein the coating includes the JNK inhibitor compound.

15. A device as claimed in any of claims 1 to 13, wherein the medical device is a graft.

16. A device as claimed in any preceding claim, wherein the JNK inhibitor compound is contained within a reservoir associated with the medical device (10; 100; 150; 200; 400).

5 17. A device as claimed in any preceding claim, wherein the JNK inhibitor compound is contained within a well or a groove (326) on a surface of the medical device (10; 100; 150; 200; 400).

18. A device as claimed in any preceding claim, wherein the JNK inhibitor compound is in or is disposed on at least one separate carrier layer on a surface of the medical device (10; 100; 150; 200; 400).

10 19. A device as claimed in any preceding claim, including a bioactive agent that is a matrix metalloproteinase inhibitor, tetracycline, a tetracycline-derivative compound, a beta blocker, a cyclooxygenase-2 (COX-2) inhibitor, an angiogenesis-converting enzyme (ACE) inhibitor, a glucocorticoid, a nitric acid synthase (NOS) inhibitor, an anti-inflammatory, an anti-oxidant, a cellular
15 adhesion molecule (CAM), a cathepsin inhibitor, and/or a phenolic tannin, and/or derivative, and/or mixtures thereof.

20. A method as claimed in claim 19, wherein the medical device is adapted to release the bioactive agent.

20 21. A medical device and a c-Jun N-terminal kinase (JNK) inhibitor for treatment of abdominal aortic aneurysm or an aortic dissection, the medical device being adapted to release the JNK inhibitor within a body lumen of a patient.

25 22. A method for treating an aneurysm or an aortic dissection (230; 530) including delivering a medical device (10; 100; 150; 200; 400) and a c-Jun N-terminal kinase (JNK) inhibitor compound to a body lumen within a subject having the aneurysm or aortic dissection, the medical device being adapted to release the JNK inhibitor within the body lumen of the subject.

23. A method as claimed in claim 22, wherein the JNK inhibitor is a 3, 5 disubstituted indazole.

24. A method for treating an aneurysm or an aortic dissection including delivering a medical device (10; 100; 150; 200; 400) as claimed in any of claims 1 to 21 to a body lumen within a subject having the aneurysm or aortic dissection.

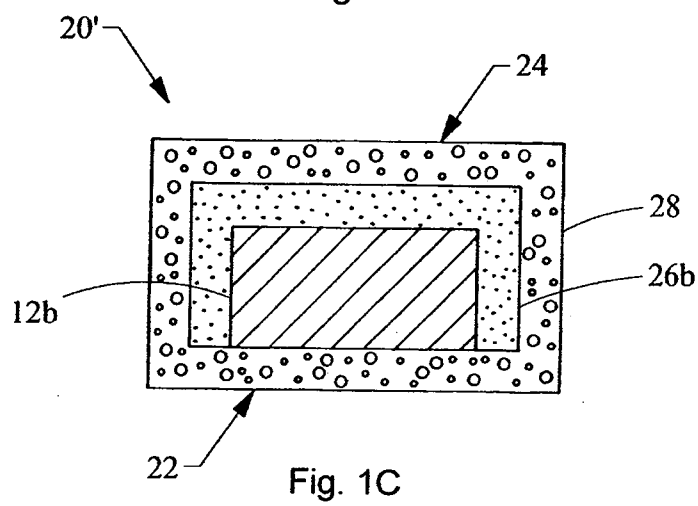
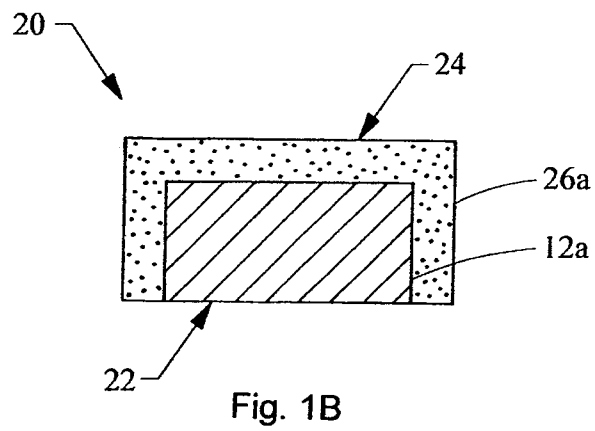
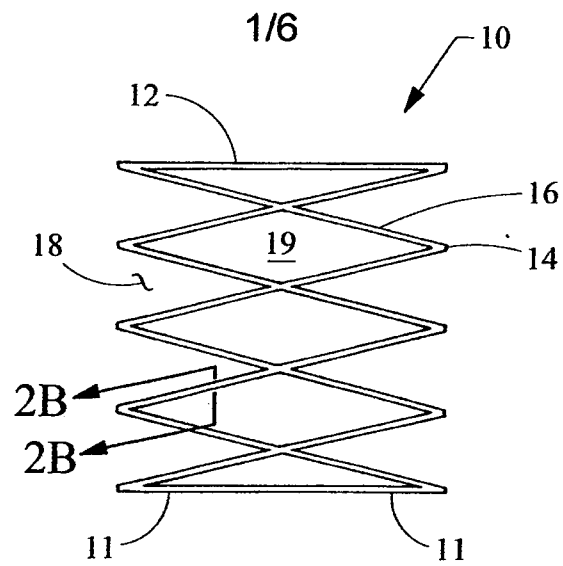
25. A method of treating an aneurysm or an aortic dissection (230; 530) including radially expanding a medical device (10; 100; 150; 200; 400) in a lumen with a balloon catheter (410), wherein the balloon catheter releases a JNK inhibitor compound.

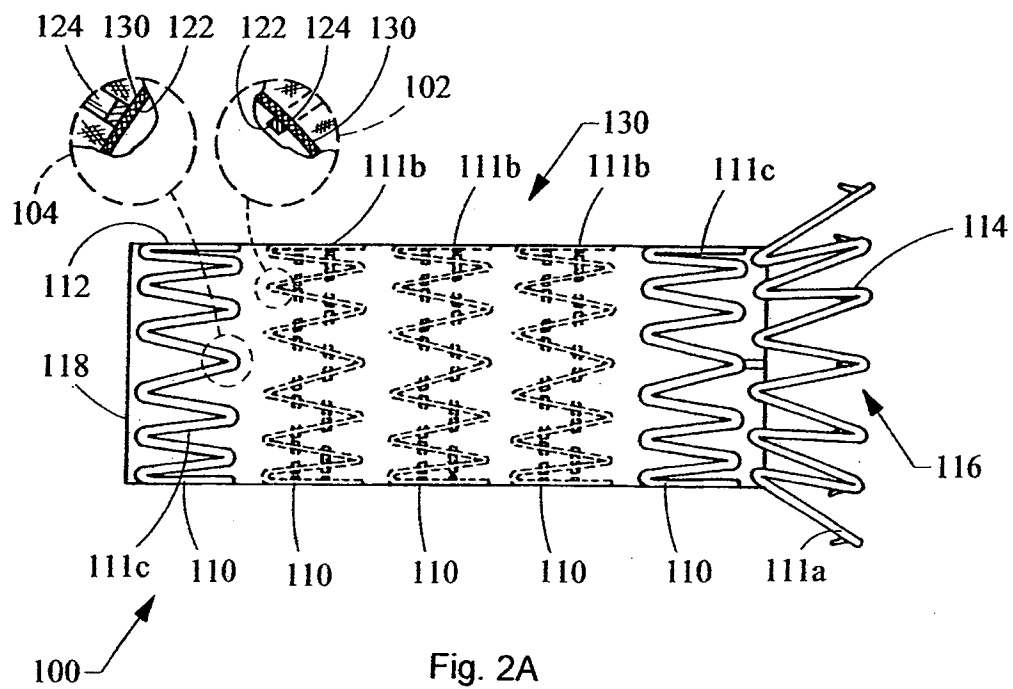
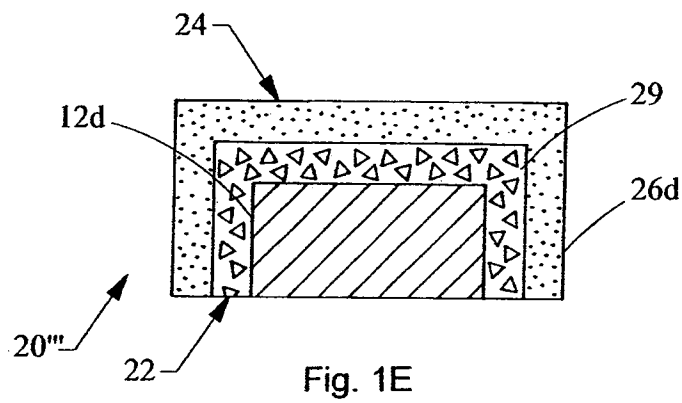
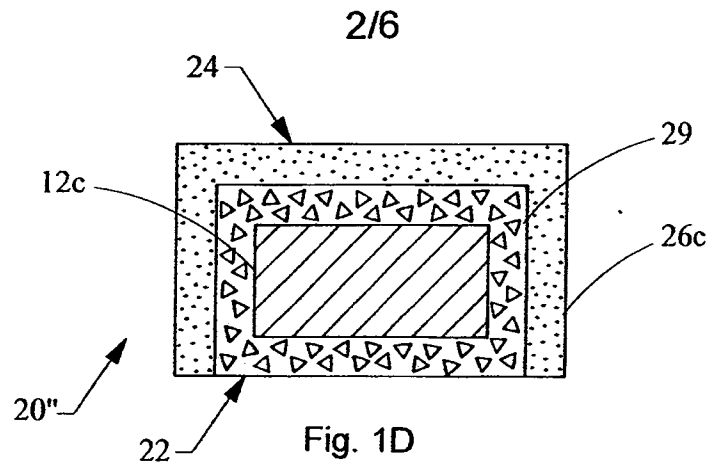
26. A method of treating an aneurysm or an aortic dissection (230; 530) including radially expanding a balloon catheter (410; 520) including a JNK inhibitor compound in a lumen, wherein the balloon catheter releases the JNK inhibitor compound within the lumen.

27. A kit including:
a medical device (10; 100; 150; 200; 400); and
a balloon catheter including a JNK inhibitor compound.

28. Use of JNK inhibitor in the manufacture of a medical device for treatment of abdominal aortic aneurysm or an aortic dissection.

29. Use of a JNK inhibitor in the manufacture of a medical device as claimed in any of claims 1 to 21 for treatment of abdominal aortic aneurysm or an aortic dissection.





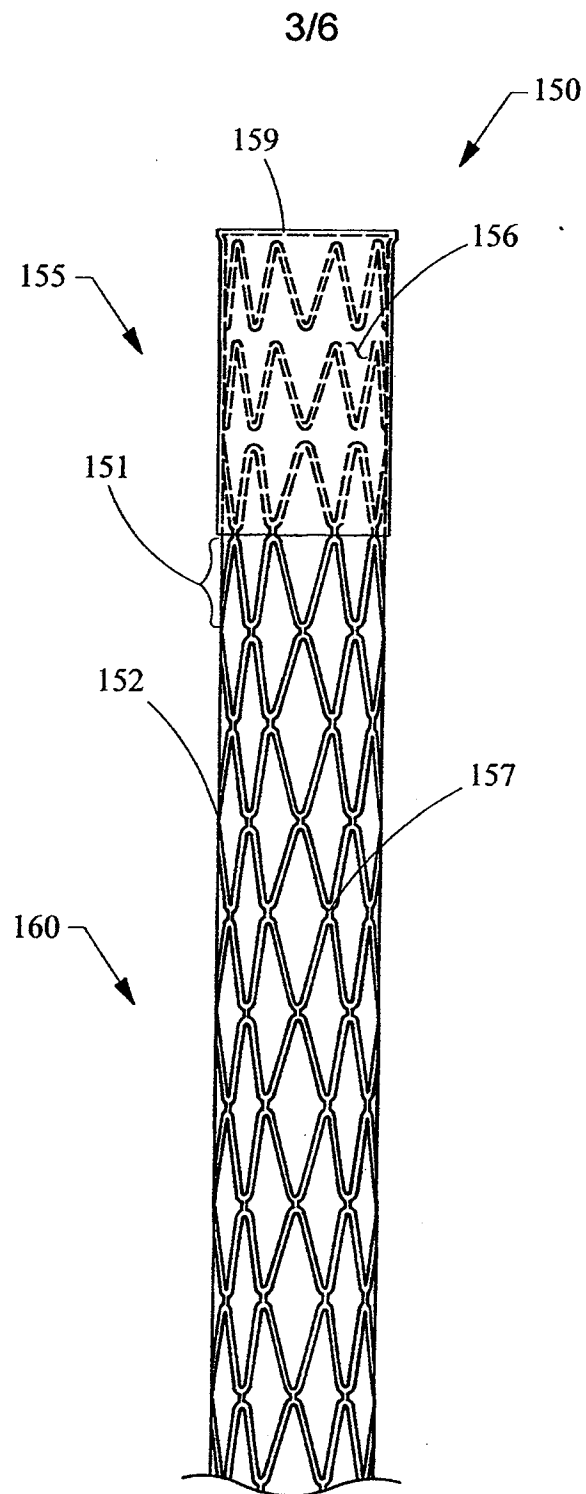


Fig. 2B

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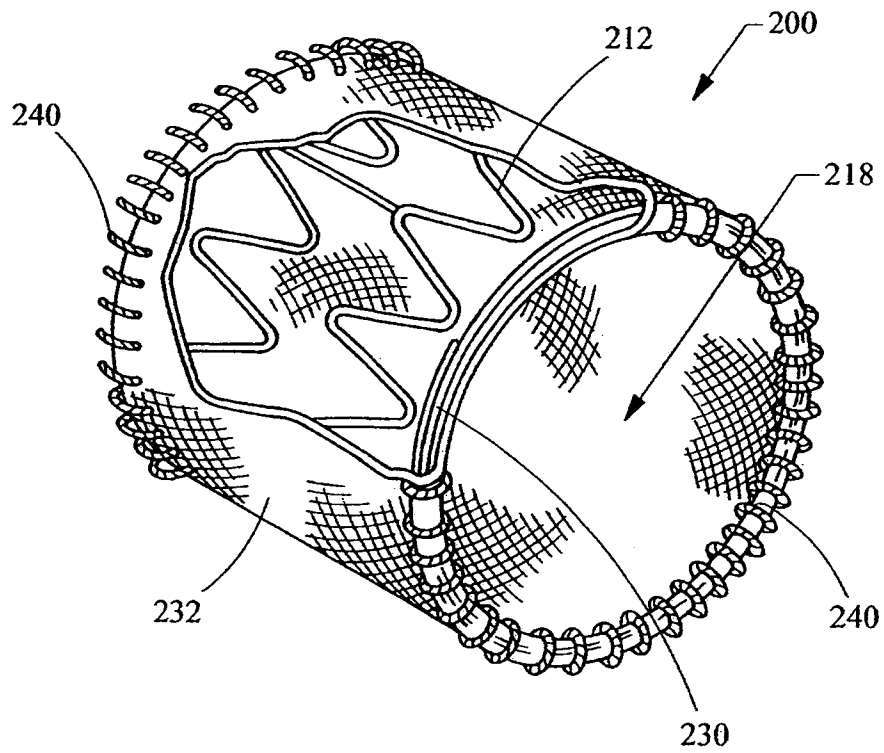


Fig. 3

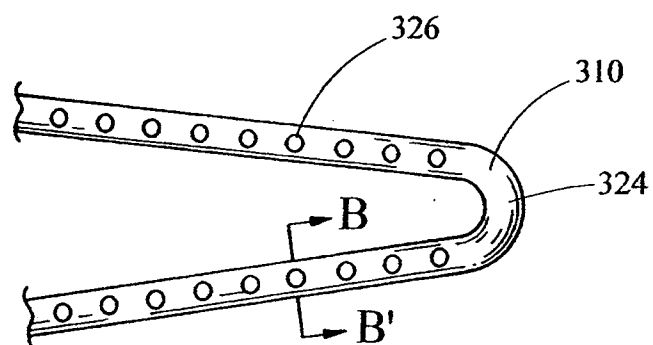


Fig. 4A

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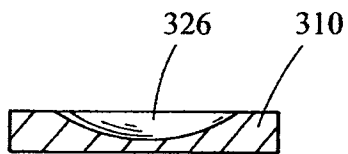


Fig. 4B

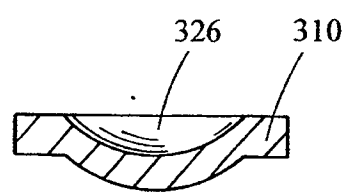


Fig. 4C

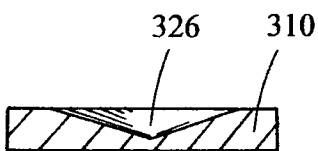


Fig. 4D

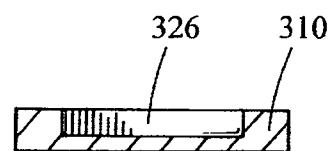


Fig. 4E

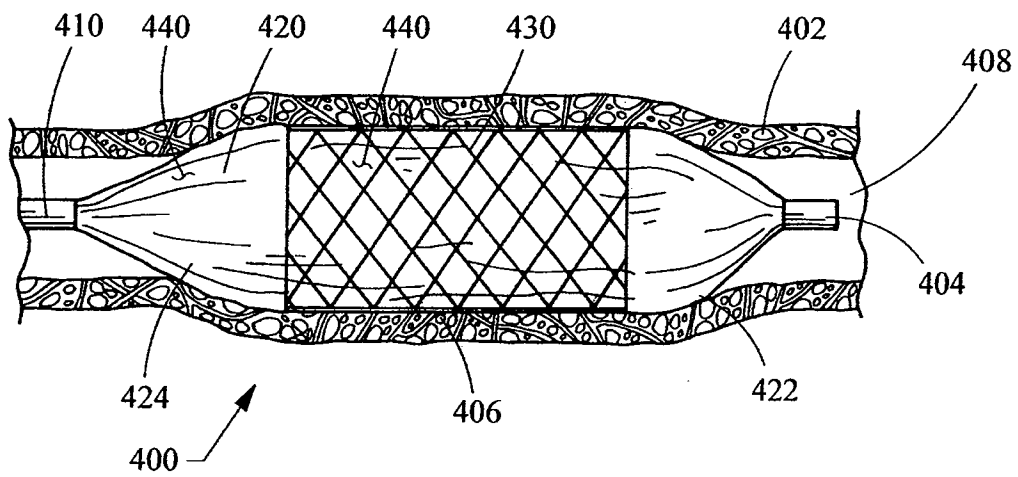


Fig. 5

