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(54) Title: MEDICAL DEVICE APPLICATIONS OF NANOSTRUCTURED SURFACES

(57) Abstract: This invention provides novel nanofiber enhanced surface area substrates and structures comprising such substrates for use in various medical devices, as well as methods and uses for such substrates and medical devices.

MEDICAL DEVICE APPLICATIONS OF NANOSTRUCTURED SURFACES**CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims priority to US Provisional Patent Application No. 60/549,711, filed March 2, 2004 and to US Patent Application No. 10/902,700 filed July 29, 2004. This application also claims priority as a continuation-in-part of US Patent Application Serial No. 10/828,100, filed April 19, 2004, as a continuation-in-part of US Patent Application Serial No. 10/833,944, filed April 27, 2004, and as a continuation-in-part of US Patent Application Serial No. 10/840,794 filed May 5, 2004, which is a continuation-in-part of US Patent Application Serial No. 10/792,402, filed March 2, 2004, each of which is incorporated by reference in their entirety herein.

**FIELD OF THE INVENTION**

[0002] The invention relates primarily to the field of nanotechnology. More specifically, the invention pertains to medical devices and methods comprising nanofibers.

**BACKGROUND OF THE INVENTION**

[0003] Medical devices including, for example, intracorporeal or extracorporeal devices (e.g., catheters), temporary or permanent implants, stents, vascular grafts, anastomotic devices, aneurysm repair devices, embolic devices, and implantable devices (e.g., orthopedic implants) are commonly infected with opportunistic bacteria and other infectious micro-organisms, in some cases necessitating the removal of implantable devices. Such infections can also result in illness, long hospital stays, or even death. The prevention of biofilm formation and infection on indwelling catheters, orthopedic implants, pacemakers, contact lenses, stents, vascular grafts, embolic devices, aneurysm repair devices and other medical devices is therefore highly desirous.

[0004] Enhancement of resistance of biomaterials to bacterial growth and promotion of rapid tissue integration and grafting of biomaterial surfaces are both areas of research. However, despite advances in sterilization and aseptic procedures as well as advances in biomaterials, bacterial and other microbial infection remains a serious issue in the use of medical implants. For example, greater than half of all nosocomial infections are caused by implanted medical devices. These infections are often the

result of biofilms forming at the insertion site of the medical implant. Unfortunately, such infections are often resistant to innate immune system responses as well as to conventional antibiotic treatments. It will be appreciated that such infections are problematic not just in treatment of humans, but also in treatment of a number of other organisms as well.

[0005] A welcome addition to the art would be medical devices having enhanced surface areas and structures/devices comprising such, as well as methods of using enhanced area surfaces in medical devices. The current invention provides these and other benefits which will be apparent upon examination of the following.

### SUMMARY OF THE INVENTION

[0006] The embodiments of the current invention comprise various medical devices, such as clamps, valves, intracorporeal or extracorporeal devices (e.g., catheters), temporary or permanent implants, stents, vascular grafts, anastomotic devices, aneurysm repair devices, embolic devices, and implantable devices (e.g., orthopedic implants) and the like which comprise nanofiber enhanced surfaces. Such enhanced surfaces provide many enhanced attributes to the medical devices in, on, or within which they are used including, e.g., to prevent/reduce bio-fouling, increase fluid flow due to hydrophobicity, increase adhesion, biointegration, etc.

[0007] In a first aspect of the invention, a medical device is disclosed comprising a body structure having one or more surfaces having a plurality of nanostructured components associated therewith. The medical device may comprise an intracorporeal or extracorporeal device, a temporary or permanent implant, a stent, a vascular graft, an anastomotic device, an aneurysm repair device, an embolic device, an implantable device, a catheter, valve or other device which would benefit from a nanostructured surface according to the teachings of the present invention. The plurality of nanostructured components may comprise, for example, a plurality of nanofibers or nanowires. The plurality of nanostructured components enhance one or more of adhesion, non-adhesion, friction, patency or biointegration of the device with one or more tissue surfaces of a body of a patient depending on the particular application of the device. The nanofibers (or other nanostructured components) on the surfaces of the medical device can optionally be embedded in a slowly-soluble biocompatible polymer (or other) matrix to make the nanofiber surfaces more robust.

The polymer matrix can protect most of the length of each nanofiber, leaving only the ends susceptible to damage. The generation of water soluble polymers can be accomplished in a number of different ways. For example, polymer chains can be formed in situ in a dilute aqueous solution primarily consisting of a monomer and an oxidizing agent. In this case, the polymer is actually created in the solution and subsequently spontaneously adsorbed onto the nanofiber surfaces as a uniform, ultra-thin film of between approximately 10 to greater than 250 angstroms in thickness, more preferably between 10 and 100 angstroms.

**[0008]** The plurality of nanofibers or nanowires may comprise an average length, for example, of from about 1 micron to at least about 500 microns, from about 5 microns to at least about 150 microns, from about 10 microns to at least about 125 microns, or from about 50 microns to at least about 100 microns. The plurality of nanofibers or nanowires may comprise an average diameter, for example, of from about 5 nm to at least about 1 micron, from about 5 nm to at least about 500 nm, from about 20 nm to at least about 250 nm, from about 20 nm to at least about 200 nm, from about 40 nm to at least about 200 nm, from about 50 nm to at least about 150 nm, or from about 75 nm to at least about 100 nm. The plurality of nanofibers or nanowires may comprise an average density on the one or more surfaces of the medical device, for example, of from about 0.11 nanofibers per square micron to at least about 1000 nanofibers per square micron, from about 1 nanofiber per square micron to at least about 500 nanofibers per square micron, from about 10 nanofibers per square micron to at least about 250 nanofibers per square micron, or from about 50 nanofibers per square micron to at least about 100 nanofibers per square micron. The plurality of nanofibers or nanowires may comprise a material independently selected from the group consisting of: silicon, glass, quartz, plastic, metal and metal alloys, polymers, TiO, ZnO, ZnS, ZnSe, ZnTe, CdS, CdSe, CdTe, HgS, HgSe, HgTe, MgS, MgSe, MgTe, CaS, CaSe, CaTe, SrS, SrSe, SrTe, BaS, BaSe, BaTe, GaN, GaP, GaAs, GaSb, InN, InP, InAs, InSb, PbS, PbSe, PbTe, AlS, AlP, AlSb, SiO<sub>1</sub>, SiO<sub>2</sub>, silicon carbide, silicon nitride, polyacrylonitrile (PAN), polyetherketone, polyimide, an aromatic polymer, and an aliphatic polymer.

**[0009]** The nanofibers or nanowires may be attached to the one or more surfaces of the body structure of the medical device by growing the nanofibers or nanowires

directly on the one or more surfaces, or the nanofibers or wires may be attached to the one or more surfaces of the body structure by attaching (e.g., via a covalent linkage) the nanofibers or nanowires to the one or more surfaces using one or more functional moieties, for example. The body structure of the medical device may be made from a variety of materials, and the plurality of nanostructured components may optionally be incorporated into the material(s) of the body structure. The nanofibers (or other nanomaterial) may be stiffened by sintering the fibers together (or otherwise cross-linking the fibers, e.g., by chemical means) prior to incorporating the nanofibers into the material of the body structure to provide enhanced rigidity and strength. The medical device may further comprise one or more biologically compatible or bioactive coatings applied to the one or more nanostructured surfaces, and/or the nanofibers or nanowires may be incorporated into a matrix material (e.g., a polymer material) to provide greater durability for the fibers or wires.

**[0010]** In another aspect of the invention, a vascular stent is disclosed which comprises a plurality of nanostructured components associated with one or more surfaces of the stent. The plurality of nanostructured components may comprise, for example, a plurality of nanofibers or nanowires. The plurality of nanofibers or nanowires may comprise, for example, a material independently selected from the group consisting of: silicon, glass, quartz, plastic, metal and metal alloys, polymers, TiO, ZnO, ZnS, ZnSe, ZnTe, CdS, CdSe, CdTe, HgS, HgSe, HgTe, MgS, MgSe, MgTe, CaS, CaSe, CaTe, SrS, SrSe, SrTe, BaS, BaSe, BaTe, GaN, GaP, GaAs, GaSb, InN, InP, InAs, InSb, PbS, PbSe, PbTe, AlS, AlP, AlSb, SiO<sub>1</sub>, SiO<sub>2</sub>, silicon carbide, silicon nitride, polyacrylonitrile (PAN), polyetherketone, polyimide, an aromatic polymer, and an aliphatic polymer. The nanofibers or nanowires may be attached to the one or more surfaces of the stent by growing the nanofibers directly on the one or more surfaces, or, for example, by separately covalently attaching the nanofibers or nanowires to the one or more surfaces by using, e.g., one or more functional moieties or linkage chemistries. The stent may be made from a variety of materials selected from Nitinol, nickel alloy, tin alloy, stainless steel, cobalt, chromium, gold, polymer, or ceramic. The stent may comprise a drug compound that is directly adsorbed to the nanostructured surface or otherwise associated with the nanostructured surface (e.g., via covalent, ionic, van der waals etc. attachment) via the use of one or more silane groups or other linkage chemistries.

[0011] In another embodiment of the invention, an aneurysm repair device is disclosed which comprises a graft member which is configured to be positioned within a patient's body in a region of an aneurysm, the graft member comprising a plurality of nanostructured components associated with one or more surfaces of the graft member. The plurality of nanostructured components may comprise, for example, a plurality of nanofibers or nanowires. The plurality of nanofibers may comprise a material independently selected from the group consisting of: silicon, glass, quartz, plastic, metal or metal alloys, polymers, TiO, ZnO, ZnS, ZnSe, ZnTe, CdS, CdSe, CdTe, HgS, HgSe, HgTe, MgS, MgSe, MgTe, CaS, CaSe, CaTe, SrS, SrSe, SrTe, BaS, BaSe, BaTe, GaN, GaP, GaAs, GaSb, InN, InP, InAs, InSb, PbS, PbSe, PbTe, AlS, AlP, AlSb, SiO<sub>1</sub>, SiO<sub>2</sub>, silicon carbide, silicon nitride, polyacrylonitrile (PAN), polyetherketone, polyimide, an aromatic polymer, and an aliphatic polymer. The nanofibers or nanowires may be attached to the one or more surfaces of the graft member by growing the nanofibers directly on the one or more surfaces, or the nanofibers or nanowires may be attached to the one or more surfaces of the graft member by attaching the nanofibers or nanowires to the one or more surfaces, e.g., via covalent, ionic, or other attachment mechanism. The graft member may be made from one or more of treated natural tissue, laboratory-engineered tissue, and synthetic polymer fabrics including without limitation a synthetic polymer selected from Dacron, Teflon, metal or alloy mesh, ceramic or glass fabrics. The graft member may comprise one or more biocompatible coatings applied to the one or more nanostructured surfaces of the graft member. In one embodiment, the graft member is configured to be positioned within an aorta of the patient in a region of an aneurysm. The graft member may be configured to be positioned proximate to a side wall of a vessel that supplies blood to or from the brain in a region of an aneurysm.

[0012] In another embodiment of the invention, a medical device is disclosed for creating an anastomosis in a patient coupling a first vessel to a second vessel in an end-to-end or end-to-side anastomosis, the device comprising a tubular member comprising a plurality of nanostructured components associated with one or more surfaces of the tubular member. The plurality of nanostructured components may comprise, for example, a plurality of nanofibers or nanowires. The plurality of nanofibers or nanowires may comprise a material independently selected from the group consisting of: silicon, glass, quartz, plastic, metal, polymers, TiO, ZnO, ZnS,

ZnSe, ZnTe, CdS, CdSe, CdTe, HgS, HgSe, HgTe, MgS, MgSe, MgTe, CaS, CaSe, CaTe, SrS, SrSe, SrTe, BaS, BaSe, BaTe, GaN, GaP, GaAs, GaSb, InN, InP, InAs, InSb, PbS, PbSe, PbTe, AlS, AlP, AlSb, SiO<sub>1</sub>, SiO<sub>2</sub>, silicon carbide, silicon nitride, polyacrylonitrile (PAN), polyetherketone, polyimide, an aromatic polymer, and an aliphatic polymer. The nanofibers or nanowires may be attached to the one or more surfaces of the tubular member by growing the nanofibers directly on the one or more surfaces or by attaching the nanofibers to the one or more surfaces, e.g., using covalent, ionic or other attachment means. The tubular member may be made from one or more of treated natural tissue, laboratory-engineered tissue, de-natured animal tissue, stainless steel, metal, alloys, ceramic or glass fabrics, polymers, plastic, silicone, and synthetic polymer fabrics. In one embodiment, the tubular member may comprise a T-tube for performing an end-to-side anastomosis or a straight tube for performing an end-to-end anastomosis. The tubular member may comprise one or more biocompatible or bioactive coatings applied to the one or more nanostructured surfaces of the tubular member. The tubular member can have a cross-sectional shape selected from circular, semi-circular, elliptical, and polygonal, for example.

**[0013]** In another embodiment of the invention, an implantable orthopedic device is disclosed which comprises a body structure comprising a plurality of nanostructured components associated with one or more surfaces of the body structure. The implantable orthopedic device may be selected from at least one of the following: total knee joints, total hip joints, ankle, elbow, wrist, and shoulder implants including those replacing or augmenting cartilage, long bone implants such as for fracture repair and external fixation of tibia, fibula, femur, radius, and ulna, spinal implants including fixation and fusion devices, maxillofacial implants including cranial bone fixation devices, artificial bone replacements, dental implants, orthopedic cements and glues comprised of polymers, resins, metals, alloys, plastics and combinations thereof, nails, screws, plates, fixator devices, wires and pins. The plurality of nanostructured components may comprise a plurality of nanofibers or nanowires, for example. The plurality of nanofibers or nanowires may comprise a material independently selected from the group consisting of: silicon, glass, quartz, plastic, metal, polymers, TiO, ZnO, ZnS, ZnSe, ZnTe, CdS, CdSe, CdTe, HgS, HgSe, HgTe, MgS, MgSe, MgTe, CaS, CaSe, CaTe, SrS, SrSe, SrTe, BaS, BaSe, BaTe, GaN, GaP, GaAs, GaSb, InN, InP, InAs, InSb, PbS, PbSe, PbTe, AlS, AlP, AlSb, SiO<sub>1</sub>, SiO<sub>2</sub>, silicon carbide, silicon

nitride, polyacrylonitrile (PAN), polyetherketone, polyimide, an aromatic polymer, and an aliphatic polymer. The nanofibers or nanowires may be attached to the one or more surfaces of the body structure by growing the nanofibers directly on the one or more surfaces or by separately attaching (e.g., covalently, ionic ally, etc.) the nanofibers to the one or more surfaces. The body structure of the device may be made from one or more of treated natural tissue, laboratory-engineered tissue, de-natured animal tissue, stainless steel, metal, alloys, ceramic or glass fabrics, polymers, plastic, silicone, and synthetic polymer fabrics. The body structure may comprise one or more biocompatible or bioactive coatings applied to the one or more nanostructured surfaces of the body structure.

**[0014]** In another embodiment of the invention, a bioengineered scaffold device for providing a scaffold for nerve regeneration is disclosed which comprises a base membrane or matrix having a plurality of nanostructured components associated therewith. The membrane or matrix may be made from one or more of the following materials: natural or synthetic polymers, electrically conducting polymers, metals, alloys, ceramics, glass fabrics, or silicone. The plurality of nanostructured components may comprise, for example, a plurality of nanofibers or nanowires. The nanostructured surface of the membrane or matrix may be impregnated or bound with one or more drugs, cells, fibroblasts, nerve growth factors (NGF), cell seeding compounds, neurotrophic growth factors or genetically engineered cells producing such factors, VEGF, laminin or other drugs or substances to encourage axonal elongation and functional nerve performance.

**[0015]** In another aspect of the invention, a medical device for implantation in the uterus or fallopian tubes is disclosed which comprises a surface and a plurality of nanofibers or nanowires associated with the surface.

**[0016]** In another aspect of the invention, a medical device in which one or more surfaces are adapted to resist crystallization of body fluids is disclosed which comprises a surface and a plurality of nanofibers or nanowires associated with the surface.



[0017] In another embodiment of the invention, a medical device is disclosed in which one or more surfaces of the device are adapted to resist formation of thrombus and which comprises a surface and a plurality of nanofibers or nanowires.

[0018] In another embodiment of the invention, a medical device in which one or more surfaces are adapted to resist tissue in-growth is disclosed which comprises a surface and a plurality of nanofibers or nanowires associated with the surface said nanofibers or nanowires adapted to be hydrophobic.

[0019] Methods of use are also disclosed for treating patients with any one or more of the medical devices disclosed herein, which include, for example, a method of therapeutically treating a patient comprising contacting the patient with a medical device comprising a surface and plurality of nanofibers associated with the surface. Methods are disclosed for administering a drug compound to a body of a patient which comprises, for example, providing a drug-eluting device comprising at least one surface, a plurality of nanofibers associated with the surface, and a drug compound associated with the plurality of nanofibers; introducing the drug-eluting device into a body of a patient; and delivering the drug compound into the body of the patient. The drug-eluting device in one embodiment comprises a coronary stent, although any device which would benefit from local drug delivery at the site of disease (e.g., lesion) could be used in the methods of the invention. Where a coronary stent is used as the drug-eluting device, the drug compound may comprise paclitaxel or sirolimus, for example, or a variety of other medications including without limitation one or more of the following: anti-inflammatory immunomodulators such as Dexamethasone, M-prednisolone, Interferon, Leflunomide, Tacrolimus, Mizoribine, statins, Cyclosporine, Tranilast, and Biorest; antiproliferative compounds such as Taxol, Methotrexate, Actinomycin, Angiopeptin, Vincristine, Mitomycin, RestenASE, and PCNA ribozyme; migration inhibitors such as Batimastat, Prolyl hydroxylase inhibitors, Halofuginone, C-proteinase inhibitors, and Probuco; and compounds which promote healing and re-endothelialization such as VEGF, Estradiols, antibodies, NO donors, and BCP671. The drug compound may be adsorbed directly to the nanofiber surface of the drug-eluting device or otherwise associated with it via the use of one or more silane groups, linker molecules or other covalent, ionic, van der waals etc. attachment means. The nanofiber surface may be configured such that the drug compound elutes slowly over time. The

plurality of nanofibers optionally are embedded in a biocompatible, non-thrombogenic polymer coating to provide enhanced durability to the nanofibers.

[0020] These and other objects and features of the invention will become more fully apparent when the following detailed description is read in conjunction with the accompanying claims.

### BRIEF DESCRIPTION OF THE DRAWINGS

[0021] **FIGURE 1:** Displays a photomicrograph of an exemplary adherent nanofiber structure of the invention.

[0022] **FIGURE 2A** is an illustration of a Prior Art stent and stent delivery catheter.

[0023] **FIGURE 2B** shows placement of the stent of Fig. 8A at the site of a lesion in a vessel of a patient such as a coronary artery.

[0024] **FIGURE 2C** displays a photomicrograph of a vascular stent prior to deposition of a nanostructured surface on the stent.

[0025] **FIGURE 2D** displays a photomicrograph of a vascular stent following growth of a plurality of nanofibers on the exposed surfaces of the stent.

[0026] **FIGURE 3A** diagrammatically illustrates an endovascular aortic prosthetic delivery system for delivering an aortic aneurysm graft having a nanostructured surface to the site of an aortic aneurysm in a body of a patient;

[0027] **FIGURE 3B** illustrates placement of an endovascular aortic graft having a nanostructured surface adjacent an aneurysm in an aorta of a body of a patient;

[0028] **FIGURE 4A** illustrates a detailed view of a patient's head region showing advancement of a neurovascular catheter delivery system for treatment of an aneurysm in a side wall of a cerebral vessel of a patient in accordance with the invention;

[0029] **FIGURE 4B** illustrates a side wall aneurysm in a cerebral vessel of a patient;

[0030] **FIGURE 4C** illustrates placement of a patch having a nanostructured surface at the site of the side wall aneurysm of Fig. 4B;

[0031] **FIGURE 4D-4F** is one example of a commercially available embolic device (i.e., Hilal Embolization Microcoils™ available commercially from Cook, Inc. (Bloomington, IN)) that can be provided with a nanostructured surface according to the teachings of the present invention to enhance the treatment of intracranial aneurysms and AV malformations;

[0032] **FIGURE 5A** is an illustration of a tubular device having a nanostructured surface for performance of an end-to-end anastomosis;

[0033] **FIGURE 5B** is an illustration of a T-tube device having a nanostructured surface for performance of an end-to-side anastomosis;

[0034] **FIGURE 6A** is a perspective view of a an exemplary orthopedic implant (in this case a hip stem) having a nanofibers attached thereto in accordance with the illustrated embodiment,

[0035] **FIGURE 6B** is a cross sectional view taken along line 6A—6A of FIG. 6A

#### DETAILED DESCRIPTION

[0036] It should be appreciated that specific embodiments and illustrations herein of uses or devices, etc., which comprise nanofiber enhanced surface areas should not be construed as limiting. In other words, the current invention is illustrated by the descriptions herein, but is not constrained by individual specifics of the descriptions unless specifically stated. The embodiments are illustrative of various uses/applications of the enhanced surface area nanofiber surfaces and constructs thereof. Again, the enumeration of specific embodiments herein is not to be taken as limiting on other uses/applications which comprise the enhanced surface area nanofiber structures of the current invention.

[0037] As seen in Figure 1, the nanofibers optionally form a complex three-dimensional structure on the medical device surfaces to which they are applied. Again, it will be appreciated that in other embodiments of the invention, the nanofibers are more uniform in height, conformation, etc. The degree of such complexity depends in part upon, e.g., the length of the nanofibers, the diameter of the nanofibers, the length:diameter aspect ratio of the nanofibers, moieties (if any) attached to the nanofibers, and the growth conditions of the nanofibers, etc. The bending, interlacing,

etc. of nanofibers, which help affect the degree of intimate contact with a secondary surface, are optionally manipulated through, e.g., control of the number of nanofibers per unit area as well as through the diameter of the nanofibers, the length and the composition of the nanofibers, etc. Thus, it will be appreciated that the bio-utility of the nanofiber substrates herein is optionally controlled through manipulation of these and other parameters. The nanofibers (or other nanomaterial) may be stiffened by sintering the fibers together (or otherwise cross-linking the fibers, e.g., by chemical means) prior to or after incorporating the nanofibers into or onto the material of the body structure to provide enhanced rigidity and strength.

[0038] It also will be appreciated that nanofibers can, in optional embodiments, curve or curl, etc., thus, presenting increased surface area for contact between the nanofibers and the substrate surfaces involved. The increased intimate contact, due to multiple touchings of a nanofiber with a second surface, increases the van der Waals attractions, friction forces, or other similar forces of adhesion/interaction between the nanofiber and the second substrate. For example, a single curling nanofiber can optionally make intimate contact with a second substrate a number of times. Of course, in some optional embodiments, a nanofiber can even retouch the first surface if it curls/curves from the second surface back to the first surface. Due to possible multiple contact points (or even larger contact points, e.g., when a curved nanofiber presents a larger intimate contact area than just its tip diameter, e.g., if a side length of a nanofiber touches a substrate surface) between a single nanofiber and a second substrate/surface, the intimate contact area from curled/curved nanofibers can be greater in some instances than when the nanofibers tend not to curl or curve (i.e., and therefore typically present a "straight" aspect to the second surface). Therefore, in some, but not all, embodiments herein, the nanofibers of the invention comprise bent, curved, or even curled forms. As can be appreciated, if a single nanofiber snakes or coils over a surface (but is still just a single fiber per unit area bound to a first surface), the fiber can still provide multiple, intimate contact points, each optionally with a relatively high contact area, with a secondary surface

### **I) Nanofiber Surfaces as Bacteriostatic, Hydrophobic & Antithrombotic Catheter Lumens**

[0039] Catheters are widely used in medical applications, e.g., for intravenous, arterial, peritoneal, pleural, intrathecal, subdural, urological, synovial, gynecological,

percutaneous, gastrointestinal, abscess drains, and subcutaneous applications. Intravenous infusions are used for introducing fluids, nutrition, blood or its products, and medications to patients. These catheters are placed for short-term, intermediate, and long-term usage. Types of catheters include standard IV, peripherally inserted central catheters (PICC)/midline, central venous catheters (CVC), angiographic catheters, guide catheters, feeding tubes, endoscopy catheters, Foley catheters, drainage catheters, and needles. Catheter complications include phlebitis, localized infection and thrombosis.

**[0040]** Intravenous therapy is a critical element in the treatment of patients. One out of eight persons will undergo intravenous therapy of some form annually in the United States. Today, infusion therapy is almost routine. In hospitals, 90 percent of surgical patients and a third of non-surgical inpatients receive some form of intravenous therapy. American medical device manufacturers dominate the catheter industry, producing 70 to 80 percent of the catheters used around the world. In 1997, worldwide sales of catheter products totaled approximately \$7.3 billion, and is growing at a healthy pace of 10.4% annually. The largest segment, however, is the renal market, which is comprised primarily of urinary catheters and dialysis catheters. It is currently a \$4 billion segment, and is expected to reach \$7.1 billion soon.

**[0041]** The best-known urology catheters are Foley catheters, which have been commercially available since the 1930s. These catheters and others, both internal and external condom-type catheters, are used for incontinence, for dying patients, and often for bladder drainage following surgery or an incapacitating injury or illness. These relatively easy-to-use catheters are used throughout the world in hospitals, nursing homes, and home-care settings. There are two types of dialysis catheters: hemodialysis and peritoneal. End users for this catheter segment are vascular surgeons and interventional radiologists, although once long-term catheter ports are in place, nephrologists monitor access sites and catheter-based dialysis treatments.

**[0042]** Therefore, in various embodiments herein, nanofiber enhanced surfaces are used in, on or within material surfaces to construct catheters and related medical devices. The bacteriostatic characteristics of the nanofiber surface catheters herein can optionally decrease infection, while the hydrophobic characteristics can optionally increase fluid flow properties. The anti-thrombotic characteristics of such devices can optionally decrease thrombosis which leads to catheter plugging and emboli. Catheter

manufacturers desire improvement of catheter materials and catheter design to make them more biocompatible, and to offer better infection control. However, in spite of progress, infection at present has remained a major problem. Use of nanofiber enhanced surfaces in construction of catheters, however, can optionally aid with such concerns.

**[0043]** The performance advantage of catheter lumens with decreased infection, increased flow and decreased clot formation arising from use of nanofiber enhanced surfaces are features of the invention. Such features can optionally lead to reduction in catheter complications and an increase in the amount of time a catheter could remain in place before having to be replaced (as a result of using the nanofiber coated catheter lumens).

**[0044]** Catheters are optionally placed anywhere in the body (i.e., the class of catheters comprises more than just IVs) and are typically plastic, which is strong enough to place in, e.g., a vein, but flexible enough to bend within the patient's body. It is typically desired to reduce catheter care (e.g., replacement time) and to decrease catheter contamination, e.g., from skin "crawling down," biofouling, etc. It is also desirable to avoid phlebotomy or any problem disturbing flow which can arise through use of a "flush" to blow clots, etc. downstream. The current embodiments avoid such because they are inherently antibacterial, hydrophobic and antithrombogenic.

**[0045]** The antifouling aspects of the current invention are also optionally useful in catheters used for wound drainage. Such catheters typically present problems with bacterial contamination, etc. Use of the embodiments of the invention can, thus, reduce drug use (e.g., antibiotics), reduce pain, reduce need for further operations, and reduce infection rates. As explained herein the catheters of the invention are also optionally coated with compounds, e.g., silver compounds, titanium oxides, antibiotics, etc. which can further help in reducing infection, etc.

## **II) Nanofiber Enhanced Surfaces in Disposable Surgical Retractors, Dental Retractors and Placement Devices.**

**[0046]** Retractors and forceps are commonly used in surgery to position or move (e.g., manipulate) organs and tissues for better visualization, surgical approach, and placement of implants. Dentistry commonly uses forceps to position small tooth restorations (e.g., crowns, inlays, onlays, veneers, implants/implant abutments, etc.)

and position gingival tissues in a variety of periodontal, oral surgical and endodontic procedures. The current existing dental device in this market sector is a sticky ended probe (Grabits™) that is disliked by dentists as it is non-sterile, cannot adhere to living tissue and is difficult to release from the implant it is adhered to.

[0047] The high traction forces generated at minimal pressures by nanofiber enhanced surfaces can optionally create minimal tissue damage in surgical organ movement and retraction. The high traction forces generated at small point loads can optionally allow for increased dental surgical control and placement of dental restorations. The advantage of a sterilizable probe that attaches to living tissue as well as inert implants is thought to provide significant advantage over existing technology.

[0048] The performance advantage, increased surgical speed and decreased tissue damage over toothed and crushing (serrated) forceps emphasizes the benefits of the current invention. Reduction in post surgery tissue trauma and consequent inflammation accompanied by an increase in healing rate are expected to arise as a result of using the nanofiber coated retractors herein, thus allowing for ease of use, increased speed of dental surgery, and security of handling implants.

[0049] Some embodiments of the invention comprise disposable retractors having nanofiber enhanced surfaces. Additionally, other embodiments involve, e.g., upside down pyramid shapes (e.g., 1 cm in height). The points of such pyramids can be used to touch nerves, etc. Also, the flat sizes can be used for larger objects, while the edges can be used for still other differently sized objects. Retractors of the invention can optionally come in a variety of sizes and shapes depending upon the specific intended use. Again, for example, in dentistry a retractor of the invention can be used for handling and placement of crowns, etc.

### **III) Enhanced Traction in Laparoscopy Clips Arising Through Use of Nanofiber Enhanced Surfaces.**

[0050] Occlusive clips are applied laparoscopically during gallbladder surgery. About 10 clips come integrated in a \$60.00 disposable cartridge. Five or six clips are typically used to seal off arteries, veins and ducts during gallbladder surgery. The small U shaped clips, about the size of a staple, are made of titanium and are crimped in place. They do not have a tractive surface and rely on the crimping force to stay in

place. Trauma caused by the clip can cause the growth of adhesions or a cut in the vessel.

[0051] The high traction forces generated at minimal pressures by the nanofiber surfaces of the invention would make such clips ideal for laparoscopic surgery, as well as for other surgeries.

[0052] The performance advantage of a significantly higher traction surface (~2x) from the nanofiber enhanced devices herein would be highly desirable. This is true especially because there are about 600,000 gallbladder removals a year in the United States alone. If other laparoscopic surgeries such as appendix removals were added in this number would grow to more than 1,000,000. If one \$60 cartridge is used per surgery the market is at least \$60,000,00.

[0053] Other applications of such clips or clamps can be to, e.g., clip or clamp the aorta, use as atraumatic clamps, etc. Such clamps are also expected to be useful in beating heart surgery to help stabilize heart motion. Such products optionally comprise arms with pads (with nanofibers, etc.). Eye and/or eyelid surgery also desires such clamps to stabilize the eye. Yet other common surgical uses include, e.g., retracting dura for opening scalp, holding pericardium in heart surgery, holding skin grafts in place, holding organs/tissues in place, etc. Yet other embodiments comprise wherein the substrate is dissolvable, e.g., liver sock, etc.

[0054] Surgeries often deal with organs, etc. that are slimy, slippery, delicate, etc. Also, while anatomical elements that are tubular or sheet-like can be grasped with suturers, etc., more irregularly shaped organs (e.g., liver, heart, etc.) are more problematic. Thus, retractors, disposable sleeves, and universal contact surfaces for myriad clamp types which comprise nanofiber surfaces are all desired. They can help eliminate constant repositioning of medical devices (e.g., point retractors can touch a tissue and hold it until release is needed). The devices of the invention also can find placement in laparoscopic devices and stabilization pads.

#### **IV) External Fixator Implant Bacteriostatic Surfacing**

[0055] External fixators are pins and wires inserted through the skin into bone for the purpose of healing bone fractures. These pins and wires are then connected externally with rods and clamps in order to provide rigidity and stability so the fractured bone can heal. The advantage of these devices over internally placed plates, screws,



pins and cerclage wires is in the decreased amount of tissue and vascular disruption caused when compared to surgical placement of internal implants. This lesser surgical invasion allows the fracture to heal much faster and with lesser muscle and subcutaneous scarring, implant-related osteosarcomas, osteoarthritic changes, or painful cold-sensation complications and obviates the need of surgical implant removal at a later date. There has been a move over the past ten years towards this "biologic" orthopedic method of healing over internal implants. Minimization of tissue damage reduces healing time which is paramount in bone healing. Complications arising from the use of external fixators are bacterial infection from the skin, and excessive movement of the pins if the connecting apparatus is insufficiently stable. The use of the nanofiber bacteriostatic surfacing is expected to decrease or eliminate what is perceived as the major of these two problems.

[0056] The nanofiber coated bacteriostatic stainless surface of external fixators would decrease the degree of skin surface bacterial communication and subsequent contamination of the threaded pin insertion, bone interface which causes pin loosening and fracture healing failure. The performance advantage of a bacteriostatic, externally placed bone pin would undoubtedly be desired especially to reduce post surgery infection and pin loosening complications. In various embodiments, all of the implanted material is coated with nanofibers. In other embodiments, screw threads, pins, and/or bonds are nanofiber coated. Other embodiments comprise nanofiber coating of the bottom of a plate and the top of a screw head, flexible wires (e.g., k-wires, k-pins, etc.), straight pins, etc. It will be appreciated that such external fixators of the invention are also optionally used in limb-lengthening procedures.

#### **V) Butterfly Skin Bandage/Patch**

[0057] Many skin lacerations are clean wounds in need of simple surface closure if suturing is unavailable or unnecessary. Currently available butterfly skin bandages function well, but fail rapidly as adhesion decreases with movement of skin and hydration at the bandage site. A hydrophobic adhesive butterfly bandage comprising nanofiber surfaces would be an elegant solution to this need.

[0058] Corneal abrasions are a common ophthalmic injury causing blepharospasm, ciliary spasm and pain. The majority of these lesions take 24 - 72 hours to heal. Corneal ulcers take 3 - 5 days to heal. Treatment with mydriatics which block

ciliary spasm, reduce pain in the ciliary body but increase photophobia. The patients are hence more comfortable in dark environments. The use of a dermal adhesive, hydrophobic butterfly patch comprising nanofiber surfaces to close the eyelids would solve the photophobia problem and increase the rate of corneal healing due to increased bathing of the cornea with lachrymal secretions under a closed palpebrum.

[0059] The high traction forces generated at minimal pressures, and hydrophobic characteristics would make nanofiber coated flexible butterfly skin patches ideal for closing skin wounds and eyelids. The performance advantage of such butterfly devices is expected to be greatly desired. In some embodiments, the adhesive device is flesh colored, or allows patients to bathe without the device loosening. Such devices help patients avoid surgery and avoid “puckers” at end of sutures (especially important for plastic surgery). Other advantages of such devices include, e.g., no curing of the adhesion needed, a good splinting material, not plaster that would need to be wet, etc., the device can be “breathable” when, e.g., the nanofibers are on a mesh material, etc. Such devices can also optionally comprise drugs or the like to be released transdermally (either continuous, concomitant with a rise in temperature, etc.). Such devices are also optionally used with decubitus ulcers, in venostasis situations (in diabetic patients, pressure on the skin and bone causes erosion and ulcer). In addition, such a wound dressing device can be coupled with a moiety, such that the moiety can enhance wound healing (e.g., cell growth). Nanofiber dimensions on the bandage can be designed to capture cells.

#### **VI) Enhanced Traction Clamping Devices for Cardiac Surgery**

[0060] Clamps are used extensively in cardiac surgery to temporarily stop blood flow. There has been a move over the past ten years towards disposable rubber atraumatic clamp inserts that reduce arterial damage compared to traditional steel jawed clamps. Minimization of damage reduces recovery time and complications due to scarring. Rubber inserts have made inroads into the market but their limited traction still requires clamping forces high enough to damage many arteries. The high traction forces generated at minimal pressures by the devices herein would make nanofiber coated clamp inserts ideal for cardiac surgery. The performance advantage of a significantly higher traction surface (~2x) would undoubtedly be desired, e.g., to reduce post surgery complications.

## **VII) Adhesive Hydrophobic Otic Plug**

[0061] Tympanic punctures, lacerations or rupture from infection are a common nuisance to patients when showering and swimming. Mechanical ear plugs are uncomfortable and often leak causing vestibulitis (loss of balance) and otitis media (inner ear infection). Reengineered otic plugs using nanofiber surface adhesion properties in combination with hydrophobic characteristics is expected to provide a significant improvement for millions of patients with open tympanums. The high traction forces generated at minimal pressures would make nanofiber coated and hydrophobic coated ear plugs more comfortable and form a better seal against water entry than existing technologies. The performance advantage of a significantly higher traction surface (~2x) would be desired, especially to reduce post otitis media complications and vestibulitis.

[0062] The hydrophobic action and traction of the nanofibers would be expected to create a secure plug. In various embodiments, the plug fits within the ear canal, while in other embodiments, it comprises a cap or disk to cover the ear or ear canal. Similar embodiments are optionally used for other meati or orifices (e.g., to prevent nose bleeds, etc.). In some embodiments, the nanofibers release from their substrate backing, e.g., to remain behind on the patient so as to, e.g., not remove a scab or clot. Other embodiments can optionally include anti-biofouling properties and/or anti-microbial properties. *See* below. Some embodiments are expected to optionally be used for urinary plugs, and the like. For example some embodiments can optionally be used for fallopian tube obstruction to prevent pregnancy.

## **VIII) Surgical Adhesion Preventative**

[0063] Post-operative adhesions are a common surgical complication. Presently, and historically, there has been a great deal of activity to develop methods for the prevention of post-operative adhesions. Some of the approaches, e.g., the ingestion of iron powder-laced oatmeal followed by the application of magnets to the abdomen to jostle the bowel and prevent adhesions, are interesting approaches. Adhesions are particularly troublesome in a variety of locations, e.g., between the pericardium and sternum following open heart surgery, in the abdominal cavity following bowel procedures and, especially, in the retroperitoneal space involved with gynecological reconstruction. Two primary approaches have been explored. The first involves

implantable barrier films prepared, for example, from hyaluronic acid or hydrogonic acid or oxidized cellulose, but has not met with success because the location of where to place the film to prevent adhesions is not determinable. The second approach involves the instillation of a bolus of solution, e.g., N,O-acetylchitosan, to wet the general area where adhesions might be expected. This seems to be the superior therapeutic direction, but no satisfactory product along this line has been commercialized. If a suitable, proven product were made available, it would have the potential to be used prophylactically in practically every surgical procedure. It should be noted that post-operative adhesions usually form during the first post-operative week and, if not formed during this time, they usually do not occur. Therefore, the task is to prevent fibroblasts (which produce the collagenous adhesions) to adhere to local tissue surfaces because, without cellular attachment during the first week, adhesions will not form. The anti-adhesion solutions of the current invention are expected to prevent such cell attachment. The anti-adhesion embodiments herein are optionally in various forms (e.g., liquid application forms, film application forms, etc.). Creation of adhesions are especially bad for fertility surgery. Because adhesions form relatively quickly, it is desired to avoid fibroblast for 5 days post operations.

[0064] An aqueous microcapsule or particle suspension prepared from an absorbable natural (e.g., collagen) or synthetic (e.g., polyglycolic acid) polymer and coated with a nanofiber surface to provide extreme lubricity is a feature of the invention. About 200 ml of this suspension could be poured into the appropriate cavity and would coat the tissue with a surface not hospitable to fibroblast cell attachment and subsequent adhesion formation. The material would be harmlessly absorbed after a few weeks. Some embodiments can optionally be a mesh (e.g., synthetic, metal, fabric) coated with nanofibers or nanowires that is laid directly over the cavity.

### **IX) Endoscopes and Catheters**

[0065] One of the more difficult aspects of endoscopy, e.g., colonoscopy, involves the frictional resistance of the device passing through the tubular organ, e.g., bowel, urethra, esophagus, trachea, blood vessel, etc. Besides being difficult to transport the scope or catheter, the friction causes significant discomfort to the patient. Slippery catheters, coated with, for example, polyvinylpyrrolidone have been designed to provide easier passage but these devices have not enjoyed wide market acceptance. A lubricious scope or catheter comprising nanofiber surfaces of the invention, would be

expected to provide significantly increased patient comfort and well as more facile transport for the physician.

### **X) Intraluminal Cameras**

[0066] One of the latest diagnostic advances is the use of miniaturized, untethered cameras to observe internal organs. Such cameras, the size of pills, may be ingested or injected and float downstream, sending images back to the medical observer. It is expected that improved lubricity due to nanofiber surfaces of the invention will enhance the performance of such devices. An appropriate nanofiber coating is expected to make it easier for the camera to be ingested and manipulated along its path. Other similar embodiments comprise nanofiber coatings on devices to, e.g., create hydrophobic shields (e.g., windows) on devices such as cameras, keep a coating layer (e.g., hyaluronic acid, etc.) on a device, to create a transparent coating on contact lenses (which optionally also helps prevent protein build-up), etc.

### **XI) Mechanical Heart Valves**

[0067] There are two types of heart valve prostheses used for replacement of aortic and mitral valves. Mechanical valves commonly are metallic cages with a disc that opens at systole to allow blood to flow and closes at diastole to prevent backflow. These valves last indefinitely but require the daily administration of an anticoagulant drug to prevent thrombotic complications. The dose must be carefully regulated to prevent thrombus formation on one hand and internal hemorrhage on the other. The other type of valve is the tissue valve, sometimes isolated en bloc from porcine hearts and sometimes constructed from bovine pericardial tissue. These leaflet valves are more like natural valves and usually do not require anticoagulant drug administration. However, they are susceptible to degradation and have more finite life expectancies than do the mechanical valves. Fortunately, they fail slowly and provide ample time for surgical replacement. It would be of inestimable medical advantage if the long lasting mechanical valves could function successfully without anticoagulation therapy. Nanofiber enhanced surfaces of the invention used thusly are part of the invention. Additionally, nanofiber surfaces also can be used in the improvement of the hemodynamic performance of left ventricular assist devices (LVADs).

[0068] With nanofiber specially designed mechanical heart valves, it is expected that: there will be improved hemodynamics resulting from laminar flow; there will be

improved blood throughput per systole; the need for anticoagulation will be eliminated or significantly reduced; the incidence of thrombosis will be eliminated or significantly reduced; and the level of hemolysis will be reduced or eliminated.

## **XII) Small Caliber Vascular Grafts**

[0069] Presently, a variety of vascular prostheses larger than about 6mm in diameter perform adequately when implanted from the thoracic aorta through the iliac/femoral regions. Below about 6 mm in diameter, such grafts fail when implanted either as interpositional or bypass grafts, secondary to full lumen thrombosis. Similarly, there is no graft material available for venous reconstruction. For many years, workers have tried to develop a small diameter vascular graft, particularly for coronary artery bypass procedures, to avoid the need to harvest saphenous veins from the leg. Generally, small diameter grafts in the 2-5 mm range fail because a 0.5-1.0 mm thick layer of protein is rapidly deposited on the luminal surface causing a further reduction in luminal diameter which, in turn, induces the formation of mural thrombi. Even conventionally non-wettable surfaces such as polytetrafluoroethylene (Teflon®) and polyurethanes do not resist protein intimal layering.

[0070] The ultra non-wettability of nanofiber enhanced surfaces may affect two factors of extreme importance. First, the avoidance of deposition of plasma protein on the luminal surface will preserve the original graft diameter. Equally important, a nanofiber surface may provide close to ideal laminar blood flow which would be expected to reduce or entirely eliminate luminal thrombus formation. This is optionally of great importance in preventing graft thrombosis and/or minimizing anastomotic intimal hyperplasia, well-know causes of graft failure secondary to turbulent flow, particularly at the sutured anastomosis.

[0071] Specifically, the nanofiber surface may be beneficially employed for the following grafts: femoral/popliteal (and infrapopliteal) reconstruction; coronary bypass grafts (possibly replacing saphenous veins and IMA procedures); A-V shunts (hemodialysis access); microvascular reconstruction (e.g., hand surgery); and vein reconstruction. Use of such for A-C bypass grafts and for peripheral vascular reconstruction, especially in the diabetic patient population, are contemplated. Microvascular and A-V shunt and vein uses are also contemplated. More detailed

descriptions of the use of nanofiber enhanced surfaces for sutureless anastomotic procedures is described further below.

### **XIII) Bulking Agent for Cosmesis**

[0072] The Collagen bulking business has taken off in the arena of cosmesis with ~800,000 procedures thought to be performed in 2003. The annual revenues of the space for the materials provider(s) is closing in on \$500Million. The primary issue with Collagen when used for cosmesis (e.g., lips and deep wrinkles, etc.) is durability. The typical collagen bulking injection will last ~3-4 months prior to subsidence of results and need for reapplication. Thus, non-resorbable, yet biocompatible micro-spheres are desired to create a durable cosmetic effect.

[0073] The ability to create non-bioburden micro-spheres injectable through a standard gauge needle, is greatly desired in this area, especially if: they are easily applied, injectable and lubricous enough for easy placement; there are durable results; there are no biocompatibility issues; and there is no migration over time. There are reasons to believe that the ability to combine an optimized lubricity (e.g., through balancing hydrophobia & hydrophilia with nanofibers) in conjunction with a non-bioburden technology on a micro-sphere carrier could create a competitive winner. Other embodiments comprise possible reduction of scar tissue and those having erodable polymers with nanofiber scaffold which is optionally functionalized.

### **XIV) Enhanced Flow and Reduced Thrombogenicity Mechanical Heart Valve**

[0074] Replacement valve implantation is a large and valuable market that is approaching \$1Billion in sales. First, there has been an on-going pendulum swing between mechanical and tissue valve implantation driven primarily by the real and perceived differences between the two in the areas of longevity, thrombogenicity and flow dynamics. Second, product based competition has ossified as new product development cycles have been protracted on the back of ever more rigorous regulatory/clinical requirements. With the possibility of modifying existing products (resulting in a much shorter regulatory path) potentially delivering improvements in 2 of the key valve metrics (thrombogenicity and fluid dynamics), nanofibers could potentially have a dramatic impact upon the market share within mechanical valve players and between mechanical and tissue valve products.

[0075] Although not entirely understood, thrombogenicity and flow dynamics are interrelated issues. In fact, the flow eddies created downstream of the hinge seat for the most popular bi-leaflet valve design is still blamed for much of the thrombogenic effect of such products. A hydrophobic surface coating such as that made possible by nanofiber enhanced surfaces may have dramatic effect in reducing such problems.

[0076] This embodiment of the invention offers the benefit of being an addendum to a current product thereby allowing a dramatically reduced cycle time while at the same time delivering true product based differential advantage.

#### **XV) More Durable Functionality of Implantable Sensors and Pacing Leads**

[0077] The implantable sensor market is in its infancy with the variety of early applications including; glucose sensors, cardiac function sensors (either on-lead or off) and neurological implants of various stripes. Many of these companies have similar problems associated with bio-fouling over time and the difficulty of creating durable reagent beds. It may be possible that the combination of reagent doping pads, arranged in concert with highly hydrophobic structures will deliver a significantly longer lasting functionality to sensors of all types. Current technologies are either accepting this shortcoming (e.g., glucose sensors limited to 3 days of functionality) or are combating it with costly and difficult to engineer solutions involving mechanically active packaging and/or massive parallelization.

[0078] A further and related application for the nanofibers herein would be the coating of pacing leads to provide both a better electrical contact with tissue and a non-fouling shaft. Much of the sensor/reagent technology employed in these markets is no longer proprietary due to the long mature run in traditional non-implant diagnostics and the packaging may in-fact be the critical proprietary technology that enables the space. How does one package a sensor (be it reagent or electrical) for long term survival in the highly corrosive and actively encapsulating environment of the human body. This is a significant challenge for all of the indwelling companies. The uniquely non-fouling approach delivered by the nanofibers herein, has the additional property that it leaves no-imprint down-stream or in proximity to the non-fouling surface. This would enable a creative packaging with reagent/sensors to garner accurate readings. Furthermore, with reagent durability being of concern, it may be possible to create reagent doped



pads comprising nanofibers in much the same way as the drug doped pads discussed in the drug-eluting stent summary below.

**[0079]** In the arena of pace-maker leads, there are two issues that bother the clinicians involved. The occasional dislodged or poorly placed lead that delivers inadequate charge to the tissue and the over-growth of tissue around the leads over time that can, in some patients who have had multiple leads placed over time, actually cause flow resistance. These can further complicate subsequent procedures/surgeries. Further, abandoned but not removed leads can cause complications. Such devices comprising nanofibers herein could likely remove both of these issues with nanofibers on the sensor head and an anti-bio-fouling coating along the shaft.

**[0080]** Glucose sensors: The holy grail of the ~\$2Billion world-wide glucose sensing market has been to get away from the finger-stick devices and into a sustained glucose device either through a truly non-invasive approach or an indwelling approach. The two paths remain in fundamental technological competition with neither approach yet showing a clear edge in embodiment or time-to-market over the other. The implantable glucose sensing technologies under development today all bring with them substantial enough limitations so as not to be considered for broad market adoption. While this cannot be said of the non-invasive approaches they face hurdles in development that have for 15 years stymied the market leaders in their quest for workable units. Nanofiber addition to such sensors would prevent/ameliorate several problems listed above.

**[0081]** Cardio Sensors: In its very earliest stages this market promises to provide full cardiac output metrics without the need for an interventional cardiological procedure (perhaps on an on-going basis as an alert) and/or to provide superior real-time control of an active cardiology device (e.g., BV-Pacer, left ventricular assist device (LVAD)). Again, addition of nanofibers to such devices would prevent/ameliorate many problems above.

**[0082]** Neuro sensors/emitters: Again, another early stage space but in this case the primary focus in the area of stimulation as opposed to sensing. Neuromodulation and neurostimulation rely on consistent, uninterrupted contact with nervous tissue. Nanofibers on the tissue contact end of the leads can secure the lead and prevent scar

formation (e.g., glial scar) leading to improved conduction. Additionally, nanofibers can be used as conductive materials in the shaft of the lead.

[0083] ICD and Pacemaker leads: The numbers in the combined market are large in unit volume with ~1,000,000 implantations per year. This is further experiencing growth as bi-ventricular pacing has taken off even more rapidly than the all ready optimistic projections. The issue with the leads has been that while they, at one time, took quite a large share of the value chain their price-point has been steadily eroded.

#### **XVI) Vascular Stents and Next Generation Drug Eluting Coronary Stents**

[0084] Vascular stents are small metallic devices which are used to keep the blood vessels open following balloon angioplasty. The development of coronary stents, for example, has revolutionized the practice of interventional cardiology over the past 10 years. More than 70 coronary stents have been approved in Europe and over 20 stents are commercially available in the United States such as the Multi-Link Vision™ Coronary Stent System available commercially from Guidant Corporation (Indianapolis, IN), and the Driver™ Coronary Stent System or BeStent2™ available commercially from Medtronic, Inc. (Minneapolis, MN).

[0085] Commercially available stents can take a variety of forms. For example, one such stent 210, as shown, for example, in Figs. 2A-B, is a stainless steel wire which is expanded by balloon dilatation. The stent 210 may be crimped onto a balloon 212, as shown in Fig 2A, for delivery to the affected region 214 of a vessel 216 such as a coronary artery. For the sake of simplicity, the multiple layers of the vessel wall 216 are shown as a single layer, although it will be understood by those skilled in the art that the lesion typically is a plaque deposit within the intima of the vessel 216.

[0086] One suitable balloon for delivery of the stent 210 is the Maverick® PTCA balloon commercially available from Boston Scientific Corporation (Natick, MA). The stent-carrying balloon 212 is then advanced to the affected area and across the lesion 214 in a conventional manner, such as by use of a guide wire and a guide catheter 205. A suitable guide wire is the 0.014" Forte™ manufactured by Boston Scientific Corp. and a suitable guiding catheter is the ET 0.76 lumen guide catheter.

[0087] Once the balloon 212 is in place across the lesion 214, as shown in Fig 2A, the balloon 212 may be inflated, again substantially in a conventional manner. In

selecting a balloon, it is helpful to ensure that the balloon will provide radially uniform inflation so that the stent 210 will expand equally along each of the peaks. The inflation of the balloon 212 causes the expansion of the stent 210 from its crimped configuration to its expanded position shown in Fig. 2B. The amount of inflation, and commensurate amount of expansion of the stent 210, may be varied as dictated by the lesion itself.

[0088] Following inflation of the balloon 212 and expansion of the stent 210 within the vessel 216, the balloon is deflated and removed. The exterior wall of the vessel 216 returns to its original shape through elastic recoil. The stent 210, however, remains in its expanded form within the vessel, and prevents further restenosis of the vessel. The stent maintains an open passageway through the vessel, as shown in Fig. 2B, so long as the tendency toward restenosis is not greater than the mechanical strength of the stent 210.

[0089] Another form of stent is a self-expanding stent device, such as those made of Nitinol. The stent is exposed at the implantation site and allowed to self expand.

[0090] Significant difficulties have been encountered with all prior art stents. Each has its percentage of thrombosis, restenosis and tissue in-growth, as well as varying degrees of difficulty in deployment. Another difficulty with at least some of the prior art stents is that they do not readily conform to the vessel shape. Anticoagulants have historically been required at least for the first three months after placement.

[0091] Thus there has been a long felt need for a stent which is effective to maintain a vessel open, without resulting in significant thrombosis, which may be easily delivered to the affected area and easily conformed to the affected vessel.

[0092] The present embodiment of the invention is generally directed to endovascular support devices (e.g., commonly referred to as "stents") that are employed to enhance and support existing passages, channels, conduits, or the like, and particularly animal, and particularly mammalian or human lumens, e.g., vasculature or other conductive organs. In particular, the present embodiment of the invention provides such stent devices that employ nanostructured components as shown, for example, in Figure 1 and Figure 2D, to enhance the interaction of the stent with the passages in which they are used. Typically, such nanostructured surfaces are employed to improve adhesion, friction, biointegration or other properties of the device to enhance

its patency in the subject passage. Such enhanced interactivity is generally provided by providing a nanostructured surface that interacts with the surface of the passage, e.g., an inner or outer wall surface, to promote integration therewith or attachment thereto. The nanostructured components (e.g., nanofibers) can either be attached to the outer or inner surface of the stent, e.g., by growing the nanofibers directly on the outer and/or inner surface of the stent, or by separately covalently or ionically attaching the fibers to the stent surfaces. In addition, the nanofibers or other nanostructures can be embedded into the stent material itself to enhance the rigidity and strength of the stent within the vessel into which it is inserted. The shape and size of the nanofibers as well as their density on the graft surfaces can be varied to tune the adhesive (or other) properties of the stent to the desired levels. In particularly preferred aspects, higher aspect ratio nanofibers are used as the nanostructures. Examples of such nanofibers include polymeric nanofibers, metallic nanofibers and semiconductor nanofibers as described previously.

**[0093]** The stents of this invention may also be coated on the inside and/or outside with other materials to still further enhance their bio-utility. Examples of suitable coatings are medicated coatings, drug-eluting coatings (as described below), hydrophilic coatings, smoothing coatings, collagen coatings, human cell seeding coatings, etc. The above-described nanofiber coatings on the stent can provide a high surface area that helps the stent to retain these coatings. The coatings can be adsorbed directly to the nanostructured surface of the stent. Alternatively, the nanostructured surface may be provided with a linking agent which is capable of forming a link to the nanostructure components (e.g., nanofibers) as well as to the coating material which is applied thereto. In such cases, the coating may be directly linked to the nanostructured surface, e.g., through silane groups, or it may be coupled via linker binding groups or other appropriate chemical reactive groups to participate in linkage chemistries (derivitization) with linking agents such as, e.g., substituted silanes, diacetylenes, acrylates, acrylamides, vinyl, styryls, silicon oxide, boron oxide, phosphorus oxide, N-(3-aminopropyl)3-mercapto-benzamide, 3-aminopropyl-trimethoxysilane, 3-mercaptopropyl-trimethoxysilane, 3-maleimidopropyl-trimethoxysilane, 3-hydrazidopropyl-trimethoxysilane, hydroxysuccinimides, maleimides, haloacetyls, pyridyl disulfides, hydrazines, ethyldiethylamino propylcarbodiimide, and/or the like.

**[0094]** The coronary stent market is enormous and hotly contested by the largest device players. There is, at the moment, a gold rush amongst competitors to gain

advantage thorough product development/acquisition in the newest sector – drug eluting coronary stents, such as the U.S. FDA-approved Cordis Cypher™ sirolimus-eluting stent and the Boston Scientific Taxus™ paclitaxel-eluting stent system. Drug eluting stents are rapidly gaining market share and may become the standard of care in coronary revascularization by the year 2005. This new therapy involves coating the outer aspect of a standard coronary stent with a thin polymer containing medication that can prevent the formation of scar tissue at the site of coronary intervention. Examples of the medications on the currently available stents are sirolimus and paclitaxel, as well as anti-inflammatory immunomodulators such as Dexamethasone, M-prednisolone, Interferon, Leflunomide, Tacrolimus, Mizoribine, statins, Cyclosporine, Tranilast, and Biorest; antiproliferative compounds such as Taxol, Methotrexate, Actinomycin, Angiopeptin, Vincristine, Mitomycin, RestenASE, and PCNA ribozyme; migration inhibitors such as Batimastat, Prolyl hydroxylase inhibitors, Halofuginone, C-proteinase inhibitors, and Probuco; and compounds which promote healing and re-endothelialization such as VEGF, Estradiols, antibodies, NO donors, BCP671, and the like. Sirolimus, for example, had been used previously to prevent rejection following organ transplantation. Unfortunately, the use of polymer coatings on stents can lead to thrombosis and other complications; anticoagulants are typically required at least for the first three months after placement to alleviate some of these issues.

[0095] However, the provision of a nanostructured surface on these newer stents according to the teachings of the present invention can eliminate the need for such polymer coatings and thus minimize some of these complications. Increasing surface area (e.g., through spring coil, micropockets, etc.) through nanofibers is quite desirable. Thus, nanofibers are optionally embedded/empended into tissue to give a more sustained benefit and better drug release. The nanofiber surfaces give greatly enhanced surface area and a longer length of elution and a more intense concentration. The drugs can be directly adsorbed to the nanofibers (or other nanostructured components) or can be linked (e.g., covalently through silane groups or other linker molecule) to the nanofibers through suitable linkage chemistries such as those described above. The linkage chemistry can be tailored to provide for customized drug elution profiles and for the controlled release of the drug compounds over time. Alternatively, a first molecule such as albumin is adsorbed to the nanofiber surface and the drug is adsorbed to the albumin.

[0096] The manufacturers of drug eluting stents are very interested in the several facets of this new technology: increased contact surface area between coated metal and arterial wall; increased depth/durability of coating for pro-longed elution times; and intriguing possibilities of multiple, layers of differing drugs for novel elution profiles. The basic stent structure (conformity, ease of deployment, branching utilization, etc.) still matters a great deal in winning doctors over from other products.

[0097] By developing a coating that enables increased contact area and “dose density”, that likely can be applied to any and all existing stents, the nanofiber devices herein can pursue a variety of market strategies, e.g., through improved fluid dynamics with a hydrophobic surface coating on the inside, drug elution improvement, etc. By applying a nanofiber coating to the outside surface of the stent it may be possible to then have a thicker and more durable drug coating on the stent than would be possible without the nanofiber technology. Furthermore, the high surface area contact intrinsic to the nanofiber technology may yield improvements in tissue response to the attached drug. Furthermore, there may be the opportunity to apply a hydrophobic coating to the inside of the stent to improve flow dynamics – particularly within small arteries. . .

[0098] In addition to coronary stents, the use of nanostructured surfaces may also be beneficially applied to other stents which are used in other parts of the body of a patient, such as urethral and biliary stents. In these body lumens, it is desired to prevent crystallization on the struts of the stents. In the biliary tree, for example, bilirubin crystals deposit on foreign surfaces such as sutures and permanent or temporary stents. Such deposition typically decreases the useful life of the stents and can require patients to undergo multiple procedures for successful therapies. A similar situation exists in the urinary tract. Uric acid precipitates on stents and leads to “stent encrustation,” which ultimately leads to device failure. Stents otherwise may be a promising therapy for conditions such as Benign Prostatic Hyperplasia (BPH). A stent with a super hydrophobic nanofiber coating would resist crystal formation because the aqueous phase would not “see” the stent and crystal inducing elements would not have a chance to deposit.

### **XVII) Small Caliber Vascular Grafts**

[0099] Presently, a variety of vascular prostheses larger than about 6mm in diameter perform adequately when implanted from the thoracic aorta through the iliac/femoral regions. Below about 6 mm in diameter, such grafts fail when implanted

either as interpositional or bypass grafts, secondary to full lumen thrombosis. Similarly, there is no graft material available for venous reconstruction. For many years, workers have tried to develop a small diameter vascular graft, particularly for coronary artery bypass procedures, to avoid the need to harvest saphenous veins from the leg. Generally, small diameter grafts in the 2-5 mm range fail because a 0.5-1.0 mm thick layer of protein rapidly is deposited on the luminal surface causing a further reduction in luminal diameter which, in turn, induces the formation of mural thrombi. Even conventionally non-wettable surfaces such as polytetrafluoroethylene (Teflon®) and polyurethanes do not resist protein intimal layering. The peripheral vascular market represents a huge, relatively untapped market because of the limitations of small diameter grafts. The nanofiber surfaces herein can aid in reducing bio-fouling, increasing hydrophobicity, etc.

**[0100]** It is suggested that the ultra non-wettability (hydrophobicity) of nanofiber surfaces may affect two factors of extreme importance. First, the avoidance of deposition of plasma protein on the luminal surface will preserve the original graft diameter. Equally important, a nanofiber surface can optionally provide close to ideal laminar blood flow which would be expected to reduce or entirely eliminate luminal thrombus formation. This may be of great importance in preventing graft thrombosis and/or minimizing anastomotic intimal hyperplasia, well-known causes of graft failure secondary to turbulent flow, particularly at the sutured anastomosis.

**[0101]** The nanofiber surface may be beneficially employed for the following grafts: Femoral/popliteal (and below the knee) revascularization; Coronary bypass grafts (possibly replacing saphenous veins and IMA procedures); A-V shunts (hemodialysis access); Cranial (Supra Temporal Artery/ Medial Cerebral Artery [STA/MCA]); Microvascular reconstruction (e.g., hand surgery); vein reconstruction. By far, coronary bypass grafts have significant medical and commercial value followed by femoral revascularization. In some embodiments the graft material is simply coated with nanofibers herein, while others comprise entirely new substrates specifically designed for nanofiber coating. A nanofiber A-C bypass graft would be quite desirable, particularly if it could be implanted using advanced least invasive surgical procedures to avoid splitting the sternum. A large market exists for peripheral reconstruction, especially in the diabetic patient population. The microvascular, A-V shunt and vein

markets are relatively small but together may form a significant business. There is potential to carry the vascular graft business into an entirely new level of performance.

**[0102]** Current grafts in small vessels present problems. Current choices include, e.g., Dacron fabric, PTFE (similar to Gortex), etc. Problems can arise with small diameters and protein layers that are put down (especially true for diameters under 6mm). Ideal grafts want the vessel to look like a wet noodle for impeding into vein structures and not have film forming. Thus, prevention of protein buildup and perfection of laminar flow in the vessel is desired. Also, less invasive procedures are desired. The current nanofiber devices can optionally fulfill these needs, e.g., be less invasive because devices could be preloaded and, e.g., stapled into the vessel. The hydrophobicity of various embodiments herein can be quite useful in typical uses. The grafts herein are optionally temporary or permanent within the patient. Other embodiments include wherein the nanofiber grafts also comprise drug coatings, etc. (e.g., heparin, etc.).

**[0103]** Other embodiments deal with concerns of, e.g., working with collagen spun vascular grafts. Also, host vessel sutured to a graft can get puckered at interface from sutures, thus, leading to eddies at interface. Thrombus can form at interface and intimal hyperplasia can lead to vessel narrowing at the anastomotic site. Such can cause narrowing of the vessels until the vessel closes down. This is not usually a problem in large vessels, but can be quite problematic in smaller vessels. Therefore, nanofiber surfaces of the invention can be incorporated into grafts at such interfaces. Also, coated spiral structures which are optionally removed are incorporated herein. Sutures, staples, etc. are also optionally nanofiber enhanced.

**[0104]** Other embodiments include nanofiber enhancement with, e.g., blood treatment, left ventricular assist devices (LVAD) treatment regimes (e.g., preventing thrombosis), patent foramen ovale (PFO), atrial septal defects (ASDs), treatment of left atrium aneurysms, treatment of diabetic small vessel disease (i.e., instead of amputation), treatment of venous thrombosis (e.g., over long term, etc.). The nanofiber surfaces herein typically provide longevity, can allow flexibility, provide strength of holding staple/suture. They can be used in, e.g., growth of specific cells for wound healing, as scaffolding for bone growth to occur, etc. For example, with respect to atrial septal defects, when there is a large hole between the right and left atria, oxygen rich blood leaks back to the right side of the heart. The result can be pulmonary



hypertension. These defects are often treated surgically, through open heart surgery. A device that could be placed percutaneously, and permanently close the hole, would be desirable over the morbidity associated with open chest surgery. A device incorporating nanofibers can be placed via a catheter through the arterial system, and serve as a patch or plug over or in the defect.

### **XVIII) Timed Release Nanowire Balls**

[0105] The past 20 years has seen many research efforts aimed at orally delivered targeted delivery drug vehicles. Specificity, controlled release and low toxicity have been difficult hurdles to overcome and most of these efforts are still in the research phase. Polymers, dendrimers, liposomes and antibodies are four well-studied drug carriers. These structures range from the micron size to several nanometers. The larger particles tend to stick to the desired tissue and then the drug erodes out, the smaller structures often carry only several drug molecules and work on contact or when a bond is broken to the carrier structure (dendrimers). Nanostructures could span this size range from small dots (3-10nm) to clusters of nanowires (20-500nm). These structures could be readily conjugated to drug molecules and can be dispersed in aqueous solution.

[0106] High drug capacity and ease of functionalization are typical advantages of the current invention. Typical embodiments are chosen based upon, e.g., toxicity testing for patient application, as well as nanofiber accumulation. Some embodiments comprise tericoated tabs and can depend on pH values in the stomach, e.g., for time release due to recognize of an enzyme or the proper pH. Other embodiments comprise air-filled nanofiber balls, e.g., as contrast agents in ultrasound and the like. Also, PEGylated liposomes not taken up by RES (reticuloendothelial system).

### **XIX) Surgical Needles**

[0107] Some embodiments herein comprise nanofiber coated surgical needles. Cutting needles are better when serrated. When passing a needle through tissue, the apparent sharpness is based on resistance (correlated to dullness). Protein attaching to the surface of such needles gives the apparent dullness. Thus, coatings (e.g., as with nanofibers) that prevent protein attachment and reduce dullness can be more important than "sharpness" of the needles. Such concepts are also applicable to scalpels, etc.

**XX) Wound Dressing**

[0108] Wound dressings are used extensively in trauma, at catheter skin-sites and post surgical applications. This is a very competitive field with an excess of OTC and ethical supply products available. Minimization of infection, allowance of air penetration, adhesion ability, water repellency, ease of application, ease of removal are all important characteristics that influence physician, nurse and patient product preference. All of these characteristics can be found in separate wound dressings but not as an “all-in-one” package. A flexible, breathable, hydrophobic, bacteriostatic sided dressing with an adhesive, bacteriostatic backside would be revolutionary to the medical field. The current nanofiber surfaces herein can optionally supply many or all of such characteristics. This dressing would be able to access ethical as well as OTC markets.

[0109] The combination of nanowire coated characteristics would allow patients to shower or bathe, avoid infection, heal, and decrease the need for painful bandage changes. Various embodiments can comprise bacteriostatic dressings and/or bactericidal dressings. Various embodiments can comprise silver and/or zinc and/or titanium oxides. Such dressings are especially contemplated for, e.g., burn victims, etc.

[0110] The current invention comprises a number of different embodiments focused on nanofiber enhanced area surface substrates and uses thereof (e.g., in medical devices/uses). As will be apparent upon examination of the present specification and claims, substrates having such enhanced surface areas present improved and unique aspects that are beneficial in a wide variety of applications for medical use. It will be appreciated that enhanced surface areas herein are sometimes labeled as “nanofiber enhanced surface areas” or “NFS” or, alternatively depending upon context, as “nanowire enhanced surface areas” or “NWS.”

[0111] A common factor in the embodiments is the special morphology of nanofiber surfaces (typically silicon oxide nanowires herein, but also encompassing other compositions and forms) which are optionally functionalized with one or more moiety.

**XXI) Abdominal (or Thoracic) Aortic Aneurysm (AAA) Medical Procedures**

[0112] The compositions, apparatus, systems and methods described herein relating to nanostructured surface enhanced coatings can be used, for example, to assist

in the device, function and deployment of prostheses during the repair of thoracic or abdominal aortic aneurysms.

[0113] An aortic aneurysm generally is an abnormal widening, stretching or ballooning of the thoracic or abdominal portion of the aorta, which is the major artery from the heart which delivers blood to the major organs of the body. The thoracic and abdominal portions of the aorta represent the upper, arched portion and lower, abdominal portion of the aorta, respectively. The exact cause of aneurysm is unknown, but risks include atherosclerosis and hypertension. A common complication is ruptured aortic aneurysm, a medical emergency in which the aneurysm breaks open, resulting in profuse bleeding. Aortic dissection occurs when the lining of the artery tears and blood leaks into the wall of the artery. An aneurysm that dissects is at even greater risk of rupture. Aortic aneurysms occur in approximately 5-7% of people over the age of 60 in the United States alone. Over 15,000 people die each year of ruptured aneurysm, the 13<sup>th</sup> leading cause of death in the U.S.

[0114] Generally, when an abdominal or thoracic aortic aneurysm reaches a size of about 5 cm, surgical intervention is necessary. To repair an abdominal or thoracic aortic aneurysm by intraoperative procedure, the thoracic cavity can be accessed by a midline or retroperitoneal incision in the case of an open procedure, or by percutaneous access in a minimally invasive endograft procedure, and an autogenous or prosthetic graft is used to isolate the aneurysm from blood flow and pressurization, thus precluding aneurysm expansion and minimizing the risk of rupture. Typically, the first choice for replacement is typically the autogenous saphenous vein (ASV), but when it is unavailable for transplant, artificial prosthetic grafts may be used. Generally they are used for large diameter vessel applications such as aortic aneurysm repair, however recent research efforts have been directed towards finding suitable methods for medium and small diameter vessel repair as well.

[0115] Inaccurate deployment of aortic prostheses can lead to inadequate sealing of the aneurysm which can cause further aneurysm expansion due to blood flow around the graft, and/or inadvertent blockage of collateral vessels supplied by the aorta, for example, such as the renal arteries. Aortic prostheses can also slip out of position. To date, as noted below, at least two stent grafts have been pulled from the market due to high rate of failure, and others continue to fail. A need exists to improve the outcome of aortic aneurysm repair by improving the materials of the grafts to make them more

adherent thereby minimizing or eliminating failures of conventional devices caused by such complications as leakage and/or mal-positioning or slippage of the prosthetic devices.

[0116] Using the methods and compositions disclosed herein, both open and minimally invasive endovascular repair procedures can be performed to ensure that an aortic prosthesis, when placed properly at the site of an aneurysm, will adhere firmly to the tissue surface and maintain its patency for longer periods of time than conventional devices. The outer (and/or inner) diameter of the graft prosthesis is coated with nanofibers (or other nanostructured material such as nanotetrapods, nanotubes, nanowires, nanodots, etc.) either by directly growing the nanofibers on the surface of the graft, or by coating the graft with harvested nanofibers, thus providing the graft with a dry adhesive surface. The disclosed methods described above and herein can provide enhanced accuracy, for example, with respect to location and orientation, in the placement of the prostheses within a region of a patient's aorta having an aneurysm or other diseased or damaged condition therein.

[0117] Although the techniques of the present invention can be used to facilitate both open and minimally invasive abdominal or thoracic aortic aneurysm procedures (or any other aneurysm procedure in the aorta or other areas of the body as well), the following illustration describes only an endovascular minimally invasive repair procedure which is less traumatic to the patient than an open-chest procedure. One of ordinary skill in the art, however, will appreciate that the techniques disclosed can be readily applied to open chest procedures as well in which access to the thoracic cavity is achieved through a midline partial or median sternotomy, a mini-thoracotomy incision, or a retroperitoneal incision, for example.

[0118] Referring now to FIGS. 3A-B, a system is schematically illustrated for placing a prosthetic graft during a closed-chest abdominal or thoracic aortic aneurysm repair procedure using the methods and compositions of the present invention. In one embodiment, a patient is anesthetized and generally prepared for surgery in a conventional manner. The procedure then involves positioning the stent graft deployment mechanism and stent graft 372 (Fig. 3B) within the abdominal aorta 354 (or thoracic aorta 356) at the site of aneurysm 370. Endovascular devices which can be used for aortic aneurysm repair include, for example, balloon-expandable or self-expandable devices. Balloon-expandable stent designs are described, for example, in

Parodi et al., *Ann. Vasc. Surg.* 1991; 5:491-499 and White et al., *J. Endovasc. Surg.* 1994; 1:16-24, the disclosures of which are incorporated by reference herein. The following devices have received FDA approval for use in the abdominal aorta and are examples of systems that can be used in practicing the present invention:

- (1) Ancure® Endograft® System (Guidant Corporation). In this system, which was approved in 1999, the endograft is placed in the aorta and expanded using balloon dilation. The graft is anchored to the vessel wall using sutureless hooks at its superior and inferior ends. On March 16, 2001, Guidant suspended production of this system and announced a recall of all existing inventories. The company reported to the FDA that they had failed to report many device malfunctions and adverse events, including severe vessel damage associated with problems with the deployment of the device. There were also manufacturing changes that were not properly reported to the FDA. The FDA issued a Public Health Notification: Problems with Endovascular Grafts for Treatment of Abdominal Aortic Aneurysm (AAA), regarding both this device and the AneuRx device.
- (2) Ancure® Aortoiliac System (Guidant Corporation). This new version was approved in 2002 and is identical to the earlier Guidant Endovascular Grafting System except that the aortoiliac Ancure® grafts have suture loops on the superior and inferior attachment systems. The device is intended for use in patients whose anatomy is not suited for the use of the single tube or bifurcated endograft device.
- (3) AneuRx® Stent Graft System (Medtronic AVE). The AneuRx system, approved in 1999, consists of a woven polyester interior surface with a self-expanding Nitinol exoskeleton. The radial force of the expanding stent embeds in the exoskeleton into the aneurysm wall, and thus constitutes the attachment mechanism. This device was also the subject of the above FDA Public Health Notification. In December 2003, the FDA published updated information on the mortality risks associated with the AneuRx® Stent Graft System based on an analysis of longer term follow-up data from the premarket study. Based on the findings of the study, the FDA recommended that the AneuRx® Stent Graft be used "only in patients who meet the appropriate risk-benefit profile and who can be treated in accordance with instructions for use."

- (4) EXCLUDER™ Bifurcated Endoprosthesis (W.L. Gore and Associates, Inc.). Approved in 2002, this device self-expands inside the aorta to the diameter of the aorta and iliac arteries, thus sealing off the aneurysm and relining the artery wall.
- (5) Zenith™ AAA Endovascular Graft and H&L-B One-Shot™ Introduction System (Cook, Inc.). This device was approved in 2003; it is self-expanding and attaches to the vessel wall via barbs.

[0119] Each of these devices are deployed across the aneurysm such that the aneurysm is effectively "excluded" from the circulation with subsequent restoration of normal blood flow. The above-referenced systems generally consist of an endograft prosthesis 372 (Fig. 3B) and a corresponding delivery catheter 330. The prosthesis is a vascular graft which isolates the aneurysm 370 from blood flow and pressurization, thus precluding aneurysm expansion and minimizing the risk of rupture. The delivery catheter 330 is an over-the wire system which is subcutaneously inserted into a femoral or iliac artery 350, 352 in the groin area using known techniques such as a cut-down or a percutaneous technique such as the Seldinger technique. The delivery catheter 330 is advanced into the aorta 354 under image (e.g., fluoroscopic, echocardiographic, MRI, or CT scan) guidance to the site of the aneurysm 370 and is designed to transport the preloaded prosthesis to the aorta. The compressed prosthesis is pre-loaded within a special delivery sheath. Some prostheses consist of modular components such that the delivery is comprised of the primary prosthesis plus one or two "docking limbs." Due to the large size of the delivery sheaths, open surgical exposure of one or both groins is required to establish vascular access. After entry into the arterial system, the prosthesis is fluoroscopically guided through the iliac arteries into the aneurysm site, followed by deployment of the prosthesis with the use of a compliant low-pressure balloon.

[0120] Artificial grafts can include, for example, treated natural tissue, laboratory-engineered tissue, and synthetic polymer fabrics. Synthetic polymers such as Dacron® and Teflon® (i.e., expanded polytetrafluoroethylene (ePTFE)) are the most commonly used of the synthetic grafts. See, for example, "Tissue Engineering of Vascular Prosthetic Grafts," P.P.Zilla, H.P. Griesler, and P. Zilla, Pub. by Landes Bioscience (May 1999), the entire contents of which are incorporated by reference herein. Other synthetic materials can be used as well such as poly (alpha-hydroxy ester)s, polyanhydrides, polyorthoesters, polyphosphazens, as well as synthetics such as tyrosine-derived polycarbonates and polyarylates, lactide based polydepsipeptide

polymer, poly(L-lactide acid-co-L-aspartic acid), and lactide based poly(ethylene glycol). Metals such as stainless steel, titanium, or Nitinol metal mesh may also be used as the synthetic graft material, as well as other alloys as well such as woven glass (e.g., knitted or spun) or ceramics. The present embodiment of the invention entails the further use of nanostructured components (e.g., nanofibers or nanowires) to enhance the interaction of the graft with the passages in which they are used as shown, for example, in Figure 1. Typically, such nanostructured surfaces are employed to improve adhesion, friction, biointegration or other properties of the device to enhance its patency in the subject passage. Such enhanced interactivity is generally provided by a nanostructured surface that interacts with the surface of the passage, e.g., an inner or outer wall surface, to promote integration therewith or attachment thereto.

**[0121]** As described above, the nanostructured components can take a variety of forms and configurations depending on the application, such as nanofibers or other nanostructured component, e.g., nanowires, nanorods, nanotetrapods, nanodots and the like as described in more detail below, which are incorporated into or onto the synthetic graft to improve its properties such as adhesion. The nanofibers can either be attached to the outer or inner surface of the synthetic graft, e.g., by growing the nanofibers directly on the outer and/or inner surface of the graft, or by separately covalently (or otherwise) attaching the fibers to the graft surfaces. In addition, the nanofibers or other nanostructures can be embedded into the graft material to provide it with enhanced properties such as improved rigidity and strength within the aorta. The shape and size of the nanofibers as well as their density on the graft surfaces can be varied to tune the adhesive properties of the graft to the desired levels.

**[0122]** The artificial grafts of this invention may also be coated (in the case of tubular grafts, on the inside and/or outside) with other materials to still further enhance their bio-utility. Examples of suitable coatings are medicated coatings, hydrophilic coatings, smoothing coatings, collagen coatings, human cell seeding coatings, etc. The above-described nanofiber coatings on the graft provide a high surface area to volume ratio that helps the graft to retain these coatings. For example, the artificial graft may be coated with additional biocompatible materials to minimize thrombogenicity of the graft. Coatings such as endothelial cell linings found in autologous vessels, polymers, polysaccharides, etc can provide a non-thrombogenic surface to increase endothelial cell proliferation. The graft can also be modified with one or more proteins or growth

factors to increase cell adhesion, growth, and proliferation such as, for example, VEGF, FGF-2 and other HBGF (Heparin Binding Growth Factors).

[0123] If used, the coatings can be adsorbed directly to the nanostructured surface of the graft. Alternatively, the nanostructured surface may be provided with a linking agent which is capable of forming a link to the nanostructured components (e.g., nanofibers) as well as to the coating material which is applied thereto. In such cases, the coating may be directly linked to the nanostructured surface, e.g., through silane groups, or it may be coupled via linker binding groups or other appropriate chemical reactive groups to participate in linkage chemistries (derivitization) with linking agents such as, e.g., substituted silanes, diacetylenes, acrylates, acrylamides, vinyl, styryls, silicon oxide, boron oxide, phosphorus oxide, N-(3-aminopropyl)3-mercapto-benzamide, 3-aminopropyl-trimethoxysilane, 3-mercaptopropyl-trimethoxysilane, 3-maleimidopropyl-trimethoxysilane, 3-hydrazidopropyl-trimethoxysilane, hydroxysuccinimides, maleimides, haloacetyls, pyridyl disulfides, hydrazines, ethyldiethylamino propylcarbodiimide, and/or the like.

## **XXII) Occlusion of Blood Vessels in the Brain and Other Organs of the Body**

[0124] The compositions, apparatus, systems and methods relating to nanostructured surface coatings described herein can further be used in the treatment of various diseases and conditions of the circulatory system and other organs of the body that are beneficially treated by the occlusion of blood vessels. Examples of the numerous diseases that can be treated by blocking associated blood vessels using, for example, intravascular coils, beads, synthetic grafts or other liquid embolic agents which are treated with nanofibers (or other nanostructured components), include arteriovenous (AV) fistulas, AV malformations, aneurysms and pseudoaneurysms, patent ductus arteriosus, patent foramen ovale, gastrointestinal bleeding, renal and pelvic bleeding, and tumors.

[0125] Placement of various substances (e.g., a liquid adhesive such as isobutylcyanoacrylate (IBCA)) within the blood vessels is one of the methods of encouraging the formation of thrombus (clot) which leads to the complete occlusion of the vessels. Occlusive coils have also been used to occlude blood vessels. The purpose of the coil is to encourage quick formation of a thrombus around the coil.



[0126] Of the many diseases that may be treated with embolic coils, cerebral aneurysms are of particular interest. Ruptured and unruptured cerebral aneurysms may in some cases be treated by a surgical approach in which the aneurysm is visualized directly and then surgically clipped thereby blocking blood flow into the aneurysm. Once the aneurysm is eliminated from the blood flow the risk of hemorrhage is eliminated. Another less invasive approach to the treatment of cerebral aneurysms is an endovascular approach, in which a catheter is introduced into the cerebral vascular system from a peripheral access point, such as a femoral artery, to access the aneurysm internally. The catheters can be used to deliver embolic devices, such as a balloon or a coil, to the site of the aneurysm to block blood flow into the aneurysm. The use of embolic coils, however, can lead to complications because the coils can compact over time and allow re-filling of the aneurysm, posing risk of rupture.

[0127] The present embodiment of the invention involves the use of an endoluminal patch for the repair of, for example, side wall aneurysms in the brain or elsewhere in the arterial vasculature. Although the present methods are discussed in relation to the treatment of cerebral side wall aneurysms in particular, it is to be appreciated that the systems and methods of the present invention may be used in connection with a variety of other embolotherapy procedures in various blood vessels and organs of the body where an embolic device, such as a coil or embolic patch material, may be deployed.

[0128] The systems and methods disclosed can be used to facilitate the accurate deployment of embolic devices and/or materials within the cerebral vasculature system of a patient, such as at the site of an aneurysm, as schematically illustrated in FIGS. 4A-C. A patch of any suitable biocompatible material including, for example, metal mesh, alloys, treated natural tissue, laboratory-engineered tissue, and synthetic polymer fabrics or other polymeric material, is coated with nanostructured components (e.g., nanofibers, nanowires, nanotetrapods, nanodots and the like) on all or select portions of its exterior (and/or interior) surface rendering it adhesive. The size, shape and density of the nanofibers can be varied as described above in relation to previous embodiments to alter and control the adhesive properties of the patch. The nanofibers, for example, may be grown directly on the external (and/or internal) surfaces of the patch or grown separately and applied to the patch material after harvesting. The nanofibers may also be incorporated directly into the material of the patch to further strengthen its rigidity.

[0129] The artificial patches of this invention may be coated with other materials to still further enhance their bio-utility. Examples of suitable coatings are medicated coatings, hydrophilic coatings, smoothing coatings, collagen coatings, human cell seeding coatings, etc. The above-described nanofiber coatings on the patch helps the patch to retain these coatings. For example, the patch may be coated with additional biocompatible materials to minimize thrombogenicity of the patch. Coatings such as endothelial cell linings found in autologous vessels, polymers, polysaccharides, etc. can provide a non-thrombogenic surface to increase endothelial cell proliferation. The patch can also be modified with one or more proteins or growth factors to increase cell adhesion, growth, and proliferation such as, for example, VEGF, FGF-2 and other HBGF (Heparin Binding Growth Factors).

[0130] The coatings can be adsorbed directly to the nanostructured surface of the patch. Alternatively, the nanostructured surface may be provided with a linking agent which is capable of forming a link to the nanostructured components (e.g., nanofibers) as well as to the coating material which is applied thereto. In such cases, the coating may be directly linked to the nanostructured surface, e.g., through silane groups, or it may be coupled via linker binding groups or other appropriate chemical reactive groups to participate in linkage chemistries (derivitization) with linking agents such as, e.g., substituted silanes, diacetylenes, acrylates, acrylamides, vinyl, styryls, silicon oxide, boron oxide, phosphorus oxide, N-(3-aminopropyl)3-mercapto-benzamide, 3-aminopropyl-trimethoxysilane, 3-mercaptopropyl-trimethoxysilane, 3-maleimidopropyl-trimethoxysilane, 3-hydrazidopropyl-trimethoxysilane, hydroxysuccinimides, maleimides, haloacetyls, pyridyl disulfides, hydrazines, ethyldiethylamino propylcarbodiimide, and/or the like.

[0131] The endoluminal patch 490 (Fig. 4C) is mounted on a compliant, low-pressure balloon catheter such as those shown in U.S. Pat. Nos. 4,739,768 and 4,884,575, the disclosures are of which are incorporated by reference herein. These procedures use catheters introduced into the cerebral vascular system from a peripheral access point, e.g. a femoral artery, to access the aneurysm internally. The catheters can be used to deliver the patch 490 to the site of the aneurysm 480 to block blood flow into the aneurysm. The embolic delivery catheter 440 is introduced into a blood vessel in the brain having a side wall aneurysm or other disease condition therein. The diseased site may be an aneurysm 480 as shown in FIG. 4A, or a fistula, AV malformation, or

other disease in which deployment at, on or near the disease condition would result in reduced or stopped flow to the abnormal area. To accomplish this, Figs. 4A-C show one exemplary use in which the embolic device, in this case a patch 490, is placed via the delivery catheter 440 over the aneurysm neck, to block blood from entering the aneurysm. The catheter 440 is typically introduced into the cerebral vasculature system of the patient from a peripheral access point such as a femoral artery and guided with the aid of fluoroscopy to the brain through the aorta 456 and through one of the carotid (or vertebral) arteries 467 in the neck. Once the insertion catheter 440 and the patch are threaded through the vasculature system to the site of the aneurysm 480 in the brain, the patch is aligned with the aneurysm neck 492 under radioscopic guidance. The patch is applied to the vessel wall by dilating the balloon catheter 440 to press-fit the patch onto the vessel wall.

[0132] In yet another embodiment, nanostructures (e.g., nanofibers) grown on an embolic device, such as aneurysm coils or beads, e.g., Hilal Embolization Microcoils™ available commercially from Cook, Inc. (Bloomington, IN) shown in Figure 4D, can enhance the thrombogenicity of the embolic device through hydrophilic native platelets from sticking and forming thrombosis.

### **XXIII) Sutureless Graft Prostheses**

[0133] The methods, devices and systems of the invention generally described above may also be used in the performance of anastomosis of blood vessels, ducts, lumens or other tubular organs, e.g., for sutureless anastomosis procedures in which one vessel is joined to another vessel without the use of sutures.

[0134] Arterial bypass surgery is a common modality for the treatment of occlusive vascular disease. Such surgery typically involves an incision and exposure of the occluded vessel followed by the joiner of a graft, e.g., a mammary artery, saphenous vein, or synthetic graft (all collectively referred to hereinafter as the "bypass graft"), to the occluded vessel (hereinafter the "native" blood vessel) distally (downstream) of the occlusion. The upstream or proximal end of the bypass graft is secured to a suitable blood vessel upstream of the occlusion, e.g., the aorta, to divert the flow of blood around the blockage. Other occluded or diseased blood vessels, such as the carotid artery, may be similarly treated. Moreover, similar procedures are conducted to place a graft between an artery and a vein in dialysis patients.

[0135] Current methods available for creating an anastomosis include hand suturing the vessels together. Suturing the anastomosis is time-consuming and often does not provide a leak-free seal and can lead to a site of turbulent blood flow on occlusion. Thus, it is desirable to reduce the difficulty of creating the vascular anastomosis and provide a rapid method for making a reliable anastomosis between a graft vessel and artery.

[0136] One method currently available involves the use of stapling devices. These instruments are not easily adaptable for use in vascular anastomosis. It is often difficult to manipulate these devices through the vessels without inadvertently piercing a side wall of the vessel. In addition to being difficult to operate, these devices often do not provide a reliable leak-free seal.

[0137] Myriad other attempts to develop a successful sutureless anastomotic technique are represented by U.S. Pat. Nos. 3,221,746, 3,357,432, 3,648,295, 3,683,926 and 4,267,842, for example. All of these feature an inner tube-like device placed inside the vessels to be anastomosed. Various other devices and methods of use have been disclosed for effecting anastomosis of blood or other vessels, ducts, lumens or other tubular organs. Examples of such devices and methods are found, for example, in U.S. Pat. Nos. 3,221,746, 3,357,432, 3,648,295, 4,366,819, 4,470,415, 4,553,542, 5,591,226, 5,586,987, 5,591,226, and 6,402,767, the contents of which are incorporated by reference herein.

[0138] The present embodiment of the invention involves improvements to conventional devices and methods for performing vascular anastomoses. The invention facilitates positioning one vessel in the fluid path of another vessel to enhance the fluid flow juncture therebetween. The invention provides artificial graft tubing by which anatomical structures, such as blood vessels, fallopian tubes, intestine, bowel, ureters, vas deferens and outer nerve sheaths are anastomosed, preferably without the use of sutures. The new tubing may be artificial graft tubing in the form of a simple tube (as shown in Fig 5A, for example), or a T-tube as shown in Fig. 5B, for example, or any other suitable tubing shape or configuration. Alternatively, the new tubing may be a combination of artificial and natural tubing (e.g., natural tubing disposed substantially concentrically inside artificial tubing).

[0139] The artificial tubing may be made from any suitable biocompatible material including, for example, a flexible, semi-porous metal mesh (e.g., Nitinol mesh, stainless steel mesh, titanium mesh and the like), treated natural tissue, laboratory-engineered tissue, and synthetic polymer fabrics or other polymeric material such as Dacron®, PTFE, polyimide mesh, ceramic, glass fabrics and the like.

[0140] The present embodiment of the invention entails the further use of nanostructured components to enhance the interaction of the tubing with the passages in which it is used as shown, for example, in Figure 1. Typically, such nanostructured surfaces are employed to improve adhesion, friction, biointegration or other properties of the device to enhance its patency in the subject passage. Such enhanced interactivity is generally provided by providing a nanostructured surface that interacts with the surface of the passage, e.g., an inner or outer wall surface, to promote integration therewith or attachment thereto.

[0141] The new tubing for sutureless anastomosis is coated with nanofibers or other nanostructured components such as nanowires, nanotetrapods, nanodots and the like on all or select portions of its exterior (and/or interior) surface rendering it adhesive. The nanofibers may also be incorporated into the tubing material itself to form a composite material with added rigidity and strength. The size, shape and density of the nanofibers can be varied as described above in relation to previous embodiments to alter and control the adhesive properties of the tubing. The nanofibers may be grown directly on the external (and/or internal) surfaces of the tubing or grown separately and applied to the tubing material after harvesting.

[0142] The artificial grafts of this invention may be coated (in the case of tubular grafts, on the inside and/or outside) with other materials to still further enhance their bio-utility. Examples of suitable coatings are medicated coatings, hydrophilic coatings, smoothing coatings, collagen coatings, human cell seeding coatings, etc. The above-described nanofiber coatings on the graft helps the graft to retain these coatings. For example, the graft tubings may be coated with additional biocompatible materials to minimize thrombogenicity of the tubing. Coatings such as endothelial cell linings found in autologous vessels, polymers, polysaccharides, etc can provide a non-thrombogenic surface to increase endothelial cell proliferation. The nanofibers or tubing material can also be modified with one or more proteins or growth factors to increase cell adhesion, growth, and proliferation such as, for example, VEGF, FGF-2 and other HBGF

(Heparin Binding Growth Factors). The coatings can be adsorbed directly to the nanostructured surface of the tubing. Alternatively, the nanostructured surface may be provided with a linking agent which is capable of forming a link to the nanostructure components (e.g., nanofibers) as well as to the coating material which is applied thereto. In such cases, the coating may be directly linked to the nanostructured surface, e.g., through silane groups, or it may be coupled via linker binding groups or other appropriate chemical reactive groups to participate in linkage chemistries (derivitization) with linking agents such as, e.g., substituted silanes, diacetylenes, acrylates, acrylamides, vinyl, styryls, silicon oxide, boron oxide, phosphorus oxide, N-(3-aminopropyl)3-mercapto-benzamide, 3-aminopropyl-trimethoxysilane, 3-mercaptopropyl-trimethoxysilane, 3-maleimidopropyl-trimethoxysilane, 3-hydrazidopropyl-trimethoxysilane, hydroxysuccinimides, maleimides, haloacetyls, pyridyl disulfides, hydrazines, ethyldiethylamino propylcarbodiimide, and/or the like. ]

**[0143]** The nanofibers on the inside and/or outside diameter of the tubing have substantial dry adhesive properties that allow a firm press-fit into the inner (or outer) diameter of the native host vessel or to connect other synthetic graft vessels.

**[0144]** An exemplary form of artificial tubing includes a tube frame of a first highly elastic material (such as Nitinol) covered with a second highly elastic material (such as silicone rubber) to substantially fill in the apertures in the frame. This combination produces an artificial graft that is distensible like natural body organ tubing such as a natural artery. Additional advantages of the artificial grafts of this invention are their elasticity and distensibility (mentioned above), their ability to be deployed through tubes of smaller diameter (after which they automatically return to their full diameter), the possibility of making them modular, their ability to accept natural body organ tubing concentrically inside themselves, their ability to support development of an endothelial layer, their compatibility with MRI procedures, their ability to be made fluoroscopically visible, etc.

**[0145]** A first method of the present invention is for coupling a first vessel 502 and a second vessel 504 in an end-to-end anastomosis (e.g., Fig. 5A) and generally includes inserting an artificial tubular graft 506 as described above with a nanofiber coating into an opening in a bypass graft vessel (which can include a natural or synthetic graft vessel) and a native vessel to be connected, and preferably radially expanding (e.g., with the use of a balloon catheter, for example) at least a portion of the

tubular graft to sealingly press-fit and secure the tubular graft to the inner wall of the vessels. The tubular graft member preferably is sufficiently rigid to substantially retain the tubular member in its preformed configuration after the tubular member is radially expanded. The tubular graft member may be radially self-expandable to a pre-formed configuration (e.g., via the use of a shape memory alloy for the tubing such as Nitinol, for example), and thus may assume a press-fit configuration within the vessels to sealingly join them without the use of an access device such as a balloon catheter. In another aspect of the present invention, the tubular member is in the form of a T-tube 508 for an end-to-side anastomosis in which a bypass graft vessel 510 is secured to an opening 511 in a side wall of the native vessel 512 as shown in Figure 5B. Although grafts in the form of tubing are described above, certain aspects of the invention are equally applicable to other graft procedures and to grafts having virtually any cross-sectional shape depending upon the desired application, including, e.g., circular, elliptical, polygonal, e.g., square, rectangular, pentagonal, hexagonal, octagonal, trapezoidal, rhomboid, etc. Further, it will be appreciated that the cross-sectional shape of the body structure of the graft may be the same as or different from the cross-sectional shape of the vessel into which it is inserted, depending upon a number of factors, including, e.g., the method used to fabricate the graft, and/or its desired application.

#### **XXIV) Orthopedic Implants**

[0146] Nanostructures (e.g., nanowires, nanorods, nanotetrapods, nanodots and other similar structures) incorporated into or onto orthopedic implants can improve biocompatibility, infection resistance, bone integration, prevention of unwanted cell growth, and durability of those implants when used in and around orthopedic tissues, such as bone, ligaments, muscles, etc. Examples of orthopedic implants that can benefit from nanofiber enhanced surfaces include without limitation total knee joints, total hip joints, ankle, elbow, wrist, and shoulder implants including those replacing or augmenting cartilage, long bone implants such as for fracture repair and external fixation of tibia, fibula, femur, radius, and ulna, spinal implants including fixation and fusion devices, maxillofacial implants including cranial bone fixation devices, artificial bone replacements, dental implants, orthopedic cements and glues comprised of polymers, resins, metals, alloys, plastics and combinations thereof, nails, screws, plates, fixator devices, wires and pins and the like that are used in such implants, and other

orthopedic implant structures as would be known to those of ordinary skill in the art. As shown in FIG. 6A, for example, an orthopedic implant 610 in the form of hip stem 612 comprises a substrate 611 and porous layer 614. Porous layer 614 can include beads, fibers, wire mesh and other known materials and shapes thereof used to form porous layer 614. Nanostructured components can be applied to substrate 611 by any of the methods described herein to form nanostructured surfaces, as shown, for example in Figure 1.

[0147] In particular, the present embodiment of the invention provides such orthopedic implantable devices with nanostructured components to enhance the interaction of the devices with the tissues, joints, cartilage, bones, and other bodily structures with which they make contact at the implantation site. The nanostructured components (e.g., nanofibers) can either be attached to the outer or inner surface of the implantable device, e.g., by growing the nanofibers directly on the outer and/or inner surface of the device, or by separately covalently attaching the fibers to the device surfaces. Nanostructures on the surface of implants can enhance bone growth reaction at the implant site by encouraging and enhancing proliferation of osteoblasts, versus fibroblasts and other undesirable cells. Enhanced bone growth activity encourages good fixation of the implant over time and prevents loosening from fibroblastic response. In addition, nanostructured surfaces on orthopedic implants can prevent infection at the implant site, e.g., by preventing the growth of bacteria and other infectious organisms such as viruses and fungus. The shape and size of the nanofibers as well as their density on the implant surfaces can be varied to allow differentiation of cell types.

[0148] Alternatively, or additionally, the nanofibers or other nanostructures can be embedded into the implant material to enhance the durability and resistance to wear that occurs in a load bearing implantation site, thereby preventing microdegradation and resultant debris in the joints.

[0149] The implants of this invention may also be coated on the inside and/or outside with other materials to still further enhance their bio-utility. Examples of suitable coatings are medicated coatings, drug-eluting coatings, drugs or other compounds, hydrophilic coatings, smoothing coatings, collagen coatings, human cell seeding coatings, etc. For example, nanostructured surfaces on orthopedic implants can deliver drugs or other compounds to the implantation site. Drugs delivered from



nanowires, for example, by elution, binding, dissolution, and/or dissolving of the nanowires themselves can prevent infection, enhance bone growth, prevent scar tissue, hyperproliferation, and prevent rejection of the implant. The above-described nanofiber coatings on the implant can provide a high surface area that helps the implant to retain these coatings. The coatings can be adsorbed directly to the nanostructured surface of the implant. Alternatively, the nanostructured surface may be provided with a linking agent which is capable of forming a link to the nanostructured components (e.g., nanofibers) as well as to the coating material which is applied thereto. In such cases, the coating may be directly linked to the nanostructured surface, e.g., through silane groups, or it may be coupled via linker binding groups or other appropriate chemical reactive groups to participate in linkage chemistries (derivitization) with linking agents such as, e.g., substituted silanes, diacetylenes, acrylates, acrylamides, vinyl, styryls, silicon oxide, boron oxide, phosphorus oxide, N-(3-aminopropyl)3-mercapto-benzamide, 3-aminopropyl-trimethoxysilane, 3-mercaptopropyl-trimethoxysilane, 3-maleimidopropyl-trimethoxysilane, 3-hydrazidopropyl-trimethoxysilane, hydroxysuccinimides, maleimides, haloacetyls, pyridyl disulfides, hydrazines, ethyldiethylamino propylcarbodiimide, and/or the like.

#### **XXV) Bioengineered Nerve Scaffolds**

[0150] Damage to peripheral and central nerves occurs during trauma, other surgical procedures, and injury. Typically, pieces of a patient's own nerve (e.g., autograft) have been used to bridge the gap in a damaged nerve and provide a scaffold for nerve regeneration. These autografts are less than 50% effective. Attempts have been made to grow new peripheral nerves on artificial substrates typically impregnated with compounds to enhance nerve growth. New micro-devices to bridge the gap and induce nerve repair would be useful, especially in connection with spinal cord injuries and brain damage.

[0151] The present invention contemplates a nanoscale bioengineered scaffold, which could be substantially three dimensional due to high surface area of the nanostructured components incorporated into and/or into the scaffold (e.g., nanofibers), to stimulate and encourage nerve cell growth. In addition, 3-D shaped nanostructures could encourage nerve regeneration. The bioengineered scaffold may comprise a base

membrane or matrix onto and/or into which the nanostructure components (e.g., nanofibers) are incorporated. The base membrane or matrix may be made from a variety of materials such as natural or synthetic polymers including electrically conducting polymers, metals, alloys, ceramics or glass fabrics, silicone, etc. A useful method for fabricating a suitable membrane or matrix from electrically conducting polymers, for example, which may be useful in the present invention is disclosed in U.S. Patent Nos. 6,095,148 and 6,696,575, the entire contents of which are incorporated by reference herein.

**[0152]** The scaffold material may be blended or coated on a suitable support such as a polymeric film or polymeric beads. As described by Langer et al., *J. Ped. Surg.* 23(1), 3-9 (1988), WO88/03785 and EPA 88900726.6 by Massachusetts Institute of Technology, the contents of which are incorporated by reference herein, a matrix for implantation to form new tissue should be a pliable, non-toxic, porous template for vascular in-growth. The pores should allow vascular in-growth and the seeding of cells without damage to the cells or patient. These are generally interconnected pores in the range of between approximately 100 and 300 microns. The matrix should be shaped to maximize surface area, to allow adequate diffusion of nutrients and growth factors to the cells. In an exemplary embodiment, the matrix is formed of a bioabsorbable, or biodegradable, synthetic polymer such as a polyanhydride, polyorthoester, or polyhydroxy acid such as polylactic acid, polyglycolic acid, and copolymers or blends thereof. Non-degradable materials can also be used to form the matrix. Examples of suitable materials include ethylene vinyl acetate, derivatives of polyvinyl alcohol, teflon, nylon, polymethacrylate and silicon polymers.

**[0153]** Alternatively, the scaffold can be made entirely of nanostructures such as, but not limited to, organic and inorganic nanocrystals as described above and below such as nanowires, nanodots, nanotetrapods, and other shapes on the nanoscale. The bioengineered scaffold can be impregnated or bound with drugs, cells (e.g., nerve cells such as Schwann cells, stem cells or embryonic cells), fibroblasts, or other specific compounds such as nerve growth factor (NGF), cell seeding compounds, neurotrophic growth factors (or genetically engineered cells producing such factors), VEGF, laminin or other such compounds, such that when implanted, the compound(s) encourage axonal elongation and functional nerve performance. Nerve explants also may be cultured and regenerated in vitro for implantation in vivo. For example, primary sciatic nerve

explants may be isolated from mammalian tissue and cultured for example in high glucose DMEM supplemented with glucose, fetal bovine serum (FBS), sodium pyruvate, and NGF. Methods for isolating the sciatic nerve from 16-d chick embryos have been described in: Y. -W. Hu and C. Mezei, *Can. J. Biochem.*, 49:320 (1971). Different compositions, including serum, serum substitutes, growth factors, such as nerve growth factor, hormones, and/or drugs can be used in the medium which are optimized for the particular nerve cell being cultured, to enhance proliferation and regeneration of nerve cells.

**[0154]** The coatings can be adsorbed directly to the nanostructured surface of the scaffold. The high surface area of the nanostructured components helps to retain the compound coatings on the scaffold. Alternatively, the nanostructured surface may be provided with a linking agent which is capable of forming a link to the nanostructured components (e.g., nanofibers) as well as to the coating material which is applied thereto. In such cases, the coating containing the desired compounds may be directly linked to the nanostructured surface, e.g., through silane groups, or it may be coupled via linker binding groups or other appropriate chemical reactive groups to participate in linkage chemistries (derivitization) with linking agents as described previously.

**[0155]** The nanofibers (or other nanostructured components) on the scaffold surfaces can optionally be embedded in a slowly-soluble biocompatible polymer (or other) matrix to make the nanofiber surfaces more robust. The polymer matrix can protect most of the length of each nanofiber, leaving only the ends susceptible to damage. The generation of water soluble polymers can be accomplished in a number of different ways. For example, polymer chains can be formed in situ in a dilute aqueous solution primarily consisting of a monomer and an oxidizing agent. In this case, the polymer is actually created in the solution and subsequently spontaneously adsorbed onto the nanofiber surfaces as a uniform, ultra-thin film of between approximately 10 to greater than 250 angstroms in thickness, more preferably between 10 and 100 angstroms.

**[0156]** Nerve gaps to be treated with such scaffold devices can range in size from between about 5 mm to about 50 mm, for example between about 10 to about 30 mm, for example between about 20 mm to 30 mm. The scaffold devices can be made in a range of sizes and configurations to fit the application, and the nanostructures can be doped as necessary to provide enhanced electrical conductivity to transmit electrical

nerve signals to nerve fibers. The scaffold devices may be implanted in vivo into a patient in need of therapy to repair or replace damaged cells or tissue, such as nervous system tissue. Materials which can be used for implantation include sutures, tubes, sheets, adhesion prevention devices (typically films, polymeric coatings applied as liquids which are polymerized in situ, or other physical barriers), and wound healing products (which vary according to the wound to be healed from films and coating to support structures).

[0157] To enhance the effectiveness of the treatment, compositions which further promote nervous tissue healing, such as proteins, antibodies, nerve growth factors, hormones, and attachment molecules, can be applied together with the scaffold, and as discussed above optionally can be covalently attached to the nanofibers and/or the scaffold support material. Those skilled in the art can readily determine exactly how to use these materials and the conditions required without undue experimentation. The scaffold may be implanted adjacent to or seeded with cells which are to be affected. The scaffold device is optionally electrically connected to a source of voltage or current. The electrical connection can be, for example, needles which are inserted to contact the scaffold, or electrodes attached to the nanostructured surfaces or scaffold membrane which can be externally connected to an appropriate electrical power source. Voltage or current may be applied to the nanostructures and/or scaffold membrane in a range which induces the desired effect on the cells while not damaging the cells.

#### **XXVI) Characteristics of Nanofiber Surface Substrates**

[0158] As noted previously, increased surface area is a property that is sought after in many fields (e.g., in substrates for assays or separation column matrices). For example, fields such as tribology and those involving separations and adsorbents are quite concerned with maximizing surface areas. The current invention offers surfaces and applications having increased or enhanced surface areas (i.e., increased or enhanced in relation to structures or surfaces without nanofibers).

[0159] A “nanofiber enhanced surface area” herein corresponds to a substrate comprising a plurality of nanofibers (e.g., nanowires, nanotubes, etc.) attached to the substrate so that the surface area within a certain “footprint” of the substrate is increased relative to the surface area within the same footprint without the nanofibers. In typical embodiments herein, the nanofibers (and often the substrate) are composed of

silicon oxides. It will be noted that such compositions convey a number of benefits in certain embodiments herein. Also, in many preferred embodiments herein, one or more of the plurality of nanofibers is functionalized with one or more moiety. *See*, below. However, it will also be noted that the current invention is not specifically limited by the composition of the nanofibers or substrate, unless otherwise noted.

**[0160]** The various embodiments of the current invention are adaptable to, and useful for, a great number of different applications. For example, as explained in more detail below, various permutations of the invention can be used in, e.g., binding applications (e.g., microarrays and the like), separations (e.g., bioscaffolds (e.g., as a base for cell culture and/or medical implants, optionally which resist formation of biofilms, etc.), and controlled release matrices, etc. Other uses and embodiments are examined herein.

**[0161]** Examined herein, are other beneficial uses of various embodiments of the current invention. For example, the distinct morphology of the nanofiber surfaces herein can be utilized in numerous biomedical applications such as scaffolding for growth of cell culture (both in vitro and in vivo). In vivo uses can include, e.g., aids in bone formation, etc. Additionally, the surface morphology of some of the embodiments produces surfaces that are resistant to biofilm formation and/or bacterial/microorganismal colonization. Other possible biomedical uses herein, include, e.g., controlled release matrices of drugs, etc. *See*, above.

**[0162]** As also will be appreciated by those of skill in the art, many aspects of the current invention are optionally variable (e.g., surface chemistries on the nanofibers, surface chemistries on any end of the nanofibers or on the substrate surface, etc.). Specific illustration of various modifications, etc. herein, should therefore not be taken as limiting the current invention. Also, it will be appreciated, and is explained in more detail below, that the length to thickness ratio of the nanofibers herein is optionally varied, as is, e.g., the composition of the nanofibers. Furthermore, a variety of methods can be employed to bring the fibers in contact with surfaces. Additionally, while many embodiments herein comprise nanofibers that are specifically functionalized in one or more ways, e.g., through attachment of moieties or functional groups to the nanofibers, other embodiments comprise nanofibers which are not functionalized

## **XVII) Nanofibers and Nanofiber Construction**

[0163] In typical embodiments herein the surfaces (i.e., the nanofiber enhanced area surfaces) and the nanofibers themselves can optionally comprise any number of materials. The actual composition of the surfaces and the nanofibers is based upon a number of possible factors. Such factors can include, for example, the intended use of the enhanced area surfaces, the conditions under which they will be used (e.g., temperature, pH, presence of light (e.g., UV), atmosphere, etc.), the reactions for which they will be used (e.g., within a patient, etc.), the durability of the surfaces and the cost, etc. The ductility and breaking strength of nanowires will vary depending on, e.g., their composition. For example, ceramic ZnO wires can be more brittle than silicon or glass nanowires, while carbon nanotubes may have a higher tensile strength.

[0164] As explained more fully below, some possible materials used to construct the nanofibers and nanofiber enhanced surfaces herein, include, e.g., silicon, ZnO, TiO, carbon, carbon nanotubes, glass, and quartz. *See*, below. The nanofibers of the invention are also optionally coated or functionalized, e.g., to enhance or add specific properties. For example, polymers, ceramics or small molecules can optionally be used as coating materials. The optional coatings can impart characteristics such as water resistance, improved mechanical or electrical properties or specificities for certain analytes. Additionally, specific moieties or functional groups can also be attached to or associated with the nanofibers herein.

[0165] Of course, it will be appreciated that the current invention is not limited by recitation of particular nanofiber and/or substrate compositions, and that, unless otherwise stated, any of a number of other materials are optionally used in different embodiments herein. Additionally, the materials used to comprise the nanofibers can optionally be the same as the material used to comprise the substrate surfaces or they can be different from the materials used to construct the substrate surfaces.

[0166] In yet other embodiments herein, the nanofibers involved can optionally comprise various physical conformations such as, e.g., nanotubules (e.g., hollow-cored structures), etc. A variety of nanofiber types are optionally used in this invention including carbon nanotubes, metallic nanotubes, metals and ceramics.

[0167] It is to be understood that this invention is not limited to particular configurations, which can, of course, vary (e.g., different combinations of nanofibers

and substrates and optional moieties, etc. which are optionally present in a range of lengths, densities, etc.). It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting. As used in this specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a nanofiber” optionally includes a plurality of such nanofibers, and the like. Unless defined otherwise, all scientific and technical terms are understood to have the same meaning as commonly used in the art to which they pertain. For the purpose of the present invention, additional specific terms are defined throughout.

### **A) Nanofibers**

[0168] The term “nanofiber” as used herein, refers to a nanostructure typically characterized by at least one physical dimension less than about 1000 nm, less than about 500 nm, less than about 250 nm, less than about 150 nm, less than about 100 nm, less than about 50 nm, less than about 25 nm or even less than about 10 nm or 5 nm. In many cases, the region or characteristic dimension will be along the smallest axis of the structure.

[0169] Nanofibers of this invention typically have one principle axis that is longer than the other two principle axes and, thus, have an aspect ratio greater than one, an aspect ratio of 2 or greater, an aspect ratio greater than about 10, an aspect ratio greater than about 20, or an aspect ratio greater than about 100, 200, or 500. In certain embodiments, nanofibers herein have a substantially uniform diameter. In some embodiments, the diameter shows a variance less than about 20%, less than about 10%, less than about 5%, or less than about 1% over the region of greatest variability and over a linear dimension of at least 5 nm, at least 10 nm, at least 20 nm, or at least 50 nm. For example, a wide range of diameters could be desirable due to cost considerations and/or to create a more random surface. Typically the diameter is evaluated away from the ends of the nanofiber (*e.g.* over the central 20%, 40%, 50%, or 80% of the nanofiber). In yet other embodiments, the nanofibers herein have a non-uniform diameter (*i.e.*, they vary in diameter along their length). Also in certain embodiments, the nanofibers of this invention are substantially crystalline and/or substantially monocrystalline.

[0170] It will be appreciated that the term nanofiber, can optionally include such structures as, e.g., nanowires, nanowhiskers, semi-conducting nanofibers, carbon nanotubes or nanotubules and the like.

[0171] The nanofibers of this invention can be substantially homogeneous in material properties, or in certain embodiments they are heterogeneous (e.g. nanofiber heterostructures) and can be fabricated from essentially any convenient material or materials. The nanofibers can comprise "pure" materials, substantially pure materials, doped materials and the like and can include insulators, conductors, and semiconductors. Additionally, while some illustrative nanofibers herein are comprised of silicon (or silicon oxides), as explained above, they optionally can be comprised of any of a number of different materials, unless otherwise stated. Composition of nanofibers can vary depending upon a number of factors, e.g., specific functionalization (if any) to be associated with or attached to the nanofibers, durability, cost, conditions of use, etc. The composition of nanofibers is quite well known to those of skill in the art. As will be appreciated by such skilled persons, the nanofibers of the invention can, thus, be composed of any of a myriad of possible substances (or combinations thereof). Some embodiments herein comprise nanofibers composed of one or more organic or inorganic compound or material. Any recitation of specific nanofiber compositions herein should not be taken as limiting.

[0172] Additionally, the nanofibers of the invention are optionally constructed through any of a number of different methods, and examples listed herein should not be taken as limiting. Thus, nanofibers constructed through means not specifically described herein, but which fall within the parameters as set forth herein are still nanofibers of the invention and/or are used with the methods of the invention.

[0173] In a general sense, the nanofibers of the current invention often (but not exclusively) comprise long thin protuberances (e.g., fibers, nanowires, nanotubules, etc.) grown from a solid, optionally planar, substrate. Of course, in some embodiments herein the nanofibers are deposited onto their ultimate substrates, e.g., the fibers are detached from the substrate on which they are grown and attached to a second substrate. The second substrate need not be planar and, in fact, can comprise a myriad of three-dimensional conformations, as can the substrate on which the nanofibers were grown originally. In some embodiments herein, the substrates are flexible. Also, as explained



in greater detail below, nanofibers of the invention can be grown/constructed in, or upon, variously configured surfaces, e.g., within capillary tubes, shunts, etc. *See, infra.*

[0174] In various embodiments herein, the nanofibers involved are optionally grown on a first substrate and then subsequently transferred to a second substrate which is to have the enhanced surface area. Such embodiments are particularly useful in situations wherein the substrate desired needs to be flexible or conforming to a particular three dimensional shape that is not readily subjected to direct application or growth of nanofibers thereon. For example, nanofibers can be grown on such rigid surfaces as, e.g., silicon wafers or other similar substrates. The nanofibers thus grown can then optionally be transferred to a flexible backing such as, e.g., rubber or the like. Again, it will be appreciated, however, that the invention is not limited to particular nanofiber or substrate compositions. For example, nanofibers are optionally grown on any of a variety of different surfaces, including, e.g., flexible foils such as aluminum or the like. Additionally, for high temperature growth processes, any metal, ceramic or other thermally stable material is optionally used as a substrate on which to grow nanofibers of the invention. Furthermore, low temperature synthesis methods such as solution phase methods can be utilized in conjunction with an even wider variety of substrates on which to grow nanofibers. For example, flexible polymer substrates and other similar substances are optionally used as substrates for nanofiber growth/attachment.

[0175] As one example, the growth of nanofibers on a surface using a gold catalyst has been demonstrated in the literature. Applications targeted for such fibers are based on harvesting them from the substrate and then assembling them into devices. However, in many other embodiments herein, the nanofibers involved in enhanced surface areas are grown in place. Available methods, such as growing nanofibers from gold colloids deposited on surfaces are, thus, optionally used herein. The end product which results is the substrate upon which the fibers are grown (i.e., with an enhanced surface area due to the nanofibers). As will be appreciated, specific embodiments and uses herein, unless stated otherwise, can optionally comprise nanofibers grown in the place of their use and/or through nanofibers grown elsewhere, which are harvested and transferred to the place of their use. For example, many embodiments herein relate to leaving the fibers intact on the growth substrate and taking advantage of the unique properties the fibers impart on the substrate. Other embodiments relate to growth of

fibers on a first substrate and transfer of the fibers to a second substrate to take advantage of the unique properties that the fibers impart on the second substrate.

**[0176]** For example, if nanofibers of the invention were grown on, e.g., a non-flexible substrate (e.g., such as some types of silicon wafers) they could be transferred from such non-flexible substrate to a flexible substrate (e.g., such as rubber or a woven layer material). Again, as will be apparent to those of skill in the art, the nanofibers herein could optionally be grown on a flexible substrate to start with, but different desired parameters may influence such decisions.

**[0177]** A variety of methods may be employed in transferring nanofibers from a surface upon which they are fabricated to another surface. For example, nanofibers may be harvested into a liquid suspension, e.g., ethanol, which is then coated onto another surface. Additionally, nanofibers from a first surface (e.g., ones grown on the first surface or which have been transferred to the first surface) can optionally be “harvested” by applying a sticky coating or material to the nanofibers and then peeling such coating/material away from the first surface. The sticky coating/material is then optionally placed against a second surface to deposit the nanofibers. Examples of sticky coatings/materials which are optionally used for such transfer include, but are not limited to, e.g., tape (e.g., 3M Scotch® tape), magnetic strips, curing adhesives (e.g., epoxies, rubber cement, etc.), etc. The nanofibers could be removed from the growth substrate, mixed into a plastic, and then surface of such plastic could be ablated or etched away to expose the fibers.

**[0178]** The actual nanofiber constructions of the invention are optionally complex. The nanofibers can form a complex three-dimensional pattern. The interlacing and variable heights, curves, bends, etc. form a surface which greatly increases the surface area per unit substrate (e.g., as compared with a surface without nanofibers). Of course, in other embodiments herein, it should be apparent that the nanofibers need not be as complex. Thus, in many embodiments herein, the nanofibers are “straight” and do not tend to bend, curve, or curl. However, such straight nanofibers are still encompassed within the current invention. In either case, the nanofibers present a non-tortuous, greatly enhanced surface area.

## **B) Functionalization**

[0179] Some embodiments of the invention comprise nanofiber and nanofiber enhanced area surfaces in which the fibers include one or more functional moiety (e.g., a chemically reactive group) attached to them. Functionalized nanofibers are optionally used in many different embodiments, e.g., to confer specificity for desired analytes in reactions such as separations or bio-assays, etc. Beneficially, typical embodiments of enhanced surface areas herein are comprised of silicon oxides, which are conveniently modified with a large variety of moieties. Of course, other embodiments herein are comprised of other nanofiber compositions (e.g., polymers, ceramics, metals that are coated by CVD or sol-gel sputtering, etc.) which are also optionally functionalized for specific purposes. Those of skill in the art will be familiar with numerous functionalizations and functionalization techniques which are optionally used herein.

[0180] For example, details regarding relevant moiety and other chemistries, as well as methods for construction/use of such, can be found, e.g., in Hermanson Bioconjugate Techniques Academic Press (1996), Kirk-Othmer Concise Encyclopedia of Chemical Technology (1999) Fourth Edition by Grayson et al. (ed.) John Wiley & Sons, Inc., New York and in Kirk-Othmer Encyclopedia of Chemical Technology Fourth Edition (1998 and 2000) by Grayson et al. (ed.) Wiley Interscience (print edition)/ John Wiley & Sons, Inc. (e-format). Further relevant information can be found in CRC Handbook of Chemistry and Physics (2003) 83<sup>rd</sup> edition by CRC Press. Details on conductive and other coatings, which can also be incorporated onto nanofibers of the invention by plasma methods and the like can be found in H. S. Nalwa (ed.), Handbook of Organic Conductive Molecules and Polymers, John Wiley & Sons 1997. See also, ORGANIC SPECIES THAT FACILITATE CHARGE TRANSFER TO/FROM NANOCRYSTALS USSN 60/452,232 filed March 4, 2003 by Whiteford et al. Details regarding organic chemistry, relevant for, e.g., coupling of additional moieties to a functionalized surface of nanofibers can be found, e.g., in Greene (1981) Protective Groups in Organic Synthesis, John Wiley and Sons, New York, as well as in Schmidt (1996) Organic Chemistry Mosby, St Louis, MO, and March's Advanced Organic Chemistry Reactions, Mechanisms and Structure, Fifth Edition (2000) Smith and March, Wiley Interscience New York ISBN 0-471-58589-0. Those of skill in the art will be familiar with many other related references and techniques amenable for functionalization of NFS herein.

[0181] Thus, again as will be appreciated, the substrates involved, the nanofibers involved (e.g., attached to, or deposited upon, the substrates), and any optional functionalization of the nanofibers and/or substrates, and the like can be varied. For example, the length, diameter, conformation and density of the fibers can be varied, as can the composition of the fibers and their surface chemistry.

### **C) Density and Related Issues**

[0182] In terms of density, it will be appreciated that by including more nanofibers emanating from a surface, one automatically increases the amount of surface area that is extended from the basic underlying substrate. This, thus, increases the amount of intimate contact area between the surface and any analyte, etc. coming into contact with the nanofiber surfaces. As explained in more detail below, the embodiments herein optionally comprise a density of nanofibers on a surface of from about 0.1 to about 1000 or more nanofibers per micrometer<sup>2</sup> of the substrate surface. Again, here too, it will be appreciated that such density depends upon factors such as the diameter of the individual nanofibers, etc. *See*, below. The nanowire density influences the enhanced surface area, since a greater number of nanofibers will tend to increase the overall amount of area of the surface. Therefore, the density of the nanofibers herein typically has a bearing on the intended use of the enhanced surface area materials because such density is a factor in the overall area of the surface.

[0183] For example, a typical flat planar substrate, e.g., a silicon oxide chip or a glass slide, can typically comprise 10,000 possible binding sites for an analyte or 10,000 possible functionalization sites, etc. per square micron (i.e., within a square micron footprint). However, if such a substrate surface were coated with nanofibers, then the available surface area would be much greater. In some embodiments herein each nanofiber on a surface comprises about 1 square micron in surface area (i.e., the sides and tip of each nanofiber present that much surface area). If a comparable square micron of substrate comprised from 10 to about 100 nanofibers per square micron, the available surface area is thus 10 to 100 times greater than a plain flat surface. Therefore, in the current illustration, an enhanced surface area would have 100,000 to 10,000,000 possible binding sites, functionalization sites, etc. per square micron footprint. It will be appreciated that the density of nanofibers on a substrate is influenced by, e.g., the diameter of the nanofibers and any functionalization of such fibers, etc.

[0184] Different embodiments of the invention comprise a range of such different densities (i.e., number of nanofibers per unit area of a substrate to which nanofibers are attached). The number of nanofibers per unit area can optionally range from about 1 nanofiber per 10 micron<sup>2</sup> up to about 200 or more nanofibers per micron<sup>2</sup>; from about 1 nanofiber per micron<sup>2</sup> up to about 150 or more nanofibers per micron<sup>2</sup>; from about 10 nanofibers per micron<sup>2</sup> up to about 100 or more nanofibers per micron<sup>2</sup>; or from about 25 nanofibers per micron<sup>2</sup> up to about 75 or more nanofibers per micron<sup>2</sup>. In yet other embodiments, the density can optionally range from about 1 to 3 nanowires per square micron to up to approximately 2,500 or more nanowires per square micron.

[0185] In terms of individual fiber dimensions, it will be appreciated that by increasing the thickness or diameter of each individual fiber, one will again, automatically increase the overall area of the fiber and, thus, the overall area of the substrate. The diameter of nanofibers herein can be controlled through, e.g., choice of compositions and growth conditions of the nanofibers, addition of moieties, coatings or the like, etc. Preferred fiber thicknesses are optionally between from about 5 nm up to about 1 micron or more (e.g., 5 microns); from about 10 nm to about 750 nanometers or more; from about 25 nm to about 500 nanometers or more; from about 50 nm to about 250 nanometers or more, or from about 75 nm to about 100 nanometers or more. In some embodiments, the nanofibers comprise a diameter of approximately 40 nm.

[0186] In addition to diameter, surface area of nanofibers (and therefore surface area of a substrate to which the nanofibers are attached) also is influenced by length of the nanofibers. Of course, it will also be understood that for some fiber materials, increasing length may yield increasing fragility. Accordingly, preferred fiber lengths will typically be between about 2 microns (e.g., 0.5 microns) up to about 1 mm or more; from about 10 microns to about 500 micrometers or more; from about 25 microns to about 250 microns or more; or from about 50 microns to about 100 microns or more. Some embodiments comprise nanofibers of approximately 50 microns in length. Some embodiments herein comprise nanofibers of approximately 40 nm in diameter and approximately 50 microns in length.

[0187] Nanofibers herein can present a variety of aspect ratios. Thus, nanofiber diameter can comprise, e.g., from about 5 nm up to about 1 micron or more (e.g., 5 microns); from about 10 nm to about 750 nanometers or more; from about 25 nm to about 500 nanometers or more; from about 50 nm to about 250 nanometers or more, or

from about 75 nm to about 100 nanometers or more, while the lengths of such nanofibers can comprise, e.g., from about 2 microns (e.g., 0.5 microns) up to about 1 mm or more; from about 10 microns to about 500 micrometers or more; from about 25 microns to about 250 microns or more; or from about 50 microns to about 100 microns or more

[0188] Fibers that are, at least in part, elevated above a surface are often preferred, e.g., where at least a portion of the fibers in the fiber surface are elevated at least 10 nm, or even at least 100 nm above a surface, in order to provide enhanced surface area available for contact with, e.g., an analyte, etc.

[0189] The nanofibers optionally form a complex three-dimensional structure. The degree of such complexity depends in part upon, e.g., the length of the nanofibers, the diameter of the nanofibers, the length:diameter aspect ratio of the nanofibers, moieties (if any) attached to the nanofibers, and the growth conditions of the nanofibers, etc. The bending, interlacing, etc. of nanofibers, which help affect the degree of enhanced surface area available, are optionally manipulated through, e.g., control of the number of nanofibers per unit area as well as through the diameter of the nanofibers, the length and the composition of the nanofibers, etc. Thus, it will be appreciated that enhanced surface area of nanofiber substrates herein is optionally controlled through manipulation of these and other parameters.

[0190] Also, in some, but not all, embodiments herein, the nanofibers of the invention comprise bent, curved, or even curled forms. As can be appreciated, if a single nanofiber snakes or coils over a surface (but is still just a single fiber per unit area bound to a first surface), the fiber can still provide an enhanced surface area due to its length, etc.

#### **D) Nanofiber Construction**

[0191] As will be appreciated, the current invention is not limited by the means of construction of the nanofibers herein. For example, while some of the nanofibers herein are composed of silicon, the use of silicon should not be construed as limiting. The formation of nanofibers is possible through a number of different approaches that are well known to those of skill in the art, all of which are amenable to embodiments of the current invention.

[0192] Typical embodiments herein can be used with existing methods of nanostructure fabrication, as will be known by those skilled in the art, as well as methods mentioned or described herein. Typical, but not all, embodiments herein comprise substances that are chosen to be non-harmful (e.g., non-reactive, non-allergenic, etc.) in medical settings. In other words, a variety of methods for making nanofibers and nanofiber containing structures have been described and can be adapted for use in various of the methods, systems and devices of the invention.

[0193] The nanofibers can be fabricated of essentially any convenient material (e.g., a semiconducting material, a ferroelectric material, a metal, ceramic, polymers, etc.) and can comprise essentially a single material or can be heterostructures. For example, the nanofibers can comprise a semiconducting material, for example a material comprising a first element selected from group 2 or from group 12 of the periodic table and a second element selected from group 16 (e.g., ZnS, ZnO, ZnSe, ZnTe, CdS, CdSe, CdTe, HgS, HgSe, HgTe, MgS, MgSe, MgTe, CaS, CaSe, CaTe, SrS, SrSe, SrTe, BaS, BaSe, BaTe, and like materials); a material comprising a first element selected from group 13 and a second element selected from group 15 (e.g., GaN, GaP, GaAs, GaSb, InN, InP, InAs, InSb, and like materials); a material comprising a group 14 element (Ge, Si, and like materials); a material such as PbS, PbSe, PbTe, AlS, AlP, and AlSb; or an alloy or a mixture thereof.

[0194] In some embodiments herein, the nanofibers are optionally comprised of silicon or a silicon oxide. It will be understood by one of skill in the art that the term "silicon oxide" as used herein can be understood to refer to silicon at any level of oxidation. Thus, the term silicon oxide can refer to the chemical structure  $\text{SiO}_x$ , wherein  $x$  is between 0 and 2 inclusive. In other embodiments, the nanofibers can comprise, e.g., silicon, glass, quartz, plastic, metal, polymers, TiO, ZnO, ZnS, ZnSe, ZnTe, CdS, CdSe, CdTe, HgS, HgSe, HgTe, MgS, MgSe, MgTe, CaS, CaSe, CaTe, SrS, SrSe, SrTe, BaS, BaSe, BaTe, GaN, GaP, GaAs, GaSb, InN, InP, InAs, InSb, PbS, PbSe, PbTe, AlS, AlP, AlSb,  $\text{SiO}_1$ ,  $\text{SiO}_2$ , silicon carbide, silicon nitride, polyacrylonitrile (PAN), polyetherketone, polyimide, aromatic polymers, or aliphatic polymers.

[0195] It will be appreciated that in some embodiments, the nanofibers can comprise the same material as one or more substrate surface (i.e., a surface to which the nanofibers are attached or associated), while in other embodiments, the nanofibers

comprise a different material than the substrate surface. Additionally, the substrate surfaces can optionally comprise any one or more of the same materials or types of materials as do the nanofibers (e.g., such as the materials illustrated herein).

[0196] As previously stated, some, but by no means all, embodiments herein comprise silicon nanofibers. Common methods for making silicon nanofibers include vapor liquid solid growth (VLS), laser ablation (laser catalytic growth) and thermal evaporation. *See*, for example, Morales et al. (1998) "A Laser Ablation Method for the Synthesis of Crystalline Semiconductor Nanowires" Science 279, 208-211 (1998). In one example approach, a hybrid pulsed laser ablation/chemical vapor deposition (PLA-CVD) process for the synthesis of semiconductor nanofibers with longitudinally ordered heterostructures, and variations thereof, can be used. *See*, Wu et al. (2002) "Block-by-Block Growth of Single-Crystalline Si/SiGe Superlattice Nanowires," Nano Letters Vol. 0, No. 0.

[0197] In general, multiple methods of making nanofibers have been described and can be applied in the methods, systems and devices herein. In addition to Morales et al. and Wu et al. (above), *see*, for example, Lieber et al. (2001) "Carbide Nanomaterials" USPN 6,190,634 B1; Lieber et al. (2000) "Nanometer Scale Microscopy Probes" USPN 6,159,742; Lieber et al. (2000) "Method of Producing Metal Oxide Nanorods" USPN 6,036,774; Lieber et al. (1999) "Metal Oxide Nanorods" USPN 5,897,945; Lieber et al. (1999) "Preparation of Carbide Nanorods" USPN 5,997,832; Lieber et al. (1998) "Covalent Carbon Nitride Material Comprising C<sub>2</sub>N and Formation Method" USPN 5,840,435; Thess, et al. (1996) "Crystalline Ropes of Metallic Carbon Nanotubes" Science 273:483-486; Lieber et al. (1993) "Method of Making a Superconducting Fullerene Composition By Reacting a Fullerene with an Alloy Containing Alkali Metal" USPN 5,196,396; and Lieber et al. (1993) "Machining Oxide Thin Films with an Atomic Force Microscope: Pattern and Object Formation on the Nanometer Scale" USPN 5,252,835. Recently, one dimensional semiconductor heterostructure nanocrystals, have been described. *See*, e.g., Bjork et al. (2002) "One-dimensional Steeplechase for Electrons Realized" Nano Letters Vol. 0, No. 0.

[0198] It should be noted that some references herein, while not specific to nanofibers, are optionally still applicable to the invention. For example, background issues of construction conditions and the like are applicable between nanofibers and other nanostructures (e.g., nanocrystals, etc.).



[0199] In another approach which is optionally used to construct nanofibers of the invention, synthetic procedures to prepare individual nanofibers on surfaces and in bulk are described, for example, by Kong, et al. (1998) "Synthesis of Individual Single-Walled Carbon Nanotubes on Patterned Silicon Wafers," Nature 395:878-881, and Kong, et al. (1998) "Chemical Vapor Deposition of Methane for Single-Walled Carbon Nanotubes," Chem. Phys. Lett. 292:567-574.

[0200] In yet another approach, substrates and self assembling monolayer (SAM) forming materials can be used, e.g., along with microcontact printing techniques to make nanofibers, such as those described by Schon, Meng, and Bao, "Self-assembled monolayer organic field-effect transistors," Nature 413:713 (2001); Zhou et al. (1997) "Nanoscale Metal/Self-Assembled Monolayer/Metal Heterostructures," Applied Physics Letters 71:611; and WO 96/29629 (Whitesides, et al., published June 26, 1996).

[0201] In some embodiments herein, nanofibers (e.g., nanowires) can be synthesized using a metallic catalyst. A benefit of such embodiments allows use of unique materials suitable for surface modifications to create enhanced properties. A unique property of such nanofibers is that they are capped at one end with a catalyst, typically gold. This catalyst end can optionally be functionalized using, e.g., thiol chemistry without affecting the rest of the wire, thus, making it capable of bonding to an appropriate surface. In such embodiments, the result of such functionalization, etc., is to make a surface with end-linked nanofibers. These resulting "fuzzy" surfaces, therefore, have increased surface areas (i.e., in relation to the surfaces without the nanofibers) and other unique properties. In some such embodiments, the surface of the nanowire and/or the target substrate surface is optionally chemically modified (typically, but not necessarily, without affecting the gold tip) in order to give a wide range of properties useful in many applications.

[0202] In other embodiments, to slightly increase or enhance a surface area, the nanofibers are optionally laid "flat" (i.e., substantially parallel to the substrate surface) by chemical or electrostatic interaction on surfaces, instead of end-linking the nanofibers to the substrate. In yet other embodiments herein, techniques involve coating the base surface with functional groups which repel the polarity on the nanofiber so that the fibers do not lay on the surface but are end-linked.

[0203] Synthesis of nanostructures, e.g., nanocrystals, of various composition is described in, e.g., Peng et al. (2000) "Shape control of CdSe nanocrystals" Nature 404:59-61; Puntès et al. (2001) "Colloidal nanocrystal shape and size control: The case of cobalt" Science 291:2115-2117; USPN 6,306,736 to Alivisatos et al. (October 23, 2001) entitled "Process for forming shaped group III-V semiconductor nanocrystals, and product formed using process"; USPN 6,225,198 to Alivisatos et al. (May 1, 2001) entitled "Process for forming shaped group II-VI semiconductor nanocrystals, and product formed using process"; USPN 5,505,928 to Alivisatos et al. (April 9, 1996) entitled "Preparation of III-V semiconductor nanocrystals"; USPN 5,751,018 to Alivisatos et al. (May 12, 1998) entitled "Semiconductor nanocrystals covalently bound to solid inorganic surfaces using self-assembled monolayers"; USPN 6,048,616 to Gallagher et al. (April 11, 2000) entitled "Encapsulated quantum sized doped semiconductor particles and method of manufacturing same"; and USPN 5,990,479 to Weiss et al. (November 23, 1999) entitled "Organo luminescent semiconductor nanocrystal probes for biological applications and process for making and using such probes."

[0204] Additional information on growth of nanofibers, such as nanowires, having various aspect ratios, including nanofibers with controlled diameters, is described in, e.g., Gudiksen et al. (2000) "Diameter-selective synthesis of semiconductor nanowires" J. Am. Chem. Soc. 122:8801-8802; Cui et al. (2001) "Diameter-controlled synthesis of single-crystal silicon nanowires" Appl. Phys. Lett. 78:2214-2216; Gudiksen et al. (2001) "Synthetic control of the diameter and length of single crystal semiconductor nanowires" J. Phys. Chem. B 105:4062-4064; Morales et al. (1998) "A laser ablation method for the synthesis of crystalline semiconductor nanowires" Science 279:208-211; Duan et al. (2000) "General synthesis of compound semiconductor nanowires" Adv. Mater. 12:298-302; Cui et al. (2000) "Doping and electrical transport in silicon nanowires" J. Phys. Chem. B 104:5213-5216; Peng et al. (2000), *supra*; Puntès et al. (2001), *supra*; USPN 6,225,198 to Alivisatos et al., *supra*; USPN 6,036,774 to Lieber et al. (March 14, 2000) entitled "Method of producing metal oxide nanorods"; USPN 5,897,945 to Lieber et al. (April 27, 1999) entitled "Metal oxide nanorods"; USPN 5,997,832 to Lieber et al. (December 7, 1999) "Preparation of carbide nanorods"; Urbau et al. (2002) "Synthesis of single-crystalline perovskite nanowires composed of barium titanate and strontium titanate" J. Am. Chem. Soc.,

124:1186; Yun et al. (2002) "Ferroelectric Properties of Individual Barium Titanate Nanowires Investigated by Scanned Probe Microscopy" Nano Letters 2, 447; and published PCT application nos. WO 02/17362, and WO 02/080280.

[0205] Growth of branched nanofibers (e.g., nanotetrapods, tripods, bipods, and branched tetrapods) is described in, e.g., Jun et al. (2001) "Controlled synthesis of multi-armed CdS nanorod architectures using monosurfactant system" J. Am. Chem. Soc. 123:5150-5151; and Manna et al. (2000) "Synthesis of Soluble and Processable Rod-, Arrow-, Teardrop-, and Tetrapod-Shaped CdSe Nanocrystals" J. Am. Chem. Soc. 122:12700-12706. Synthesis of nanoparticles is described in, e.g., USPN 5,690,807 to Clark Jr. et al. (November 25, 1997) entitled "Method for producing semiconductor particles"; USPN 6,136,156 to El-Shall, et al. (October 24, 2000) entitled "Nanoparticles of silicon oxide alloys"; USPN 6,413,489 to Ying et al. (July 2, 2002) entitled "Synthesis of nanometer-sized particles by reverse micelle mediated techniques"; and Liu et al. (2001) "Sol-Gel Synthesis of Free-Standing Ferroelectric Lead Zirconate Titanate Nanoparticles" J. Am. Chem. Soc. 123:4344. Synthesis of nanoparticles is also described in the above citations for growth of nanocrystals, and nanofibers such as nanowires, branched nanowires, etc.

[0206] Synthesis of core-shell nanofibers, e.g., nanostructure heterostructures, is described in, e.g., Peng et al. (1997) "Epitaxial growth of highly luminescent CdSe/CdS core/shell nanocrystals with photostability and electronic accessibility" J. Am. Chem. Soc. 119:7019-7029; Dabbousi et al. (1997) "(CdSe)ZnS core-shell quantum dots: Synthesis and characterization of a size series of highly luminescent nanocrystallites" J. Phys. Chem. B 101:9463-9475; Manna et al. (2002) "Epitaxial growth and photochemical annealing of graded CdS/ZnS shells on colloidal CdSe nanorods" J. Am. Chem. Soc. 124:7136-7145; and Cao et al. (2000) "Growth and properties of semiconductor core/shell nanocrystals with InAs cores" J. Am. Chem. Soc. 122:9692-9702. Similar approaches can be applied to growth of other core-shell nanostructures. *See*, for example, USPN 6,207,229 (March 27, 2001) and USPN 6,322,901 (November 27, 2001) to Bawendi et al. entitled "Highly luminescent color-selective materials."

[0207] Growth of homogeneous populations of nanofibers, including nanofibers heterostructures in which different materials are distributed at different locations along the long axis of the nanofibers is described in, e.g., published PCT application nos. WO

02/17362, and WO 02/080280; Gudiksen et al. (2002) "Growth of nanowire superlattice structures for nanoscale photonics and electronics" Nature 415:617-620; Bjork et al. (2002) "One-dimensional steeplechase for electrons realized" Nano Letters 2:86-90; Wu et al. (2002) "Block-by-block growth of single-crystalline Si/SiGe superlattice nanowires" Nano Letters 2, 83-86; and US patent application 60/370,095 (April 2, 2002) to Empedocles entitled "Nanowire heterostructures for encoding information." Similar approaches can be applied to growth of other heterostructures and applied to the various methods and systems herein.

**[0208]** In some embodiments the nanofibers used to create enhanced surface areas can be comprised of nitride (e.g., AlN, GaN, SiN, BN) or carbide (e.g., SiC, TiC, Tungsten carbide, boron carbide) in order to create nanofibers with high strength and durability. Alternatively, such nitrides/carbides are used as hard coatings on lower strength (e.g., silicon or ZnO) nanofibers. While the dimensions of silicon nanofibers are excellent for many applications requiring enhanced surface area (e.g., *see*, throughout and "Structures, Systems and Methods for Joining Articles and Materials and Uses Therefore," filed April 17, 2003, USSN 60/463,766, etc.) other applications require nanofibers that are less brittle and which break less easily. Therefore, some embodiments herein take advantage of materials such as nitrides and carbides which have higher bond strengths than, e.g., Si, SiO<sub>2</sub> or ZnO. The nitrides and carbides are optionally used as coatings to strengthen the weaker nanofibers or even as nanofibers themselves.

**[0209]** Carbides and nitrides can be applied as coatings to low strength fibers by deposition techniques such as sputtering and plasma processes. In some embodiments, to achieve high strength nanocoatings of carbide and nitride coatings, a random grain orientation and/or amorphous phase are grown to avoid crack propagation. Optimum conformal coating of the nanofibers can optionally be achieved if the fibers are growing perpendicular to a substrate surface. The hard coating for fibers in such orientation also acts to enhance the adhesion of the fibers to the substrate. For fibers that are randomly oriented, the coating is preferential to the upper layer of fibers.

**[0210]** Low temperature processes for creation of silicon nanofibers are achieved by the decomposition of silane at about 400°C in the presence of a gold catalyst. However, as previously stated, silicon nanofibers are too brittle for some applications to form a durable nanofiber matrix (i.e., an enhanced surface area). Thus,

formation and use of, e.g., SiN is optionally utilized in some embodiments herein. In those embodiments, NH<sub>3</sub>, which has decomposition at about 300°C, is used to combine with silane to form SiN nanofibers (also by using a gold catalyst). Other catalytic surfaces to form such nanofibers can include, e.g., Ti, Fe, etc.

[0211] Forming carbide and nitride nanofibers directly from a melt can sometimes be challenging since the temperature of the liquid phase is typically greater than 1000°C. However, a nanofiber can be grown by combining the metal component with the vapor phase. For example, GaN and SiC nanofibers have been grown (*see, e.g., Peidong, Lieber, supra*) by exposing Ga melt to NH<sub>3</sub> (for GaN) and graphite with silane (SiC). Similar concepts are optionally used to form other types of carbide and nitride nanofibers by combining metal-organic vapor species, e.g., tungsten carbolic [W(CO)<sub>6</sub>] on a carbon surface to form tungsten carbide (WC), or titanium dimethoxy dodecanoate on a carbon surface to form TiC. It will be appreciated that in such embodiments, the temperature, pressure, power of the sputtering and the CVD process are all optionally varied depending upon, e.g., the specific parameters desired in the end nanofibers. Additionally, several types of metal organic precursors and catalytic surfaces used to form the nanofibers, as well as, the core materials for the nanofibers (e.g., Si, ZnO, etc.) and the substrates containing the nanofibers, are all also variable from one embodiment to another depending upon, e.g., the specific enhanced nanofiber surface area to be constructed.

[0212] The present invention can be used with structures that may fall outside of the size range of typical nanostructures. For example, Haraguchi et al. (USPN 5,332,910) describes nanowhiskers which are optionally used herein. Semi-conductor whiskers are also described by Haraguchi et al. (1994) "Polarization Dependence of Light Emitted from GaAs p-n junctions in quantum wire crystals" J. Appl. Phys. 75(8):4220-4225; Hiruma et al. (1993) "GaAs Free Standing Quantum Sized Wires," J. Appl. Phys. 74(5):3162-3171; Haraguchi et al. (1996) "Self Organized Fabrication of Planar GaAs Nanowhisker Arrays"; and Yazawa (1993) "Semiconductor Nanowhiskers" Adv. Mater. 5(78):577-579. Such nanowhiskers are optionally nanofibers of the invention. While the above references (and other references herein) are optionally used for construction and determination of parameters of nanofibers of the invention, those of skill in the art will be familiar with other methods of nanofiber construction/design, etc. which can also be amenable to the methods and devices herein.

[0213] Some embodiments herein comprise repetitive cycling of nanowire synthesis and gold fill deposition to make “nano-trees” as well as the co-evaporation of material that will not form a silicon eutectic, thus, disrupting nucleation and causing smaller wire formation

[0214] Such methods are utilized in the creation of ultra-high capacity surface based structures through nanofiber growth technology for, e.g., adhesion promotion between surfaces, non-fouling surfaces, etc.). Use of single-step metal film type process in creation of nanofibers limits the ability to control the starting metal film thickness, surface roughness, etc., and, thus, the ability of control nucleation from the surface. The present methods address these issues

[0215] In some embodiments of nanofiber enhanced surfaces it can be desirable to produce multibranched nanofibers. Such multibranched nanofibers could allow an even greater increase in surface area than would occur with non-branched nanofiber surfaces. To produce multibranched nanofibers gold film is optionally deposited onto a nanofiber surface (i.e., one that has already grown nanofibers). When placed in a furnace, fibers perpendicular to the original growth direction can result, thus, generating branches on the original nanofibers. Colloidal metal particles can optionally be used instead of gold film to give greater control of the nucleation and branch formation. The cycle of branching optionally could be repeated multiple times, e.g., with different film thicknesses, different colloid sizes, or different synthesis times, to generate additional branches having varied dimensions. Eventually, the branches between adjacent nanofibers could optionally touch and generate an interconnected network. Sintering is optionally used to improve the binding of the fine branches.

[0216] In yet other embodiments, it is desirable to form finer nanofibers (e.g., nanowires). To accomplish this, some embodiments herein optionally use a non-alloy forming material during gold or other alloy forming metal evaporation. Such material, when introduced in a small percentage can optionally disrupt the metal film to allow it to form smaller droplets during wire growth and, thus, correspondingly finer wires.

[0217] Such approaches can allow improved control of nanofiber formation and allow generation of finer and more numerous nanofibers from a slightly thicker initial metal film layer. In applications such as nanoarrays, etc., the improved control can optionally improve the signal ratio from the nanofibers to the planar surface or just add

a greater degree of control. Possible materials for use in finer nanofiber construction include, e.g., Ti, Al<sub>2</sub>O<sub>3</sub> and SiO<sub>2</sub>.

[0218] In yet other embodiments, post processing steps such as vapor deposition of glass can allow for greater anchoring or mechanical adhesion and interconnection between nanofibers, thus, improving mechanical robustness in applications requiring additional strength as well as increasing the overall surface to volume of the nanostructure surface.

### **E) Interaction of Biomaterials and Nanofiber Enhanced Surface Area Substrates**

[0219] In typical embodiments, the nanofiber enhanced surface area substrates of the invention are used in various medical product applications. For example, coatings on medical products for drug release, lubricity, cell adhesion, low bio-adsorption, electrical contact, etc. *See* above. For example, the application of surface texture (e.g., as with the present invention) to the surfaces of polymer implants has been shown to result in significant increases in cellular attachment. *See*, e.g., Zhang et al. "Nanostructured Hydroxyapatite Coatings for Improved Adhesion and Corrosion Resistance for Medical Implants" Symposium V: Nanophase and Nanocomposite Materials IV, Kormareni et al. (eds.) 2001, MRS Proceedings, vol. 703. Other medical applications of the current embodiments include, e.g., slow-release drug delivery. For example, drugs can be incorporated into various pharmaceutically acceptable carriers which allow slow release over time in physiological environments (e.g., within a patient). Drugs, etc. incorporated into such carriers (e.g., polymer layers, etc.) are shielded, at least partially, from direct exposure to body fluids due to incorporation into the carrier layer (e.g., present interstitially between the nanofibers). Drugs, etc. at the interface between the body fluids and the carrier layer (at the top of the nanofiber layer) diffuse out fairly quickly, while drugs deeper within the carrier layer diffuse out slowly (e.g., once body fluid diffuses into the carrier layer and then diffuses back out with the drug). Such carriers are well known to those of skill in the art and can be deposited or wicked onto the surface of a nanofiber substrate (i.e., amongst the nanofibers).

[0220] Biofilm formation and infection on indwelling catheters, orthopedic implants, pacemakers and other medical devices represents a persistent patient health danger. Therefore, some embodiments herein comprise novel surfaces which minimize

bacterial colonization due to their advantageous morphology. In contrast, yet other embodiments herein utilize the unique surface morphology of nanofiber enhanced surface area substrates to foster cell growth under desired conditions or in desired locations. The high surface area/non-tortuous aspect of the current invention allows greater attachment area and accessibility (in certain embodiments) for nutrients/fluids, etc. and initial attachment benefits over porous surfaces where growth, etc. is limited by space (both in terms of surface area and space within the pores for the cells to grow out).

[0221] The substrates of the invention, because of their high surface areas and ready accessibility (e.g., non-tortuous paths), are extremely useful as bioscaffolds, e.g., in cell culture, implantation, and controlled drug or chemical release applications. In particular, the high surface area of the materials of the invention provide very large areas for attachment of desirable biological cells in, e.g., cell culture or for attachment to implants. Further, because nutrients can readily access these cells, the invention provides a better scaffold or matrix for these applications. This latter issue is a particular concern for implanted materials, which typically employ porous or roughened surfaces in order to provide tissue attachment. In particular, such small, inaccessible pores, while providing for initial attachment, do not readily permit continued maintenance of the attached cells, which subsequently deteriorate and die, reducing the effectiveness of the attachment. Another advantage of the materials of the invention is that they are inherently non-biofouling, e.g., they are resistant to the formation of biofilms from, e.g., bacterial species that typically cause infection for implants, etc.

[0222] Without being bound to a particular theory or method of action, the unique morphology of a nanofiber surface can reduce the colonization rate of bacterial species such as, e.g., *S. epidermidis* by about ten fold. For example, embodiments such as those comprising silicon nanowires grown from the surface of a planar silicon oxide substrate by chemical vapor deposition process, and which comprise diameters of approximately 60 nanometers and lengths of about 50-100 microns show reduced bacterial colonization. *See*, below. It will be appreciated that while specific bacterial species are illustrated in examples herein, that the utility of the embodiments, does not necessarily rest upon use against such species. In other words, other bacterial species are also optionally inhibited in colonization of the nanofiber surfaces herein. Additionally, while examples herein utilize silicon oxide nanowires on similar



substrates, it will be appreciated other embodiments are optionally equally utilized (e.g., other configurations of nanofibers; nanofibers on non-silicon substrates such as plastic, etc.; patterns of nanofibers on substrates, etc.).

[0223] It will be noticed that substrates herein that are covered with high densities of nanofibers (e.g., silicon nanowires) resist bacterial colonization and mammalian cell growth. For example, approximately 10x less (or even less) bacterial growth occurs on a nanowire covered substrate as compared to an identical planar surface. In various embodiments herein, the physical and chemical properties of the nanofiber enhanced surface area substrates are varied in order to optimize and characterize their resistance to bacterial colonization.

[0224] In contrast to prevention of bacterial colonization, other embodiments herein comprise substrates that induce the attachment of mammalian cells to the nanofiber surface by functionalization with extra-cellular binding proteins, etc. or other moieties, thus, achieving a novel surface with highly efficient tissue integration properties.

[0225] In some embodiments herein where NFS substrates are to be used in settings requiring, e.g., sterility, etc., the nanofibers are optionally coated with, or composed of, titanium dioxide. Such titanium dioxide confers self-sterilizing or oxidative properties to such nanofibers. Nanofibers which comprise titanium dioxide, thus, allow rapid sterilization and oxidation compared to conventional planar  $\text{TiO}_2$  surfaces while maintaining rapid diffusion to the surface.

[0226] In embodiments herein which involve nanowires comprising titanium oxides (e.g., coated nanowires, etc.), such can optionally be achieved through any of a number of methods. For example, in some embodiments herein the nanowires can be designed and implemented through an approach which involves analytical monitoring of  $(\text{SiO}_4)_x(\text{TiO}_4)_y$  nanowires by coating and a molecular precursor approach. The layer thickness and porosity are optionally controlled through concentration of reagent, dip speed, and or choice of precursor for dip coating such as tetraethoxytitanate or tetrabutoxytitanate, gelation in air, air drying and calcinations. Molecular precursors such as  $\text{M}[(\text{OSi}(\text{O}^t\text{Bu})_3)_4]$ , where  $\text{M} = \text{Ti}, \text{Zr}$ , or other metal oxides, can be decomposed to release 12 equivalents of isobutylene and 6 equivalents of water to form mesoporous materials or nanowires. These precursors can also be used in conjunction with CVD or

detergents in nanocrystal syntheses (wet chemistry) to produce dimetallic nanocrystals of desired size distribution. Material can be made via wet chemistry standard inorganic chemistry techniques and oxidative properties determined by simple kinetics monitoring of epoxidation reactions (GC or GCMS) using alkene substrates. Porosity can be monitored by standard BET porosity analysis. Copolymer polyether templates can also be used to control porosity as part of the wet chemistry process.

[0227] Titanium oxide materials are well known oxidation catalysts. One of the keys to titanium oxide materials is control of porosity and homogeneity of particle size or shape. Increased surface area typically affords better catalytic turnover rates for the material in oxidation processes. This has been difficult as the kinetics of oxide formation (material morphology) can be difficult to control in solution.

[0228] As described, recent interest in  $\text{TiO}_2$  for oxidative catalytic surfaces (self-cleaning surfaces) shows promise for marketing "green chemistry" cleaning materials. However, the self-cleaning efficiency of the material is dependent upon, e.g., the surface area and porosity. Nanowires have a much higher surface areas than bulk materials (e.g., ones with a nanofiber enhanced surface) that are currently used for self-cleaning materials. Thus, the combination of silicon nanowire technology coated with  $\text{TiO}_2$  or  $\text{TiO}_2$  nanowires or molecular precursors to form wires can optionally provide access to previously unknown materials that are useful in self-cleaning, sterilizing, and/or non-biofouling surfaces.

[0229] In some embodiments, such sterilizing activity arises in conjunction with exposure to UV light or other similar excitation. Such factors are optionally important in applications such as, e.g., sterile surfaces in medical settings or food processing settings. The increased surface area due to the NFS of the invention (e.g., increasing area 100-1000 times or the like), therefore, could vastly increase the disinfection rate/ability of such surfaces.

#### **i) Current Means of Preventing Bacterial Contamination of Medical Devices**

[0230] A variety of methods have been used to combat surface colonization of biomedical implants by bacteria and other microorganisms as well as the resulting biofilm formed. Previous methods have included varying the fundamental biomaterial used in the devices, applying hydrophilic, hydrophobic or bioactive coatings or creating

porous or gel surfaces on the devices that contain bioactive agents. The task of generating universal biomaterial surfaces is complicated by species' specificity to particular materials. For example *S. epidermidis* has been reported to bind more readily to hydrophobic than to hydrophilic surfaces. *S. aureus* has a greater affinity for metals than for polymers, while *S. epidermidis* forms a film more rapidly on polymers than metals.

[0231] Antimicrobial agents, such as antibiotics and polyclonal antibodies integrated into porous biomaterials have been shown to actively prevent microbial adhesion at the implant site. However, the effectiveness of such local-release therapies is often compromised by the increasing resistance of bacteria to antibiotic therapy and the specificity associated with antibodies. Recent in vitro studies have also explored the use of biomaterials that release small molecules such as nitrous oxide in order to non-specifically eliminate bacteria at an implant surface. Nitrous oxide release must, however, be localized to limit toxicity.

#### **ii) Prevention of Biofilm Formation by Nanofiber Enhanced Area Surfaces**

[0232] Results of the inventors have shown that silicon nanowire surfaces aggressively resist colonization by the bacteria *S. epidermidis* as well as the growth of CHO, MDCK and NIH 3T3 cell lines. This is found to be the case when the bacteria or cells were cultured in contact with a native hydrophilic nanowire surface or with a fluorinated hydrophobic nanowire surface. Since silicon oxide flat control surfaces and polystyrene flat control surfaces supported profuse growth of *S. epidermidis* and the three cell lines, it is inferred that the nanowire morphology renders the surface cytophobic. Of course, again, it will be realized that the utility of the current invention is not limited by specific theories or modes of action. However, surface morphology is thought to be basis for the antimicrobial activity. The nanofibers on such substrates are spaced tightly enough to prohibit the bacteria from physically penetrating to the solid surface below. The amount of presentable surface area available for attachment is typically less than 1.0% of the underlying flat surface. In typical embodiments, the nanofibers are approximately 40 nm in diameter and rise to a height about 20  $\mu\text{m}$  above the solid surface. Thus, unlike a typical membrane surface that would be found on a medical device, the nanowire surfaces herein are discontinuous and spiked and have no regular structure to aid in cell attachment. In fact, the current surfaces are almost the

exact opposite of a conventional membrane; rather than a solid surface with holes, they are open spiked surfaces. It is thought that this unique morphology discourages normal biofilm attachment irrespective of the hydrophobic or hydrophilic nature of the nanofibers involved.

[0233] As detailed throughout, the nanofiber growth process can be conducted on a wide variety of substrates that can have planar or complex geometries. Thus, various substrates of the invention can be completely covered, patterned or have nanofibers in specific locations. However, for ease of focus herein, silicon nanofibers on silicon oxide or metallic substrates are discussed in most detail. Again, however, nanofibers from a wide variety of materials are also contemplated as is growing such on plastic, metal and ceramic substrates. The versatility of the nanofiber production process lends itself to the eventual scale-up and commercialization of a wide variety of products with nanofiber surfaces for the bio-medical field.

[0234] It is thought that, although absolute surface area is increased on substrates growing nanofibers, the low solid surface volume, lack of continuity and nanoscale aspect of the fibers discourages cellular attachment. The nanowire surfaces used in these illustrations herein was produced for an electronics application and was not optimized for this use, yet, as will be noted, such surfaces still reduced biofilm accumulation. The silicon wires utilized were ~40 nm in diameter and 50 to 100 um in length and were grown on a four inch silicon substrate. The nanowire preparation method is described below. In the current example, the nanowire pieces used in this experiment were about 0.25 cm<sup>2</sup>. Immediately before introduction into the culture media they were soaked in 100% ethanol and blown dry with a stream of nitrogen. Silicon wafer controls (i.e., without nanowires) were also soaked in ethanol and blown dry. *S. epidermidis* was grown in LB broth for 6 hours at 37°C with gentle shaking in 35mm Petri dishes. Wafer sections were then placed in the culture and left for 24 hours at 37°C in the original media. The wafer slices were removed after 24 hours incubation, washed briefly in fresh media, rapidly immersed in water and then heat fixed for 30 seconds prior to staining in a 0.2% crystal violet solution. The wafer segments were rinsed thoroughly in water. Any microbes attached to the wafers were visualized by conventional brightfield microscopy. Images were captured with a digital camera. The results showed approximately a ten fold decrease in bacteria on the nanowire substrate as compared to the silicon wafer control. Quantitation was performed on the

microscope by focusing through the nanowires since the thickness of the nanowire layer was greater than the depth of field of the microscope.

[0235] To illustrate the nanofiber surfaces' repulsion of mammalian cells, CHO cells were maintained in culture in complete media (Hams F12 media supplemented with 10% fetal bovine serum) at 37°C in a 5% CO<sub>2</sub> atmosphere. Wafer segments were placed in 35 mm cell culture treated Petri dishes. CHO cells were seeded into the dishes at a density of 10<sup>6</sup> cell/ml in complete media after trypsinization from confluent culture. The cells were allowed to adhere overnight and were then observed microscopically every 24 hours. The surface of the 35 mm Petri dish was confluent at 48 hours when the first observation was made. No cell growth was observed directly on the nanowire surface. Where the nanowires had been removed by scratching the surface with a knife the cells adhered and grew. Silicon wafer controls became confluent with cells. In these experiments complete retardation of mammalian cellular growth and approximately a 10x reduction in bacterial growth was observed. The control surfaces were chemically identical to the nanowires so it is thought that reduction in cell and bacterial growth is due to the unique surface morphology of the nanofiber enhanced surface area substrates.

[0236] *S. epidermidis* was used in the illustrations herein because it is a representative bacteria involved in infections of medical devices. Additionally, *S. epidermidis* has been widely used in the evaluation of biomaterials and has been identified as a dominant species in biomaterial centered infections. Other bacteria implicated in biomaterial related infections such as *S. aureus*, *Pseudomonas aeruginosa* and B-hemolytic streptococci are also contemplated as being prohibited through use of current embodiments. In addition to CHO cells illustrated herein, other common tissue culture lines such as, e.g., MDCK, L-929 and HL60 cells are also contemplated as being prohibited through use of current embodiments. Such cell lines represent a wide diversity of cell types. The CHO and MDCK cells are representative of epithelial cells, L-929 cells participate in the formation of connective tissue and the HL60 line represents immune surveillance cells. Thus, the nanofiber enhanced surface areas herein are contemplated against these cell types and other common in vivo cell types. The nanofibers used in the in vitro illustration herein were made of silicon, and, as detailed throughout, several methods have been reported in the literature for the synthesis of silicon nanowires. For example, laser ablating metal-containing silicon

targets, high temperature vaporizing of Si/SiO<sub>2</sub> mixture, and vapor-liquid-solid (VLS) growth using gold as the catalyst. *See*, above. While any method of construction is optionally used, the approach to nanowire synthesis is typically VLS growth since this method has been widely used for semiconductor nanowire growth. Description of such method is provided elsewhere herein.

[0237] As mentioned previously, it is thought that the primary means of biofilm prevention by nanofiber surfaces herein is due to the unique morphology of the substrate, however, it is also possible that such substrates comprise inherent cytophobicity activity.

[0238] The effect of surface hydrophilicity or hydrophobicity on growth is also optionally modified on the nanofiber substrates herein to specifically tailor biofilm prevention in different situations. Such functionalization goes along with variability in wire length, diameter and density on the substrate. The silicon oxide surface layer of the typical nanofiber substrates is quite hydrophilic in its native state. Water readily wets the surface and spreads out evenly. This is partially due to the wicking properties of the surface. Functionalization of the surface is facilitated by the layer of native oxide that forms on the surface of the wires. This layer of SiO<sub>2</sub> can be modified using standard silane chemistry to present a functional groups on the outside of the wire. For example the surface can be treated with gaseous hexamethyldisilane (HMDS) to make it extremely hydrophobic. *See*, above.

### **iii) Attachment of Extra-Cellular Proteins onto Nanofiber Surfaces**

[0239] As shown herein, nanofiber surfaces do not readily support the growth of mammalian cells or bacteria. Yet, in other instances, the growth of mammalian cell lines on surfaces is advantageous. Thus, embodiments of the current invention, by attaching extra-cellular proteins or other moieties to nanofibers encourages such cell growth. The deposition of the proteins on the nanofibers can be through simple nonspecific adsorption. Other embodiments contemplate covalent attachment of cells/proteins to a nanofiber surface. Proteins with known extra-cellular binding functions such as Collagen, Fibronectin, Vitronectin and Laminin are contemplated in use. In embodiments where grafting and/or bonding of nanofiber substrates and, e.g., biological material such as bone or medical devices such as metal bone pins, etc. is to occur, different embodiments can have different patterns of nanofibers upon the

substrate. Thus, for example, nanofibers can optionally only exist on an area of a medical implant where grafting or bonding is to occur. Again, standard protein attachment methods can be used to make the covalent linkage to the nanofibers.

[0240] Additionally various sol-gel coatings can be deposited upon nanofiber surfaces herein to encourage bio-compatibility and/or bio-integration applications. Previous work on devices concerned with bone integration has used porous materials on titanium implants to encourage bone growth. In some embodiments herein, the current intention utilizes addition of similar materials in conjunction with the nanofiber surfaces herein. For example, hydroxyapatite, a common calcium based mineral, can optionally be deposited on nanofiber surfaces to facilitate bone integration into/with the nanofiber surface. Common sol-gel techniques can optionally be used to produce the hydroxyapatite deposition. Such hydroxyapatite coated nanofiber surfaces optionally could have the benefit of both promoting bone integration and displaying anti-biofouling properties, thus, resulting in a greater likelihood that proper bone growth/healing will occur.

[0241] In an alternative embodiment, the nanowires, by virtue of being crystalline in nature, can induce or hasten the crystallization of hydroxyapatite directly in the vicinity of the nanowires. Such results are not surprising in light of the fact that bioactive glass has been utilized for many years as a component of orthopedic materials and the osseointegration has been shown to be superior. With the current invention, high surface area bioactive glass can essentially be grown on the surface of an orthopedic implant, creating a platform on the implant for both control of surface topography as well as altering the biochemical nature of the surface through chemical attachment, adsorption, and other techniques detailed in this invention.

[0242] Those of skill in the art will readily appreciate that the current invention also includes use of deposition of ceramic-type materials and the like through sol-gel techniques to produce a wide range of, e.g., compatibility applications (i.e., in addition to those involving hydroxyapatite and bone growth).

### **XVIII) Kits/Systems**

[0243] In some embodiments, the invention provides kits for practice of the methods described herein and which optionally comprise the substrates of the invention. In various embodiments, such kits comprise one or more nanofiber enhanced surface

area substrate, e.g., one or more catheter, heat exchanger, superhydrophobic surface or, one or more other device comprising a nanofiber enhanced surface area substrate, etc.

[0244] The kit can also comprise any necessary reagents, devices, apparatus, and materials additionally used to fabricate and/or use a nanofiber enhanced surface area substrate, or any device comprising such.

[0245] In addition, the kits can optionally include instructional materials containing directions (i.e., protocols) for the synthesis of a nanofiber enhanced surface area substrate and/or for adding moieties to such nanofibers and/or use of such nanofiber structures. Preferred instructional materials give protocols for utilizing the kit contents.

[0246] In certain embodiments, the instructional materials teach the use of the nanofiber substrates of the invention in the construction of one or more devices (such as, e.g., medical devices, etc.). The instructional materials optionally include written instructions (e.g., on paper, on electronic media such as a computer readable diskette, CD or DVD, or access to an internet website giving such instructions) for construction and/or utilization of the nanofiber enhanced surfaces of the invention.

[0247] While the foregoing invention has been described in some detail for purposes of clarity and understanding, it will be clear to one skilled in the art from a reading of this disclosure that various changes in form and detail can be made without departing from the true scope of the invention. For example, all the techniques and apparatus described above can be used in various combinations. All publications, patents, patent applications, or other documents cited in this application are incorporated by reference in their entirety for all purposes to the same extent as if each individual publication, patent, patent application, or other document were individually indicated to be incorporated by reference for all purposes.



**What is claimed is:**

1. A medical device comprising a body structure having one or more surfaces having a plurality of nanostructured components associated therewith.
2. The device of claim 1, wherein the medical device is an intracorporeal or extracorporeal device, a temporary or permanent implant, a stent, a vascular graft, an anastomotic device, an aneurysm repair device, an embolic device, or an implantable device.
3. The device of claim 1, wherein the plurality of nanostructured components comprises a plurality of nanofibers.
4. The device of claim 3, wherein the plurality of nanofibers comprise an average length of from about 1 micron to at least about 500 microns, from about 5 micron to at least about 150 microns, from about 10 microns to at least about 125 microns, or from about 50 microns to at least about 100 microns.
5. The device of claim 3, wherein the plurality of nanofibers comprise an average diameter of from about 5 nm to at least about 1 micron, from about 5 nm to at least about 500 nm, from about 20 nm to at least about 250 nm, from about 20 nm to at least about 200 nm, from about 40 nm to at least about 200 nm, from about 50 nm to at least about 150 nm, or from about 75 nm to at least about 100 nm.
5. The device of claim 3, wherein the plurality of nanofibers comprise an average density of from about 0.11 nanofibers per square micron to at least about 1000 nanofibers per square micron, from about 1 nanofiber per square micron to at least about 500 nanofibers per square micron, from about 10 nanofibers per square micron to at least about 250 nanofibers per square micron, or from about 50 nanofibers per square micron to at least about 100 nanofibers per square micron.
6. The device of claim 3, wherein the plurality of nanofibers comprise a material independently selected from the group consisting of: silicon, glass, quartz, plastic, metal and metal alloys, polymers, TiO, ZnO, ZnS, ZnSe, ZnTe, CdS, CdSe, CdTe, HgS, HgSe, HgTe, MgS, MgSe, MgTe, CaS, CaSe, CaTe, SrS, SrSe, SrTe, BaS, BaSe, BaTe, GaN, GaP, GaAs, GaSb, InN, InP, InAs, InSb, PbS, PbSe,

PbTe, AlS, AlP, AlSb, SiO<sub>1</sub>, SiO<sub>2</sub>, silicon carbide, silicon nitride, polyacrylonitrile (PAN), polyetherketone, polyimide, an aromatic polymer, and an aliphatic polymer.

7. The device of claim 1, wherein the nanostructured components comprise hollow nanotubular structures.
8. The device of claim 1, wherein the nanostructured components comprise nanowires.
9. The device of claim 3, wherein the nanofibers are attached to the one or more surfaces of the body structure by growing the nanofibers directly on the one or more surfaces.
10. The device of claim 3, wherein the nanofibers are attached to or otherwise associated with the one or more surfaces of the body structure by covalently attaching the nanofibers to the one or more surfaces.
11. The device of claim 1, wherein the body structure is made from at least a first material, and the plurality of nanostructured components are incorporated into the at least first material.
12. The device of claim 1, wherein the nanostructured components are attached to the one or more surfaces of the body structure, the medical device further comprising one or more biologically compatible or bioactive coatings applied to the one or more nanostructured surfaces.
13. The medical device of claim 1, wherein the plurality of nanostructured components enhance one or more of adhesion, non-adhesion, friction, patency, or anti-biofouling of the device with one or more tissue surfaces of a body of a patient.
14. A vascular stent comprising a plurality of nanostructured components associated with one or more surfaces of the stent.
15. The stent of claim 14, wherein the plurality of nanostructured components comprises a plurality of nanofibers.

16. The stent of claim 15, wherein the plurality of nanofibers comprise a material independently selected from the group consisting of: silicon, glass, quartz, plastic, metal and metal alloys, polymers, TiO, ZnO, ZnS, ZnSe, ZnTe, CdS, CdSe, CdTe, HgS, HgSe, HgTe, MgS, MgSe, MgTe, CaS, CaSe, CaTe, SrS, SrSe, SrTe, BaS, BaSe, BaTe, GaN, GaP, GaAs, GaSb, InN, InP, InAs, InSb, PbS, PbSe, PbTe, AlS, AlP, AlSb, SiO<sub>1</sub>, SiO<sub>2</sub>, silicon carbide, silicon nitride, polyacrylonitrile (PAN), polyetherketone, polyimide, an aromatic polymer, and an aliphatic polymer.
17. The stent of claim 14, wherein the nanostructured components comprise hollow nanotubular structures.
18. The stent of claim 14, wherein the nanostructured components comprise nanowires.
19. The stent of claim 15, wherein the nanofibers are attached to the one or more surfaces of the stent by growing the nanofibers directly on the one or more surfaces.
20. The stent of claim 15, wherein the nanofibers are attached to the one or more surfaces of the stent by separately covalently attaching the nanofibers to the one or more surfaces.
21. The stent of claim 14, wherein the stent is made from one or more materials selected from Nitinol, nickel alloy, tin alloy, stainless steel, cobalt, chromium, gold, polymer, or ceramic.
22. The stent of claim 14, wherein the stent comprises a drug compound that is directly adsorbed to or otherwise associated with the nanostructured surface via the use of one or more silane groups.
23. The stent of claim 14, wherein the stent comprises a drug compound that is adsorbed to or otherwise associated with the nanostructured surface via the use of one or more linker molecules.
24. An aneurysm repair device comprising a graft member which is configured to be positioned within a patient's body in a region of an aneurysm, the graft

member comprising a plurality of nanostructured components associated with one or more surfaces of the graft member.

25. The device of claim 24, wherein the plurality of nanostructured components comprises a plurality of nanofibers.

26. The device of claim 25, wherein the plurality of nanofibers comprise a material independently selected from the group consisting of: silicon, glass, quartz, plastic, metal or metal alloys, polymers, TiO, ZnO, ZnS, ZnSe, ZnTe, CdS, CdSe, CdTe, HgS, HgSe, HgTe, MgS, MgSe, MgTe, CaS, CaSe, CaTe, SrS, SrSe, SrTe, BaS, BaSe, BaTe, GaN, GaP, GaAs, GaSb, InN, InP, InAs, InSb, PbS, PbSe, PbTe, AlS, AlP, AlSb, SiO<sub>1</sub>, SiO<sub>2</sub>, silicon carbide, silicon nitride, polyacrylonitrile (PAN), polyetherketone, polyimide, an aromatic polymer, and an aliphatic polymer.

27. The device of claim 24, wherein the nanostructured components comprise hollow nanotubular structures.

28. The device of claim 24, wherein the nanostructured components comprise nanowires.

29. The device of claim 25, wherein the nanofibers are attached to the one or more surfaces of the graft member by growing the nanofibers directly on the one or more surfaces.

30. The device of claim 25, wherein the nanofibers are attached to the one or more surfaces of the graft member by attaching the nanofibers to the one or more surfaces.

31. The device of claim 24, wherein the graft member is made from one or more of treated natural tissue, laboratory-engineered tissue, and synthetic polymer fabrics.

32. The device of claim 24, wherein the graft member is made from a synthetic polymer selected from Dacron, Teflon, metal or alloy mesh, ceramic or glass fabrics.

33. The device of claim 24, wherein the graft member comprises one or more biocompatible coatings applied to the one or more nanostructured surfaces of the graft member.

34. The device of claim 24, wherein the graft member is configured to be positioned within an aorta of the patient in a region of an aneurysm.

35. The device of claim 24, wherein the graft member is configured to be positioned proximate to a side wall of a vessel that supplies blood to or from the brain in a region of an aneurysm.

36. A device for creating an anastomosis in a patient by coupling a first vessel to a second vessel in an end-to-end or end-to-side anastomosis, the device comprising a tubular member comprising a plurality of nanostructured components associated with one or more surfaces of the tubular member.

37. The device of claim 36, wherein the plurality of nanostructured components comprises a plurality of nanofibers.

38. The device of claim 37, wherein the plurality of nanofibers comprise a material independently selected from the group consisting of: silicon, glass, quartz, plastic, metal, polymers, TiO, ZnO, ZnS, ZnSe, ZnTe, CdS, CdSe, CdTe, HgS, HgSe, HgTe, MgS, MgSe, MgTe, CaS, CaSe, CaTe, SrS, SrSe, SrTe, BaS, BaSe, BaTe, GaN, GaP, GaAs, GaSb, InN, InP, InAs, InSb, PbS, PbSe, PbTe, AlS, AlP, AlSb, SiO<sub>1</sub>, SiO<sub>2</sub>, silicon carbide, silicon nitride, polyacrylonitrile (PAN), polyetherketone, polyimide, an aromatic polymer, and an aliphatic polymer.

39. The device of claim 36, wherein the nanostructured components comprise hollow nanotubular structures.

40. The device of claim 36, wherein the nanostructured components comprise nanowires.

41. The device of claim 37, wherein the nanofibers are attached to the one or more surfaces of the tubular member by growing the nanofibers directly on the one or more surfaces.

42. The device of claim 37, wherein the nanofibers are attached to the one or more surfaces of the tubular member by attaching the nanofibers to the one or more surfaces.

43. The device of claim 36, wherein the tubular member is made from one or more of treated natural tissue, laboratory-engineered tissue, de-natured animal tissue, stainless steel, metal, alloys, ceramic or glass fabrics, polymers, plastic, silicone, and synthetic polymer fabrics.

44. The device of claim 36, wherein the tubular member comprises a T-tube for performing an end-to-side anastomosis.

45. The device of claim 36, wherein the tubular member comprises one or more biocompatible or bioactive coatings applied to the one or more nanostructured surfaces of the tubular member.

46. The device of claim 36, wherein the tubular member has a cross-sectional shape selected from circular, semi-circular, elliptical, and polygonal.

47. The device of claim 36, wherein one of the first vessel and second vessel comprises a synthetic bypass graft vessel.

48. The device of claim 36, wherein the tubular member comprises a straight tube.

49. An implantable orthopedic device comprising a body structure comprising a plurality of nanostructured components associated with one or more surfaces of the body structure.

50. The device of claim 49, wherein the plurality of nanostructured components comprises a plurality of nanofibers.

51. The device of claim 50, wherein the plurality of nanofibers comprise a material independently selected from the group consisting of: silicon, glass, quartz, plastic, metal, polymers, TiO, ZnO, ZnS, ZnSe, ZnTe, CdS, CdSe, CdTe, HgS, HgSe, HgTe, MgS, MgSe, MgTe, CaS, CaSe, CaTe, SrS, SrSe, SrTe, BaS, BaSe, BaTe, GaN, GaP, GaAs, GaSb, InN, InP, InAs, InSb, PbS, PbSe, PbTe, AlS, AlP, AlSb, SiO<sub>1</sub>,

SiO<sub>2</sub>, silicon carbide, silicon nitride, polyacrylonitrile (PAN), polyetherketone, polyimide, an aromatic polymer, and an aliphatic polymer.

52. The device of claim 49, wherein the nanostructured components comprise hollow nanotubular structures.

53. The device of claim 49, wherein the nanostructured components comprise nanowires.

54. The device of claim 50, wherein the nanofibers are attached to the one or more surfaces of the body structure by growing the nanofibers directly on the one or more surfaces.

55. The device of claim 50, wherein the nanofibers are attached to the one or more surfaces of the body structure by attaching the nanofibers to the one or more surfaces.

56. The device of claim 49, wherein the body structure is made from one or more of treated natural tissue, laboratory-engineered tissue, de-natured animal tissue, stainless steel, metal, alloys, ceramic or glass fabrics, polymers, plastic, silicone, and synthetic polymer fabrics.

57. The device of claim 49, wherein the body structure comprises one or more biocompatible or bioactive coatings applied to the one or more nanostructured surfaces of the body structure.

58. The device of claim 49, wherein the implantable orthopedic device is selected from at least one of the following: total knee joints, total hip joints, ankle, elbow, wrist, and shoulder implants including those replacing or augmenting cartilage, long bone implants such as for fracture repair and external fixation of tibia, fibula, femur, radius, and ulna, spinal implants including fixation and fusion devices, maxillofacial implants including cranial bone fixation devices, artificial bone replacements, dental implants, orthopedic cements and glues comprised of polymers, resins, metals, alloys, plastics and combinations thereof, nails, screws, plates, fixator devices, wires and pins.

59. A bioengineered scaffold device for providing a scaffold for nerve regeneration comprising a base membrane or matrix having a plurality of nanostructured components associated therewith.
60. The scaffold device of claim 59, wherein the membrane or matrix is made from one or more of the following materials: natural or synthetic polymers, electrically conducting polymers, metals, alloys, ceramics, glass fabrics, or silicone.
61. The scaffold device of claim 60, wherein the base membrane or matrix is made from an electrically conducting polymer.
62. The device of claim 59, wherein the plurality of nanostructured components comprise a plurality of nanofibers or nanowires.
63. The device of claim 59, wherein the nanostructured surface of the membrane or matrix is impregnated or bound with one or more drugs, cells, fibroblasts, nerve growth factors (NGF), cell seeding compounds, neurotrophic growth factors or genetically engineered cells producing such factors, VEGF, or laminin to encourage axonal elongation and functional nerve performance.
64. The device of claim 59, wherein the plurality of nanostructured components are embedded in a biocompatible polymer.
65. A medical device for implantation in the uterus or fallopian tubes comprising a surface and a plurality of nanofibers associated with the surface.
66. A medical device in which one or more surfaces are adapted to resist crystallization of body fluids comprising a surface and a plurality of nanofibers associated with the surface.
67. A medical device in which one or more surfaces are adapted to resist thrombus formation comprising a surface and a plurality of nanofibers associated with the surface.
68. A medical device in which one or more surfaces are adapted to resist tissue in-growth comprising a surface and a plurality of nanofibers associated with the surface, said nanofibers adapted to be hydrophobic.



69. A method of therapeutically treating a patient comprising contacting a region of said patient with a medical device comprising a surface and plurality of nanofibers associated with said surface.

70. A method of administering a drug compound to a body of a patient comprising:

providing a drug-eluting device comprising at least one surface, a plurality of nanofibers associated with the surface, and a drug compound associated with the plurality of nanofibers;

introducing the drug-eluting device into a body of a patient; and

delivering the drug compound into the body of the patient.

71. The method of claim 70, wherein the drug-eluting device comprises a coronary stent.

72. The method of claim 71, wherein the drug compound comprises paclitaxel or sirolimus.

73. The method of claim 70, wherein the drug compound is adsorbed to the nanofiber surface of the drug-eluting device.

74. The method of claim 70, wherein the drug compound is attached to the nanofiber surface via the use of one or more silane groups.

75. The method of claim 70, wherein the drug compound is attached to the nanofiber surface via the use of one or more linker molecules.

76. The method of claim 70, wherein the drug compound is covalently or ionically attached to the nanofiber surface of the drug-eluting device.

77. The method of claim 70 wherein the drug-eluting device comprises a coronary stent, and the delivering the drug compound comprises eluting the drug compound at the site of a lesion in a coronary vessel.

78. The method of claim 77, wherein the drug compound elutes into the coronary vessel at the site of the lesion following expansion of the coronary stent.

79. The method of claim 78, wherein the nanofiber surface is configured such that the drug compound elutes slowly over time.

80. The method of claim 70, wherein the plurality of nanofibers are embedded in a polymer coating to provide enhanced durability to the nanofibers.

81. The method of claim 70, wherein the drug compound is selected from one or more of the following: anti-inflammatory immunomodulators such as Dexamethasone, M-prednisolone, Interferon, Leflunomide, Tacrolimus, Mizoribine, statins, Cyclosporine, Tranilast, and Biorest; antiproliferative compounds such as Taxol, Methotrexate, Actinomycin, Angiopeptin, Vincristine, Mitomycin, RestenASE, and PCNA ribozyme; migration inhibitors such as Batimastat, Prolyl hydroxylase inhibitors, Halofuginone, C-proteinase inhibitors, and ProbucoI; and compounds which promote healing and re-endothelialization such as VEGF, Estradiols, antibodies, NO donors, and BCP671.

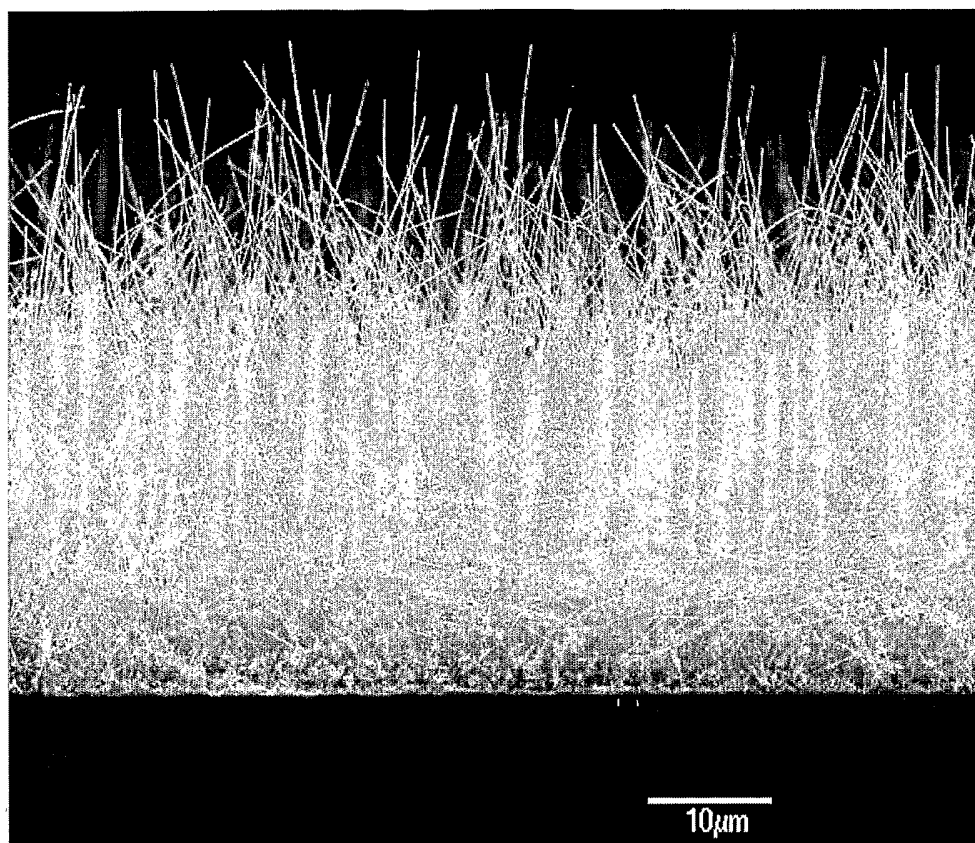
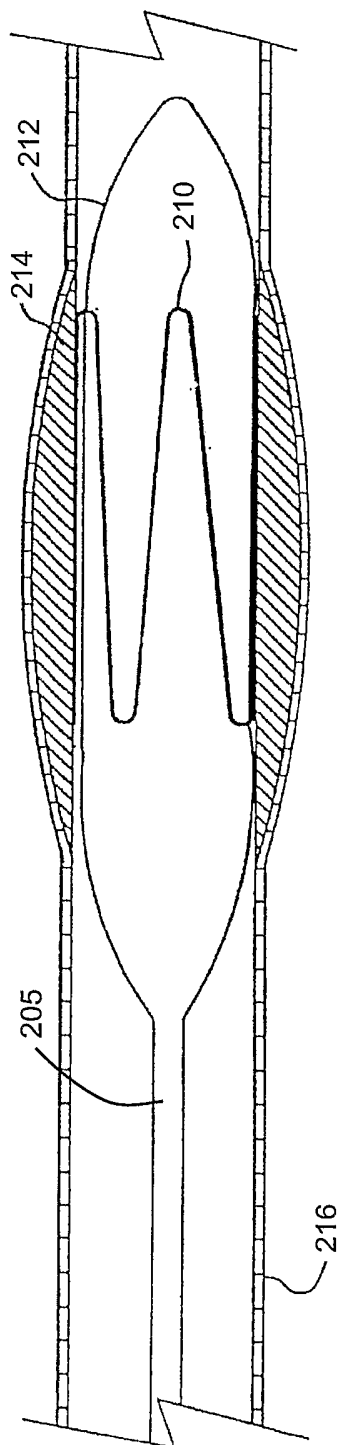
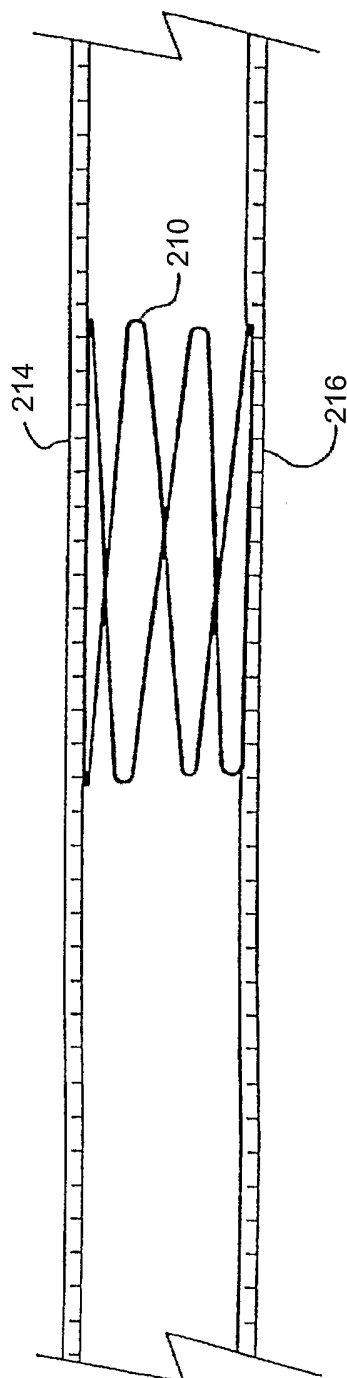


FIG. 1



(PRIOR ART) FIG. 2A



(PRIOR ART) FIG. 2B

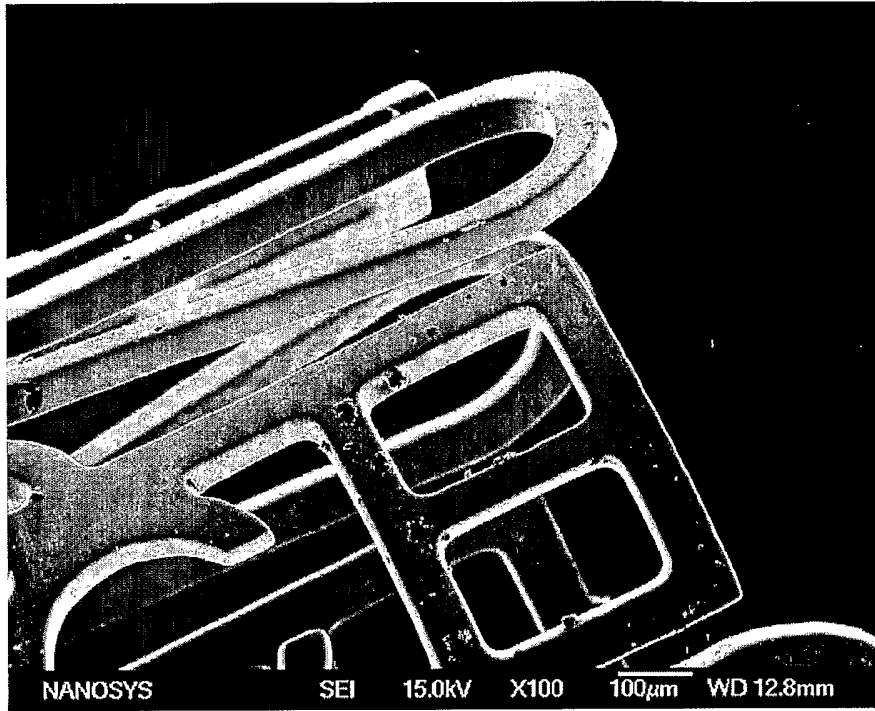


FIG. 2C

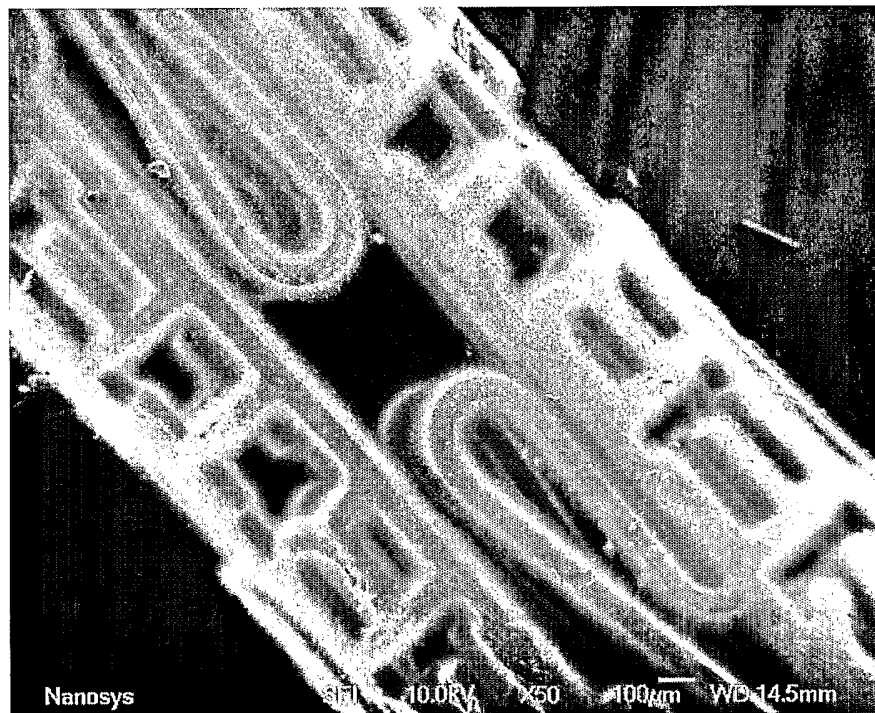


FIG. 2D

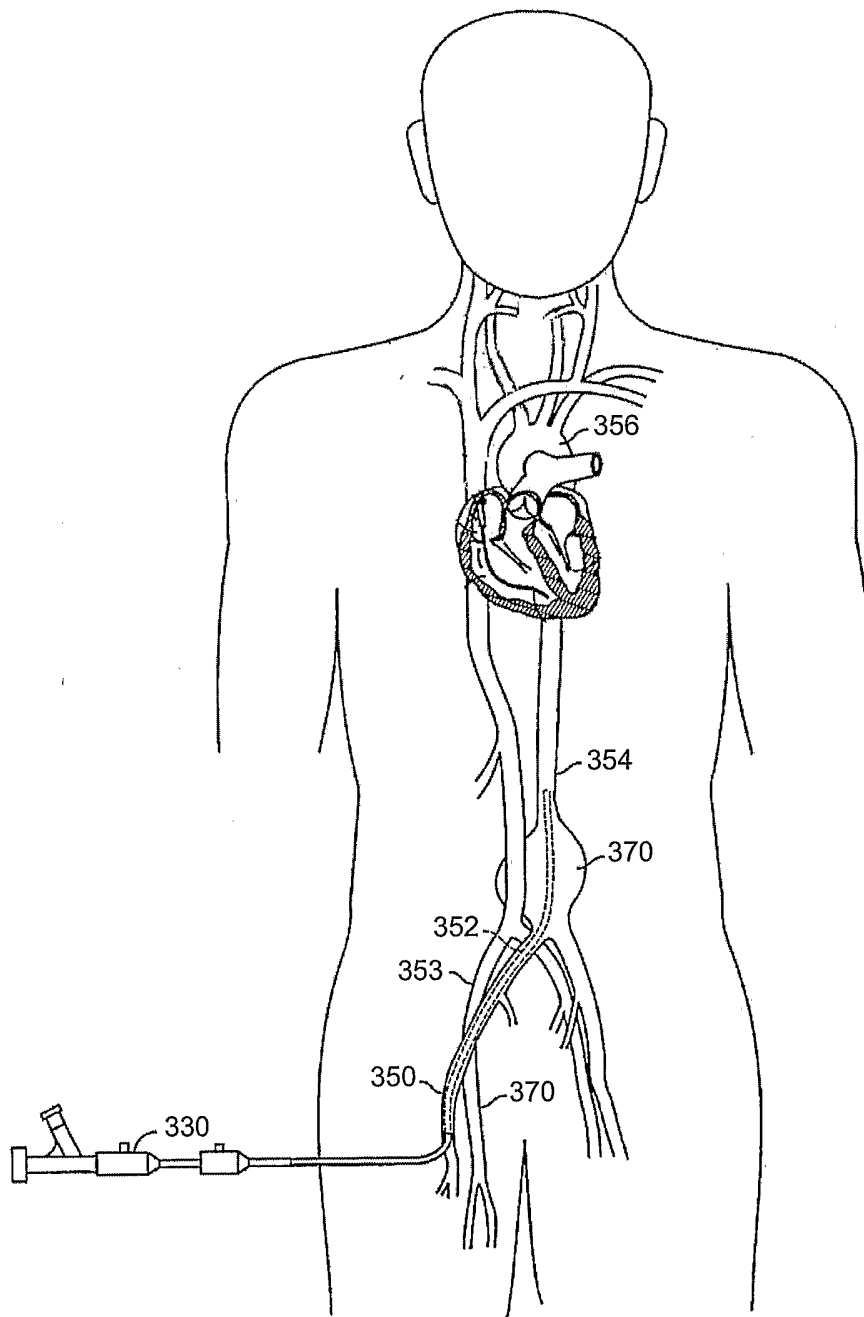


FIG. 3A

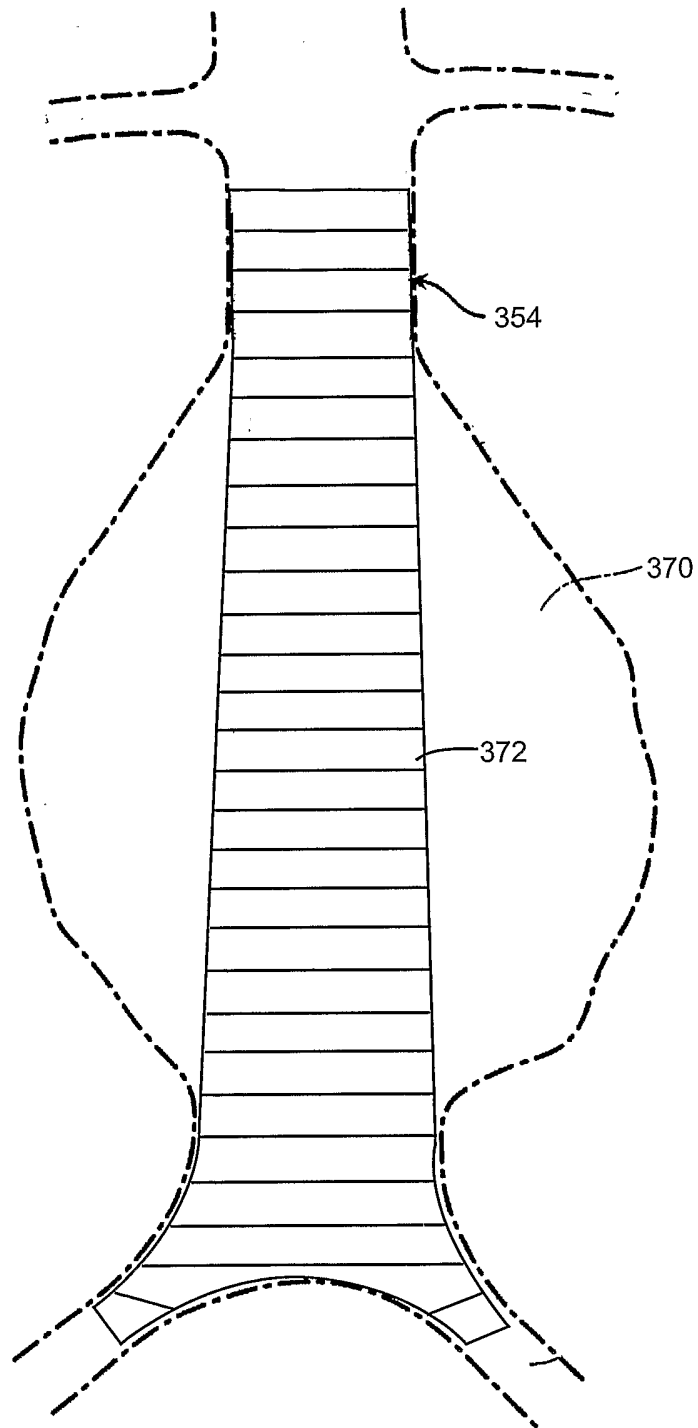


FIG. 3B

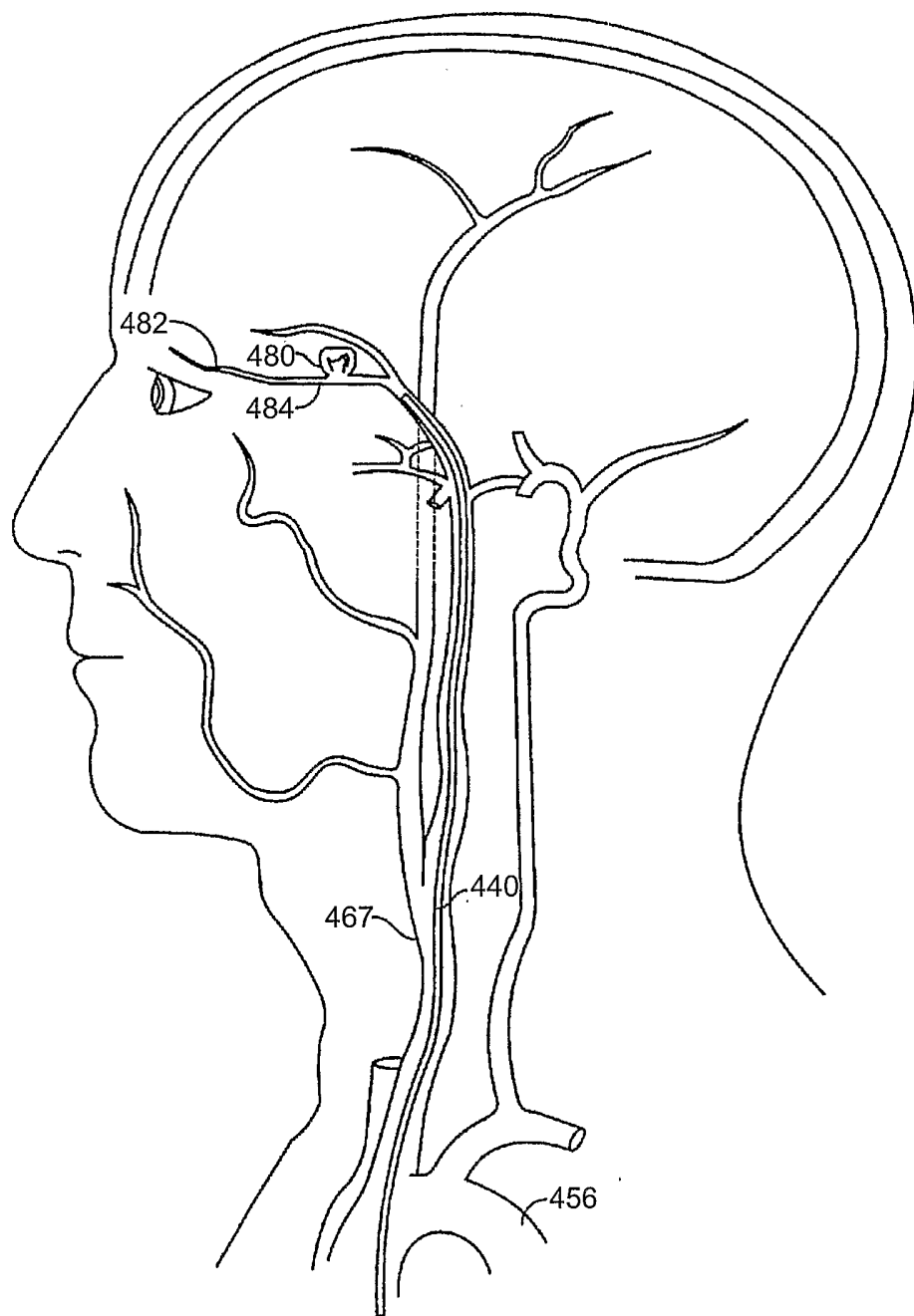


FIG. 4A



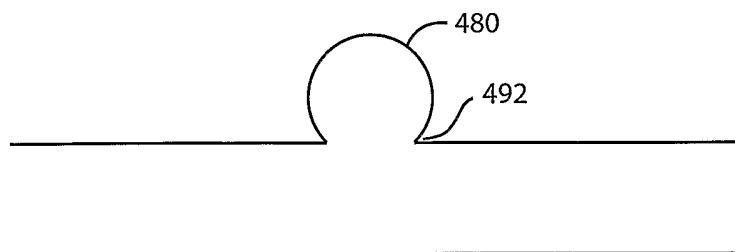


FIG. 4B

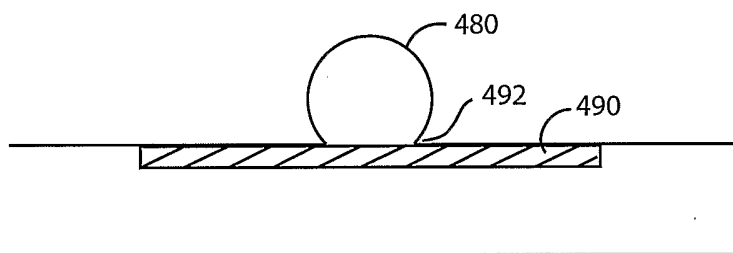


FIG. 4C



FIG. 4D

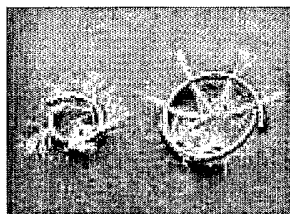


FIG. 4E

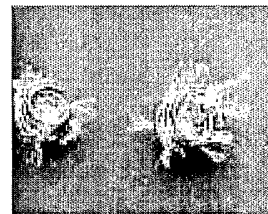


FIG. 4F

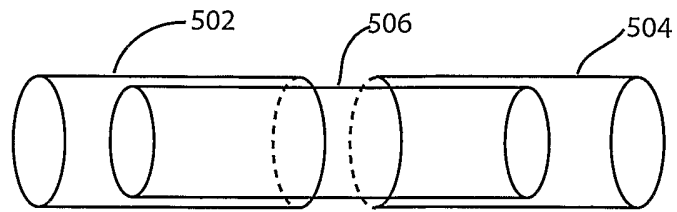


FIG. 5A

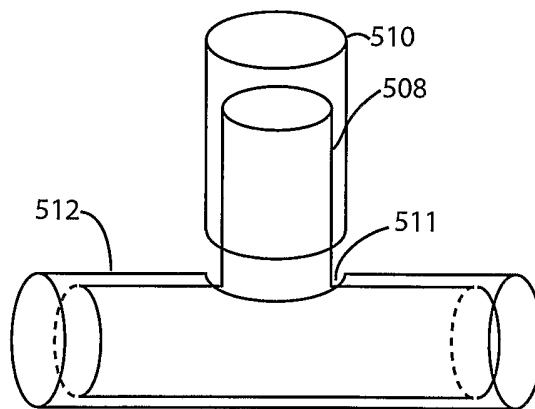


FIG. 5B

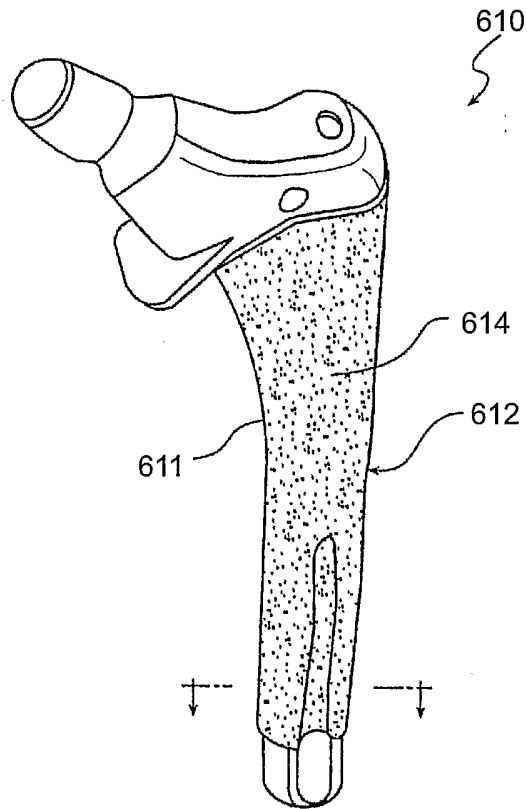


FIG. 6A

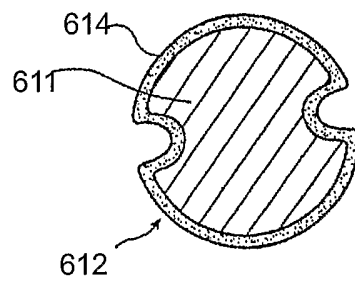
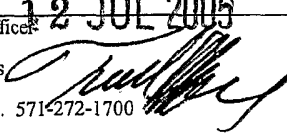


FIG. 6B

**INTERNATIONAL SEARCH REPORT**

International application No.  
PCT/US05/06807

<p><b>A. CLASSIFICATION OF SUBJECT MATTER</b>                  IPC(7) : A61F 2/06                  US CL : 623/1.1-1.22; 977/DIG1                  According to International Patent Classification (IPC) or to both national classification and IPC</p>																							
<p><b>B. FIELDS SEARCHED</b>                  Minimum documentation searched (classification system followed by classification symbols)                  U.S. : 623/1.1-1.22; 977/DIG1                  Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched                  Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)</p>																							
<p><b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b></p> <table border="1"> <thead> <tr> <th>Category *</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X</td> <td>US 2003/0195611 A1 (GREENHALGH et al.) 16 October 2003 (16.10.2003), Abstract, [0010-0018, 0076, 0144].</td> <td>1-23, 49-58</td> </tr> <tr> <td>X</td> <td>WO 00/44357 (LEONHARDT) 03 August 2000 (03.08.2000), Abstract</td> <td>1-23, 49-58</td> </tr> <tr> <td>X</td> <td>WO 01/26702 A2 (SMITH et al.) 19 April 2001 (19.04.2001), Abstract, p. 1, lines 14-19, p. 2, lines 25-32, p. 3, lines 1-6, p. 4, lines 1-3</td> <td>1-23, 49-58</td> </tr> <tr> <td>A</td> <td>US 5,634,946 (SLEPIAN) 03 June 1997 (03.06.1997), the whole document</td> <td></td> </tr> <tr> <td>A</td> <td>US 6,515,009 B1 (KUNZ et al.) 04 February 2003 (04.02.2003), the whole document.</td> <td></td> </tr> <tr> <td>A</td> <td>US 6,656,966 B2 (GARVEY et al.) 02 December 2003 (02.12.2003), the whole document.</td> <td></td> </tr> </tbody> </table>			Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	US 2003/0195611 A1 (GREENHALGH et al.) 16 October 2003 (16.10.2003), Abstract, [0010-0018, 0076, 0144].	1-23, 49-58	X	WO 00/44357 (LEONHARDT) 03 August 2000 (03.08.2000), Abstract	1-23, 49-58	X	WO 01/26702 A2 (SMITH et al.) 19 April 2001 (19.04.2001), Abstract, p. 1, lines 14-19, p. 2, lines 25-32, p. 3, lines 1-6, p. 4, lines 1-3	1-23, 49-58	A	US 5,634,946 (SLEPIAN) 03 June 1997 (03.06.1997), the whole document		A	US 6,515,009 B1 (KUNZ et al.) 04 February 2003 (04.02.2003), the whole document.		A	US 6,656,966 B2 (GARVEY et al.) 02 December 2003 (02.12.2003), the whole document.	
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A	US 6,656,966 B2 (GARVEY et al.) 02 December 2003 (02.12.2003), the whole document.																						
<p><input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.</p>																							
<p>* Special categories of cited documents:</p> <table border="0"> <tr> <td>"A" document defining the general state of the art which is not considered to be of particular relevance</td> <td>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td> </tr> <tr> <td>"E" earlier application or patent published on or after the international filing date</td> <td>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td> </tr> <tr> <td>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td> <td>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td> </tr> <tr> <td>"O" document referring to an oral disclosure, use, exhibition or other means</td> <td>"&amp;" document member of the same patent family</td> </tr> <tr> <td>"P" document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </table>			"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	"P" document published prior to the international filing date but later than the priority date claimed												
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"P" document published prior to the international filing date but later than the priority date claimed																							
<p>Date of the actual completion of the international search 22 June 2005 (22.06.2005)</p>		<p>Date of mailing of the international search report 12 JUL 2005</p>																					
<p>Name and mailing address of the ISA/US                  Mail Stop PCT, Attn: ISA/US                  Commissioner for Patents                  P.O. Box 1450                  Alexandria, Virginia 22313-1450                  Facsimile No. (703) 305-3230</p>		<p>Authorized officer                  Terrel Morris                   Telephone No. 571-272-1700</p>																					

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/06807

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:  
Please See Continuation Sheet

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: 1-23 and 49-58
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**  The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US05/06807

### BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

- Group I. Claims 1-23, drawn to a medical device with nanoscale components
- Group II. Claims 24-48, drawn to an aneurysm repair device
- Group III. Claims 49-58, drawn to an implantable orthopedic device
- Group IV. Claims 59-64, drawn to a bioengineered scaffold for nerve regeneration
- Group V. Claim 65, drawn to an implant for uterus or fallopian tubes
- Group VI. Claims 66-68, drawn to a nonorthombic device
- Group VII. Claims 69-81, drawn to a method of drug delivery

The inventions listed as Groups I-VII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The special technical feature of Groups I-VII, a medical device comprising a body structure having one or more surfaces having a plurality of nanostructured components associated therewith, does not contribute over the prior art. Erlanger et al. (WO03/007881) teach the use of antibodies attached to nanotubes affixed to substrates.