US 20060264368A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2006/0264368 A1

Ganesan et al. (43) Pub. Date: Nov. 23, 2006

(54) METHODS AND DEVICES FOR CONTRIBUTING TO THE TREATMENT OF ANEURYSMS

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(21) Appl. No.: **11/279,641**

(22) Filed: **Apr. 13, 2006**

Related U.S. Application Data

(63) Continuation of application No. 10/977,545, filed on Oct. 28, 2004.

Publication Classification

(51) **Int. Cl.**
A61K 38/39 (2006.01)
A61K 38/18 (2006.01)

(52) **U.S. Cl.** **514/12**

(57) **ABSTRACT**

The present invention relates to methods and devices to contribute to the treatment of aneurysms. More specifically, the present invention relates to methods and devices to contribute to contribute to the treatment of aneurysms by delivering bioactive agents via various delivery devices of collagen III and/or collagen III and thrombin.

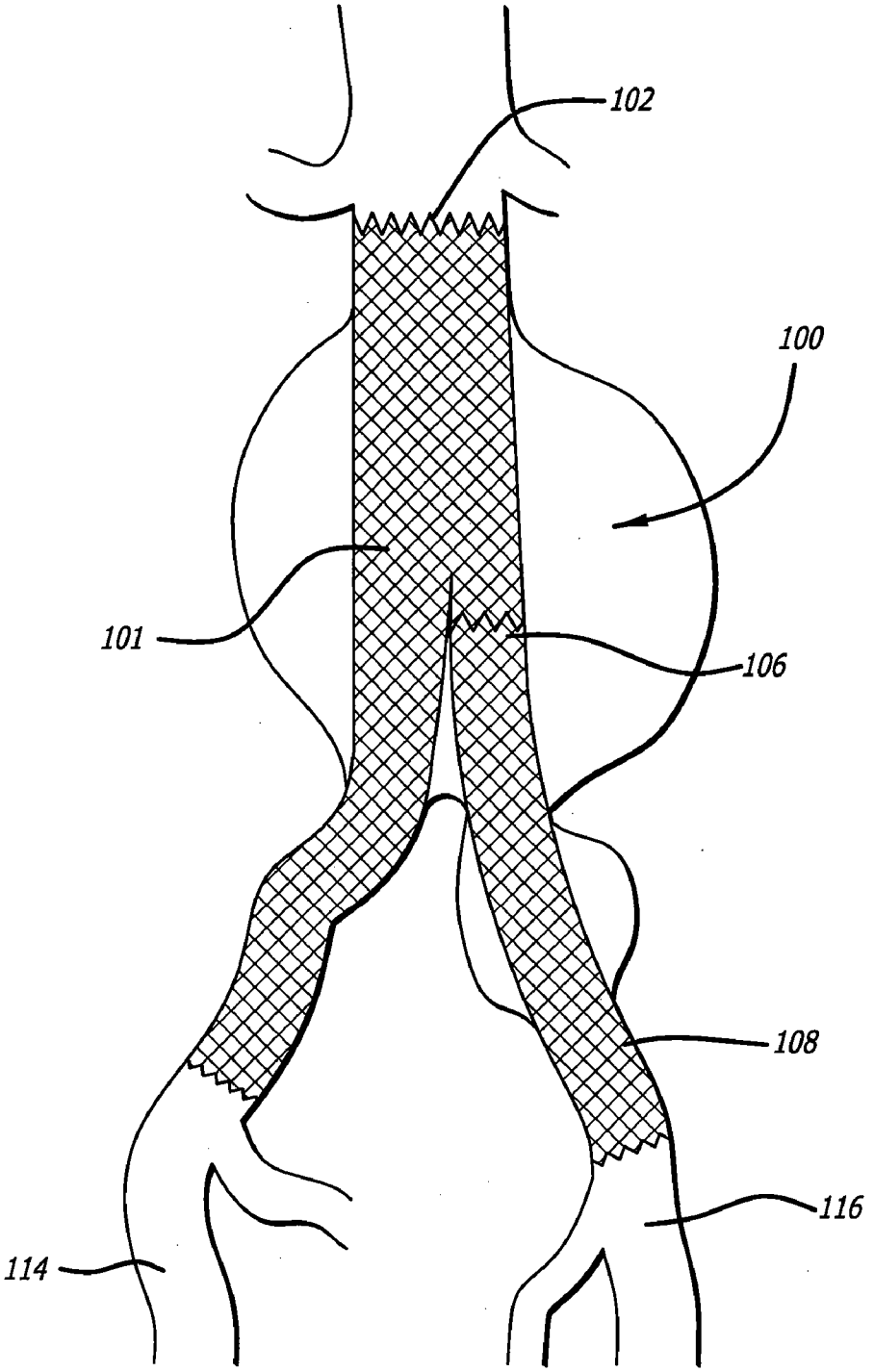
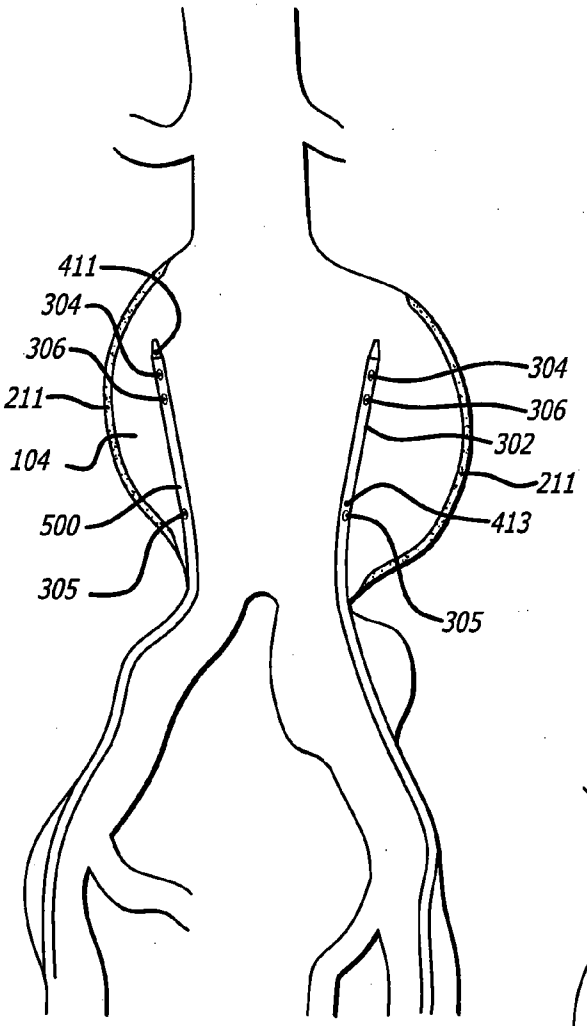


FIG. 1

FIG. 2


411
304
306
211
104
500
305
304
306
302
211
413
305

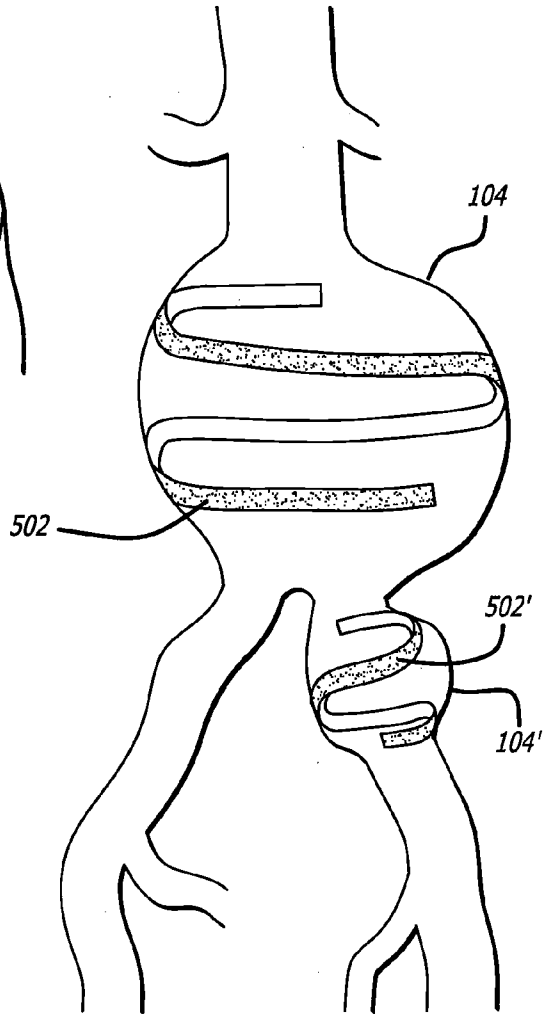

104
502
502'
104'

FIG. 3

FIG. 4

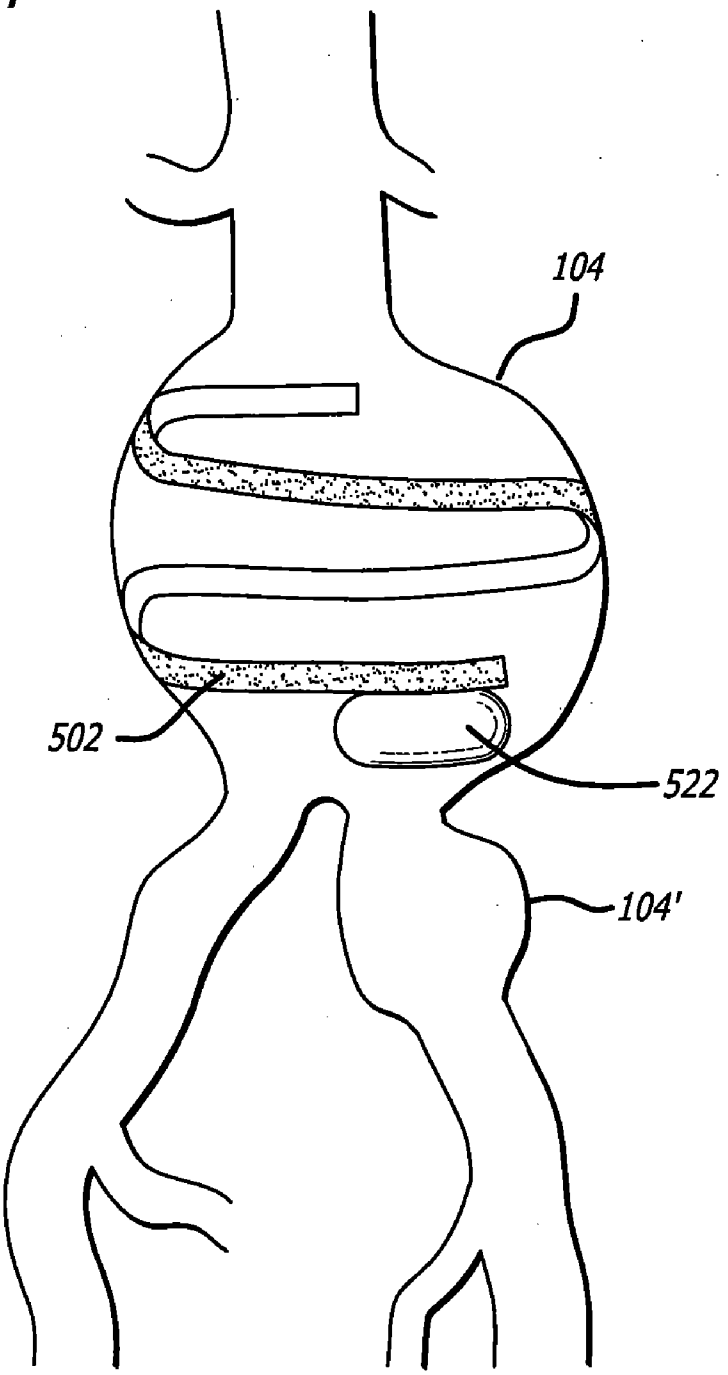
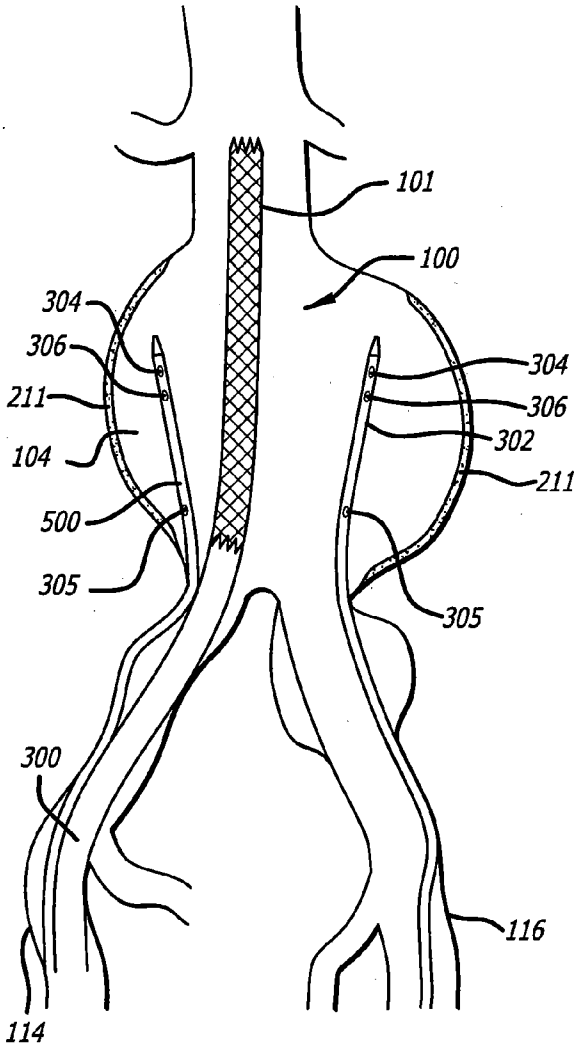


FIG. 5A


101
100
304
306
211
104
500
305
304
306
302
211
305
300
116
114

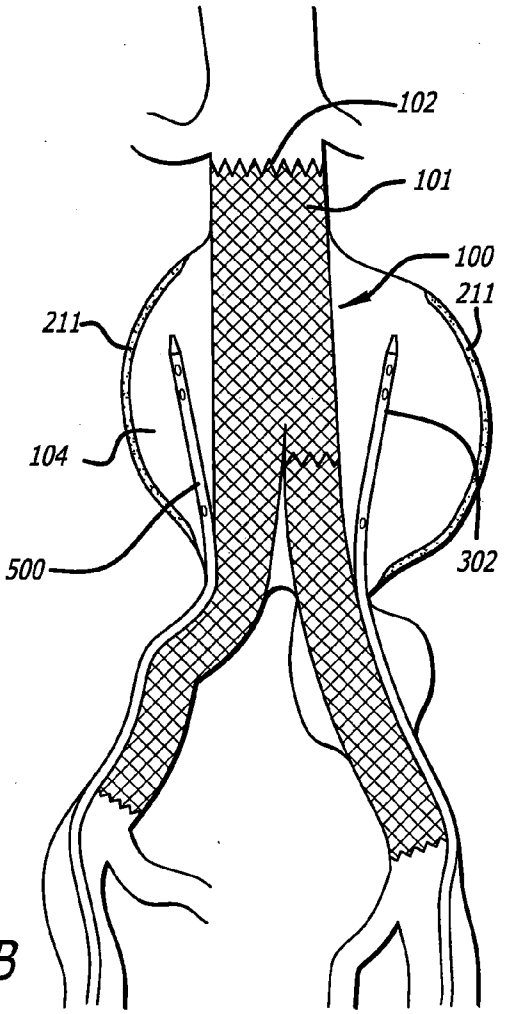
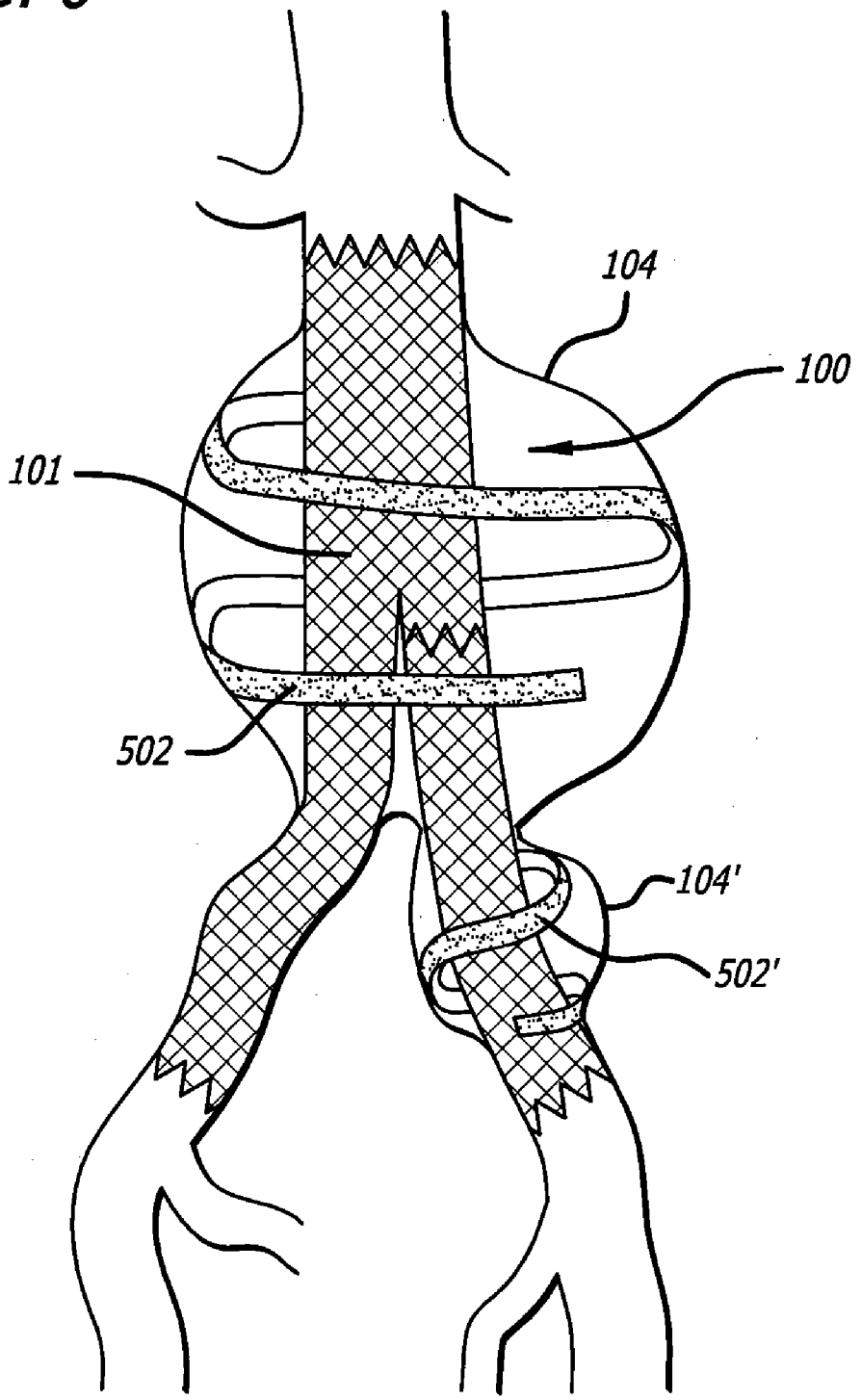

102
101
100
211
211
104
500
302

FIG. 5B

FIG. 6



METHODS AND DEVICES FOR CONTRIBUTING TO THE TREATMENT OF ANEURYSMS

CROSS REFERENCES TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of co-pending U.S. patent application Ser. No. 10/977,545 filed Oct. 28, 2004, which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to methods and devices to contribute to the treatment of aneurysms. More specifically, the present invention relates to methods and devices to contribute to the treatment of aneurysms by providing various methods through which to administer collagen III and/or collagen III and thrombin compositions to an aneurysm site.

BACKGROUND OF THE INVENTION

[0003] An aneurysm is a localized dilation of a blood vessel wall usually caused by degeneration of the vessel wall. These weakened sections of vessel walls can burst, causing an estimated 32,000 deaths in the United States each year. Additionally, aneurysm deaths are suspected of being underreported because sudden unexplained deaths, about 450,000 in the United States alone, are often simply misdiagnosed as heart attacks or strokes while many of them may be due to aneurysms.

[0004] U.S. surgeons treat approximately 50,000 abdominal aortic aneurysms each year, typically by replacing the abnormal section of vessel with a polymeric graft in an open surgical procedure. A less-invasive procedure that has more recently been used is the placement of a stent graft at the aneurysm site. Stent grafts are tubular devices that span the aneurysm site to provide support without replacing a section of the vessel. The stent graft, when placed within a vessel at an aneurysm site, acts as a barrier between blood flow and the weakened wall of a vessel, thereby decreasing pressure on the damaged portion of the vessel. Patients whose multiple medical comorbidities make them excessively high risk for conventional aneurysm repair are candidates for stent grafting.

[0005] While stent grafts can represent improvements over previously-used vessel treatment options, there are still risks associated with their use. The most common of these risks is migration of the stent graft due to matrix remodeling and/or hemodynamic forces within the vessel. Stent graft migrations can lead to endoleaks, or leaking of blood into the aneurysm sac between the outer surface of the graft and the inner lumen of the blood vessel which can increase the risk of vessel rupture. Such migrations of stent grafts are especially possible in curved portions of vessels where asymmetrical forces place uneven forces on the stent graft.

[0006] Based on the foregoing, one goal of treating aneurysms is to provide stent grafts that do not migrate. To achieve this goal, stent grafts with stainless steel anchoring barbs that engage the vessel wall have been developed. Additionally, endostaples that fix stent grafts more securely to the vessel wall have been developed. While these physical anchoring devices have proven to be effective in some patients, they have not sufficiently ameliorated stent graft migration associated with current treatment methods in all cases.

[0007] An additional way to reduce the risk of stent graft migration is to administer to the treatment site, either before, during or relatively soon after implantation, one or more growth factors. The administration of one or more growth factors can be beneficial because, normally, the material of the stent graft does not provide a hospitable environment for cells in the area to grow. As a result, the stent graft rests against the vessel wall, and may not be incorporated into the vessel wall. If one or more growth factors are administered immediately before, during, or relatively soon after stent graft deployment and implantation, the smooth muscle cells and fibroblasts will be stimulated to proliferate. As these cells proliferate they can grow around the stent graft such that the device becomes physically attached to the vessel wall rather than merely resting against it. This tissue in-growth can help to prevent stent graft migration, although it may not be successful in all circumstances. Therefore, there is still room for improvement in the treatment of aneurysms.

[0008] Another approach in the treatment of aneurysms, generally applied to cerebral aneurysms, includes the use of coil embolization. Coils used in this process are generally comprised of platinum and coated with a polymer. They are placed within an aneurysm sac and expected to block blood flow into the aneurysm sac and eventually lead to clot formation, thus shielding the aneurysm sac from the pressure of blood flow. In theory, the more organized clot formation and the more local connective tissue formation that occurs, the more resistant the aneurysm will be to pressure exerted by the general circulation.

[0009] Again, while coil embolization has proven beneficial in some patients, it is not successful in all patients. Coil embolization is not always successful because if it fails to sufficiently close off the aneurysm sac from blood flow, a process called "recanalization" occurs. In this process, blood flow moves into the area not completely closed off by clot and connective tissue formation and "reopens" the aneurysm site. Thus, improved aneurysm treatments are still required. The present invention provides methods and devices to further contribute to aneurysm treatment.

SUMMARY OF THE INVENTION

[0010] Embodiments according to the present invention provide methods and devices through which collagen III or collagen III and thrombin can be used to contribute to the treatment of aneurysms. For example, embodiments according to the present invention employ a collagen III ribbon to reinforce vessel walls and to deliver therapeutic agents to an aneurysm sac. Embodiments according to the present invention also provide for flowable collagen III or flowable collagen III/thrombin administration to an aneurysm site to mechanically reinforce the vessel walls. Collagen III and thrombin are excellent candidates for these functions due to their roles in cell proliferation and tissue in-growth. These various treatments can be employed alone or in combination and can also be employed in conjunction with more conventional stent grafting. When employed with a stent graft, embodiments according to the present invention can contribute to improved stent graft seal and fixation thus contributing to a reduction in the risk of endoleaks and stent graft migration.

[0011] Specifically, one embodiment according to the present invention comprises a method comprising contributing to the treatment of an aneurysm by placing a ribbon that administers collagen III at the aneurysm site.

[0012] In another embodiment the ribbon administers collagen III and an additional bioactive agent. In another embodiment the additional bioactive agent is a growth factor. In another embodiment the bioactive agent is one or more agents selected from the group consisting of collagen I, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), plated-derived epidermal growth factor (PDEGF), basic fibroblast growth factor (bFGF), fibroblast growth factors (FGFs), transforming growth factor-beta (TGF-β), platelet-derived angiogenesis growth factor (PDAF) and autologous platelet gel (APG) including platelet rich plasma (PRP) and platelet poor plasma (PPP) and thrombin.

[0013] In another embodiment the ribbon is a polymer ribbon.

[0014] In another embodiment the ribbon further comprises an osmotic mini-pump. In another embodiment the osmotic mini-pump releases a bioactive agent. In another embodiment the bioactive agent is selected from one or more of the group consisting of collagen I, collagen III, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), plated-derived epidermal growth factor (PDEGF), basic fibroblast growth factor (bFGF), fibroblast growth factors (FGFs), transforming growth factor-beta (TGF-β), platelet-derived angiogenesis growth factor (PDAF) and autologous platelet gel (APG) including platelet rich plasma (PRP) and platelet poor plasma (PPP) and thrombin.

[0015] In another embodiment the method further comprises deployment of a stent graft at the aneurysm site. In another embodiment the method further comprises administering flowable collagen III to the aneurysm site through an injection catheter. In another embodiment the method further comprises administering flowable collagen III and flowable thrombin to the aneurysm site through an injection catheter. In another embodiment the method further comprises deployment of a stent graft at the aneurysm site and administering flowable collagen III to the aneurysm site through an injection catheter. In another embodiment the method further comprises deployment of a stent graft at the aneurysm site, administering flowable collagen III to the aneurysm site through an injection catheter and administering flowable thrombin to the aneurysm site through an injection catheter.

[0016] Embodiments according to the present invention also include ribbons. In one embodiment the ribbon comprises collagen III and is deployed at an aneurysm site in conjunction with a treatment selected from the group consisting of the administration of collagen III to the aneurysm site through an injection catheter; the deployment of a stent graft at the aneurysm site; and the administration of collagen III to the aneurysm site through an injection catheter and the deployment of a stent graft at the aneurysm site. In another embodiment of the ribbons, when flowable collagen III is administered to the aneurysm site through an injection catheter, flowable thrombin is also administered to the aneurysm site through an injection catheter.

[0017] In another embodiment of the ribbons, the ribbon administers collagen III and an additional bioactive agent. In another embodiment of the ribbons, the additional bioactive agent is a growth factor. In another embodiment of the ribbons, the bioactive agent is selected from one or more of the group consisting of collagen I, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), plated-derived epidermal growth factor (PDEGF), basic fibroblast growth factor (bFGF), fibroblast growth factors (FGFs), transforming growth factor-beta (TGF-β), platelet-derived angiogenesis growth factor (PDAF) and autologous platelet gel (APG) including platelet rich plasma (PRP) and platelet poor plasma (PPP) and thrombin.

[0018] In another embodiment of the ribbons, the ribbon is a polymer ribbon.

[0019] In another embodiment of the ribbons, the ribbon further comprises an osmotic mini-pump. In another embodiment of the ribbons, the osmotic mini-pump releases a bioactive agent. In another embodiment of the ribbons, the osmotic mini-pump releases a bioactive agent selected from one or more of the group consisting of collagen I, collagen III, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), plated-derived epidermal growth factor (PDEGF), basic fibroblast growth factor (bFGF), fibroblast growth factors (FGFs), transforming growth factor-beta (TGF-β), platelet-derived angiogenesis growth factor (PDAF) and autologous platelet gel (APG) including platelet rich plasma (PRP) and platelet poor plasma (PPP) and thrombin.

BRIEF DESCRIPTION OF THE FIGURES

[0020] **FIG. 1** depicts a schematic diagram of a representative stent graft as stent grafts are conventionally used in the treatment of aneurysms.

[0021] **FIG. 2** depicts injection catheters at an aneurysm site that can be used to deliver flowable collagen III and/or flowable collagen III and thrombin in accordance with the present invention.

[0022] **FIG. 3** depicts a schematic diagram of collagen III ribbons within aneurysmal sacs in accordance with the present invention.

[0023] **FIG. 4** depicts a schematic diagram of a collagen III ribbon with an osmotic mini pump within an aneurysm sac in accordance with the present invention.

[0024] **FIGS. 5A and 5B** depict injection catheters at an aneurysm site useful to deliver flowable collagen III and/or flowable collagen III and thrombin in combination with a stent graft in accordance with the present invention.

[0025] **FIG. 6** depicts a schematic diagram of collagen III ribbons within aneurysmal sacs in combination with a stent graft in accordance with the present invention.

DEFINITION OF TERMS

[0026] Prior to setting forth embodiments according to the present invention, it may be helpful to an understanding thereof to set forth definitions of certain terms that will be used hereinafter. Unless otherwise explained, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The singular terms "a,""an," and "the" include plural referents unless context clearly indicates otherwise. Similarly, the word "or" is intended to

include "and" unless the context clearly indicates otherwise. The term "comprises" means "includes."

[0027] Aneurysm: As used herein "aneurysm" shall include a weak section of an artery wall in an animal.

[0028] Abdominal aortic aneurysm: As used herein "abdominal aortic aneurysm" shall include a weak section of an artery wall in the abdominal section of the aorta of an animal.

[0029] Animal: As used herein "animal" shall include mammals, fish, reptiles and birds. Mammals include, but are not limited to, primates, including humans, dogs, cats, goats, sheep, rabbits, pigs, horses and cows.

[0030] Drug(s): As used herein "drug" shall include any bioactive compound or composition having a therapeutic effect in an animal. Exemplary, non limiting examples include small molecules, peptides, proteins, hormones, DNA or RNA fragments, genes, cells, genetically-modified cells, growth factors, matrix metalloproteinase inhibitors and autologous platelet gel.

[0031] Stent graft: As used herein "stent graft" shall include a tube comprising fabric, metal, composite, and/or derivations and combinations of these materials that reinforces a weakened or diseased portion of a vessel (in one instance, an aneurysm).

[0032] "Treatment" or "contributing to the treatment of": As used herein "treatment" or "contributing to the treatment of" include preventing the growth or progressoin of an aneurysm, retarding the progression or growth of an aneurysm, shrinking an aneurysm or eliminating an aneurysm.

[0033] "Administers": As used herein "administers" shall include providing a bioactive agent in the vicinity of a target. In one embodiment the target is the site of an aneurysm. Injection catheters can be used to administer bioactive agents. Ribbons and stent grafts can also administer bioactive agents. When a ribbon or stent graft administers a bioactive agent, the bioactive agent can remain on the ribbon or stent graft (in one embodiment on the surface of the ribbon or stent graft) or the bioactive agent can be released from the ribbon or stent graft through diffusion or other processes.

[0034] Endoleak: As used herein "endoleak" refers to the presence of blood flow past the seal between the end of a stent graft and the vessel wall, and into the aneurysm sac, when all such flow should be contained within the stent graft's lumen.

[0035] Migration: As used herein "migration" refers to displacement of a stent graft from its intended implantation site.

[0036] Placed or implanted stent graft: As used herein "placed stent graft" or "implanted stent graft" shall include a surgically placed or implanted stent graft, either by invasive or non-invasive techniques.

[0037] Bioactive Agents: As used herein, "bioactive agents" include any agent that can promote cell growth and includes, without limitation, collagen I, collagen III, thrombin, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), plated-derived epidermal growth factor (PDEGF), basic fibroblast growth factor (bFGF), fibroblast growth factors (FGFs), transforming growth factor-beta (TGF-β), platelet-derived angiogenesis growth factor (PDAF) and autologous platelet gel (APG) including platelet rich plasma (PRP) and platelet poor plasma (PPP).

DETAILED DESCRIPTION

[0038] Embodiments of the present invention include methods and devices that are useful in contributing to the treatment of aneurysms. One embodiment provides methods and devices useful for contributing to or stimulating thrombosis at an aneurysm site to reduce the likelihood or occurrence of endoleaks. Embodiments according to the present invention contribute to stimulating thrombosis of vessel walls at aneurysm sites by providing various mechanisms to deliver collagen III and/or collagen III and thrombin to these sites. In one embodiment a flowable collagen III or flowable collagen III/thrombin composition is administered through an injection catheter to promote thrombosis within an aneurysm sac. In another embodiment a collagen III ribbon is used to deliver therapeutic agents to an aneurysm sac. Collagen III is an excellent candidate for these functions due to its roles in cell adhesion and wound healing. These various treatments can be employed alone or in combination and can also be employed in conjunction with more conventional stent grafting. Embodiments according to the present invention also provide for the delivery of other therapeutic agents including, without limitation, a variety of bioactive agents. When stent grafts are employed in combination with embodiments according to the present invention, these embodiments can also contribute to enhanced stent graft fixation at the vessel treatment site.

[0039] As discussed above, an aneurysm is a dilation, or expansion of a vessel lumen at a defined point and is generally associated with a vessel wall defect. Aneurysms are often multi-factorial asymptomatic vessel diseases that if left unchecked can result in spontaneous rupture, often with fatal consequences. One method to treat aneurysms involves a highly invasive surgical procedure where the affected vessel region is removed and replaced with a synthetic graft that is sutured in place. However, this procedure is extremely risky and generally only employed in patients who can be expected to survive the associated surgical trauma. Feeble patients are not candidates for these aneurysmal surgeries, and, before the development of stent grafts, remained untreated and at continued risk for sudden death.

[0040] In contrast to the described invasive surgical procedures, other treatments can be performed using minimally invasive procedures. Essentially, a catheter having a treatment mechanism compressed and fitted into the catheter's distal tip is advanced through an artery to the aneurysmal site. The treatment is then performed within the vessel lumen juxtaposed to the weakened vessel wall. One treatment option that adopts this approach is the implantation of a stent graft at an aneurysm site. In this procedure, a stent graft is provided "pre-loaded" into a delivery catheter (not shown). In the embodiment depicted in **FIG. 1**, the stent graft **100** has a body section **101** and a leg section **108**. In stent graft deployment protocols, the body section **101** of stent graft **100** is fully deployed through the right iliac artery **114** to an aneurysm site through a first delivery catheter (not shown). The body section **101** of stent graft **100** has a distal end **102**. The leg section **108** of stent graft **100** is deployed

in a second delivery catheter and anchors the stent graft **100** in the iliac artery **116**. The body section **101** and the leg section **108** of stent graft **100** are joined with an overlap between the two segments **106**. Problems with stent graft migration after implantation, however, prevent this treatment option from performing adequately in all patients. Thus, additional treatment options are required.

[**0041**] Collagen, a major component of the extracellular matrix, is in some forms a fibrous protein that provides tensile strength to tissues. It strengthens blood vessels and plays an important role in tissue development. Collagen can provide a unique ligand for platelets during endothelialization and tissue in-growth due to the fact that it both causes platelet activation and supports adhesion thus leading to platelet aggregate formation.

[**0042**] Collagen exists in several different forms. Collagen I is composed of 2 α1(I) and one α2(I) chains while collagen III is a homotrimeric procollagen comprised of three identical pro-α (III) chains (NCBI Protein Sequence Listing Accession Number PO2461). Collagen III is found co-localized with collagen I in blood vessels, tissues and skin. While collagen I is more abundant than collagen III, collagen III appears first at wound sites and initiates hemostatic processes. Collagen III can also demonstrate superior adhesion strength, larger surface area and higher hemostatic activity than collagen I. Thus, collagen III provides an important method to stimulate adhesion and tissue in-growth at implantable medical device implantation sites.

[**0043**] Thrombin is a pluripotent serine protease that also plays a central role in hemostasis following tissue injury by converting soluble plasma fibrinogen into an insoluble fibrin clot and by promoting platelet aggregation (Chambers et al., J. Biol. Chem. 275(45):35584-35591, Nov. 10, 2000). In addition to these procoagulant effects, thrombin also influences a number of cellular responses that play important roles in subsequent inflammatory and tissue repair processes. Thrombin influences the recruitment and trafficking of inflammatory cells and is a potent mitogen for a number of cell types, including endothelial cells, fibroblasts, and smooth muscle cells. Thrombin also promotes the production and secretion of extracellular matrix proteins and influences tissue remodeling processes. There is increasing in vivo evidence that the pro-inflammatory and profibrotic effects of thrombin play an important role in vascular repair.

[**0044**] Most of the cellular effects elicited by thrombin are mediated via a family of widely expressed G-protein-coupled receptors that are activated by limited proteolytic cleavage of the N-terminal extracellular domain. Once thrombin has interacted with its receptor, it exerts its cellular effects either directly or via the induction and release of secondary mediators, including classical growth factors, pro-inflammatory cytokines, and vasoactive peptides and amines.

[**0045**] Due to these complementary effects, collagen III and thrombin either alone or in combination can provide mechanisms for the treatment of aneurysms. Administration of these agents at an aneurysm site can lead to clotting and local organization of thrombus thus stabilizing the aneurysm sac and diffusing the pressure from blood flow. Thus, as shown in **FIG. 2**, one embodiment according to the present invention involves administering flowable collagen III and/or flowable collagen III and thrombin to an aneurysm sac **104** using injection catheters **500**, **302** inserted via the left and/or right iliac artery. If required, a guide wire lumen can also be included. Bioactive agents including, without limitation, collagen III and/or collagen III and thrombin can be injected simultaneously or sequentially between the two injection catheters **500**, **302** to form coatings **211** (note that one injection catheter can also be used in accordance with the presently described embodiment). Injection catheters **500**, **302** have injection ports **304**, **305** and **306** through which one or more bioactive agents, including without limitation flowable collagen III and/or flowable collagen III and thrombin can be delivered to the treatment site (as will be understood by one of ordinary skill in the art, injection catheters **500**, **302** can include different appropriate numbers of injection lumens and ports including, without limitation, one, two, three, four or five). Alternatively, the catheter could be a multilumen catheter with one lumen reserved for collagen III injection and the other reserved for thrombin injection. The injection catheters **500**, **302** can then be retrieved. The administration of these agents can provide a coating **211** on the weakened vessel walls or the already formed thrombus within the aneurysm sac that can stimulate organized thrombus formation at the site thus contributing to the stabilization of the aneurysm sac and overall aneurysm treatment.

[**0046**] In this embodiment depicted in **FIG. 2**, sensors **411**, **413** are also provided on the injection catheters. In embodiments according to the present invention, these sensors can be one or more of pressure sensors, temperature sensors, pH sensors, blood sugar sensors, blood oxygen sensors, motion sensors, flow sensors, velocity sensors, acceleration sensors, force sensors, strain sensors, acoustic sensors, moisture sensors, osmolarity sensors, light sensors, turbidity sensors, radiation sensors, electromagnetic field sensors, chemical sensors, ionic sensors and/or enzymatic sensors. In one embodiment, the sensors can employ wireless telemetry to deliver information from the implantation site to an instrument external to the body. In another embodiment, the sensors of the present invention can be constructed in accordance with the teachings of U.S. Pat. No. 5,704,352 to Tremblay and Buckles which is incorporated by reference. Alternatively, sensors as described in U.S. Pat. No. 6,632,196 to Houser, which is incorporated by reference can also be used. Other appropriate sensors include, without limitation, optical-fiber based transducers as manufactured by RJC Enterprises of Woodinville, Wash. and described in U.S. Pat. No. 6,052,613 to Takaki or as described in "Fiber-optic Transducer Aids Heart Monitoring," Engineering News, Jun. 7, 1999, both of which are incorporated herein by reference. A model FOP-M in vivo pressure sensor, manufactured by FISO Technologies, of Quebec, Canada, also can be used in accordance with the present invention as well as other sensor constructions that are known to those of ordinary skill in the art.

[**0047**] **FIG. 3** depicts an alternative collagen III and/or collagen III and thrombin delivery method according the present invention. In this embodiment a polymer coated with collagen III ribbon(s) are placed within aneurysmal sac(s). Essentially, a catheter including a ribbon according to the present invention is advanced to a treatment site **104**, **104'** and the ribbon **502**, **502'** is deployed with the use of a super-compliant balloon that can be used to press the ribbon **502**, **502'** against the aneurysm sac wall. In this embodiment, the collagen III and/or thrombin combination acts as an

adhesive, to create better adhesion between the ribbon and vessel wall or sac thrombus. The binding properties of collagen III and/or thrombin allow it to adhere to the inner aneurysm sac with far superiority to a polymer ribbon with no coating. In this embodiment the collagen III can also act as a drug delivery matrix for itself and/or another therapeutic that can reduce the size or rate of expansion of the aneurysm sac. As shown in **FIG. 4**, collagen III ribbons **502** according to the present invention can also comprise an osmotic mini pump **522** to deliver additional therapeutic agents to the treatment sites **104**, **104'**. Such a pump can be, without limitation, an appropriate programmable pump from Medtronic P. L., (Minneapolis, Minn.) or an Alzet osmotic mini-pump.

[**0048**] Embodiments according to the present invention can also be used in conjunction with more conventional stent grafting. For example, **FIGS. 5A and 5B**, depict how collagen III and/or collagen III and thrombin could be administered to provide collagen III and/or collagen III and thrombin coatings **211** through injection catheters **500**, **302** in conjunction with an independent stent graft delivery catheter **300**. While the administration of collagen III and/or collagen III and thrombin can be extremely beneficial, this administration at an aneurysm site where a stent graft will be deployed can also be problematic, because an increase in volume and internal pressure caused by the administration of these exogenous substance can increase internal pressure and the resulting possibility of further expansion of the aneurysm sac. Thus, the embodiment depicted in **FIGS. 5A and 5B** employs injection catheters **500** and **302** that can deliver collagen III and/or collagen III and thrombin while maintaining nearly-constant pressure in the area. The depicted injection catheters **500** and **302** achieve nearly-constant pressure by providing at least one exit lumen **511** as well as injection lumens **304**, **306**. As collagen III and/or collagen III and thrombin are administered to the site through the one or more injection lumens **304**, **306**, displaced blood or other fluids in the area that would normally contribute to an increase in internal pressure at the administration site, instead leaves the site through exit port and lumen **511**. Thus, nearly-constant pressure at the administration site can be maintained despite the addition of collagen III and/or collagen III and thrombin within this confined space. As will be understood by one of ordinary skill in the art, the exit port(s) and exit lumen(s) used in accordance with the present invention can adopt various appropriate forms. For example, in one embodiment, the exit port and lumen can consist of a tube with a diameter that is larger than the diameter of the injection catheter that splits off from the injection catheter within the aneurysm sac.

[**0049**] In the embodiment depicted in **FIGS. 5A and 5B**, the body portion **101** of a stent graft is radially compressed into a stent graft chamber of stent delivery catheter **300** (second delivery catheter for leg section not shown). Stent delivery catheter **300** is then deployed to a treatment site via the right iliac artery **114** (note that it could also be delivered via the left iliac artery). Multilumen injection catheters **500**, **302** are also deployed to the treatment site through the left iliac artery **116** and the right iliac artery **114**. The multilumen injection catheters **500**, **302** can be coaxial catheters with one or two injection lumens and one or two exit lumens. If required, a guide wire lumen can also be included. Injection catheters **500**, **302** have injection ports **304** and **306** through which one or more bioactive agents, including without limitation flowable collagen III and/or flowable collagen III and thrombin can be delivered to the treatment site. As stated, exit port **305** provides an avenue for fluids in the area of the treatment site to exit before a significant increase in internal pressure in the area occurs.

[**0050**] In the first step of the deployment scheme depicted in **FIG. 5A**, the stent delivery catheter **300** and the injection catheters **500**, **302** are deployed independently to the treatment site. As shown in **FIG. 5B**, the injection catheters **500**, **302** can remain at the treatment site after stent graft **100** deployment and removal of the delivery catheter. Here, the injection ports are not aligned with the proximal end **102** of the stent graft **100**, but instead are found within the aneurysm sac **104**. In other embodiments, however, these injection ports could be positioned at any location at the treatment site including, without limitation, at the proximal end **102** of the body section **101** of the stent graft **100** and/or the distal end of the leg portion of the stent graft in the iliac artery. Bioactive agents including, without limitation, collagen III and/or collagen III and thrombin can be injected simultaneously or sequentially between the two injection catheters **500**, **302** to form coatings **211**. Alternatively, the catheter could be a multilumen catheter with one lumen reserved for collagen III injection and the other reserved for thrombin injection. The injection catheters **500**, **302** can then be retrieved. This same procedure can be repeated as necessary to apply bioactive agents to the stent graft and/or luminal wall and/or at other locations as needed.

[**0051**] **FIG. 6** depicts polymer ribbons coated with collagen III and/or thrombin in accordance with the present invention employed in conjunction with a stent graft. In this embodiment, the collagen/thrombin coated ribbons **502**, **502'** would be used to deliver a bioactive agent to the aneurysm. The collagen/thrombin coated ribbons are first deployed to the treatment sites **104**, **104'** as previously described. After deployments of the collagen/thrombin coated ribbons **502**, **502**, a stent graft **100** can be delivered and implanted as described in reference to **FIG. 1**. Employing these treatment options in combination could provide for better aneurysm treatment than use of either treatment alone. Importantly, when stent grafts are employed in combination with embodiments according to the present invention, collagen III and/or collagen III and thrombin can be used to deliver therapeutic, bioactive agents that would contribute to the stabilization of the aneurysm sac. Stabilization of the aneurysm sac includes preventing or delaying matrix remodeling within the aneurysm wall. This allows the stent graft to remain in it originally deployed position, allowing it to maintain seal and fixation.

[**0052**] Additional devices and methods related to the use of collagen III and/or thrombin in the seal and fixation of stent grafts to vessel wall at an aneurysm site are described in co-pending U.S. patent application Ser. No. _____, entitled "Methods and Devices for Contributing to Improved Stent Graft Fixation" filed on date even with the present application and known to all by attorney docket number PA1937, which is hereby incorporated by reference in its entirety.

[**0053**] Incorporation by tissue in-growth of treatment devices in accordance with the present invention can be further stimulated by inclusion of (either by coating onto a stent graft, incorporating into or coating onto a ribbon or by

injection at the treatment site), without limitation, at least one growth factor including vascular endothelial growth factor (VEGF) and fibroblast growth factors 1 and 2 (FGF-1, FGF-2) and basic fibroblast growth factor (bFGF). The discussion of these factors is for exemplary purposes only, as those of skill in the art will recognize that numerous other growth factors have the potential to induce cell-specific migration and proliferation. Co-pending U.S. patent application Ser. No. 10/977,545, filed Oct. 28, 2004 which is hereby incorporated by reference for all it discloses regarding bioactive agents, discloses injecting autologous platelet gel (APG) into the aneurysm sac and/or between an implanted stent graft and the vessel wall to induce incorporation of the stent graft into the vessel wall to prevent stent graft migration, loss of seal, and resulting endoleak. The development of genetically-engineered growth factors also is anticipated to yield more potent cell-specific growth factors. Delivery of cells that are genetically modified to deliver specific growth factors are another promising route for growth factor delivery. Additionally it may be possible to identify small molecule drugs that can induce cell migration, proliferation, and chemotaxis. Thus, the stent grafts of the present invention can improve tissue in-growth through providing substances that induce cell migration and/or cell proliferation, and possibly promote inflammatory responses near the ends of the stent graft, and in some embodiments further by providing and releasing a bioactive agent at one or more ends or along the length of the stent graft.

[0054] The field of medical device coatings is well established and methods for coating stent grafts with drugs, with or without added polymers, are well known to those of skill in the art. Non-limiting examples of coating procedures include spraying, dipping, waterfall application, heat annealing, etc. The amount of coating applied to a stent graft can vary depending upon the desired effect of the compositions contained within the coating. The coating may be applied to the entire stent graft or to a portion of the stent graft. Thus, various drug coatings applied to the presently-claimed stent grafts are within the scope of the present invention.

[0055] Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques. Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements.

[0056] The terms "a" and "an" and "the" and similar referents used in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g. "such as") provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the invention.

[0057] Groupings of alternative elements or embodiments of the invention disclosed herein are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other members of the group or other elements found herein. It is anticipated that one or more members of a group may be included in, or deleted from, a group for reasons of convenience and/or patentability. When any such inclusion or deletion occurs, the specification is herein deemed to contain the group as modified thus fulfilling the written description of all Markush groups used in the appended claims.

[0058] Certain embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Of course, variations on these described embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventor expects skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

[0059] Furthermore, numerous references have been made to patents and printed publications throughout this specification. Each of the above cited references and printed publications are herein individually incorporated by reference in their entirety.

[0060] In closing, it is to be understood that the embodiments of the invention disclosed herein are illustrative of the principles of the present invention. Other modifications that may be employed are within the scope of the invention. Thus, by way of example, but not of limitation, alternative configurations of the present invention may be utilized in accordance with the teachings herein. Accordingly, the present invention is not limited to that precisely as shown and described.

What is claimed is:

1. A method comprising contributing to the treatment of an aneurysm by placing a ribbon that administers collagen III at the aneurysm site.

2. A method according to claim 1 wherein said ribbon administers collagen III and an additional bioactive agent.

3. A method according to claim 2 wherein said additional bioactive agent is selected from one or more of the group consisting of collagen I, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), plated-derived epidermal growth factor (PDEGF), basic fibroblast growth factor (bFGF), fibroblast growth factors (FGFs), transforming growth factor-beta (TGF-β), platelet-derived angiogenesis growth factor (PDAF) and autologous platelet gel (APG) including platelet rich plasma (PRP) and platelet poor plasma (PPP) and thrombin.

4. A method according to claim 1, wherein said ribbon is a polymer ribbon.

5. A method according to claim 1 wherein said ribbon further comprises an osmotic mini-pump.

6. A method according to claim 5 wherein said osmotic mini-pump releases a bioactive agent.

7. A method according to claim 6 wherein said bioactive agent is selected from one or more of the group consisting of collagen I, collagen III, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), plated-derived epidermal growth factor (PDEGF), basic fibroblast growth factor (bFGF), fibroblast growth factors (FGFs), transforming growth factor-beta (TGF-β), platelet-derived angiogenesis growth factor (PDAF) and autologous platelet gel (APG) including platelet rich plasma (PRP) and platelet poor plasma (PPP) and thrombin.

8. A method according to claim 1 further comprising deployment of a stent graft at said aneurysm site.

9. A method according to claim 1 wherein said method further comprises administering flowable collagen III to said aneurysm site through an injection catheter.

10. A method according to claim 9 wherein said method further comprises administering flowable thrombin to said aneurysm site through an injection catheter.

11. A method according to claim 9 further comprising deployment of a stent graft at said aneurysm site.

12. A ribbon comprising collagen III wherein said ribbon is deployed at an aneurysm site in conjunction with a treatment selected from the group consisting of the administration of flowable collagen III to said aneurysm site through an injection catheter; the deployment of a stent graft at said aneurysm site; and the administration of flowable collagen III to said aneurysm site through an injection catheter and the deployment of a stent graft at said aneurysm site.

13. A ribbon according to claim 12 wherein said ribbon administers collagen III and an additional bioactive agent.

14. A ribbon according to claim 13 wherein said bioactive agent is selected from one or more of the group consisting of collagen I, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), plated-derived epidermal growth factor (PDEGF), basic fibroblast growth factor (bFGF), fibroblast growth factors (FGFs), transforming growth factor-beta (TGF-β), platelet-derived angiogenesis growth factor (PDAF) and autologous platelet gel (APG) including platelet rich plasma (PRP) and platelet poor plasma (PPP) and thrombin.

15. A ribbon according to claim 12 wherein said ribbon is a polymer ribbon.

16. A ribbon according to claim 12 wherein said ribbon further comprises an osmotic mini-pump.

17. A ribbon according to claim 16 wherein said osmotic mini-pump releases a bioactive agent.

18. A ribbon according to claim 17 wherein said bioactive agent is selected from one or more of the group consisting of collagen I, collagen III, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), plated-derived epidermal growth factor (PDEGF), basic fibroblast growth factor (bFGF), fibroblast growth factors (FGFs), transforming growth factor-beta (TGF-β), platelet-derived angiogenesis growth factor (PDAF) and autologous platelet gel (APG) including platelet rich plasma (PRP) and platelet poor plasma (PPP) and thrombin.

19. A ribbon according to claim 12 wherein when said flowable collagen III is administered to said aneurysm site through an injection catheter, flowable thrombin is also administered to said aneurysm site through an injection catheter.

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