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(54) Titre : SYSTEME POUR GENERER UN ECOULEMENT DE FLUIDE DANS LES TISSUS NERVEUX
 (54) Title: SYSTEM FOR PROVIDING FLUID FLOW TO NERVE TISSUES

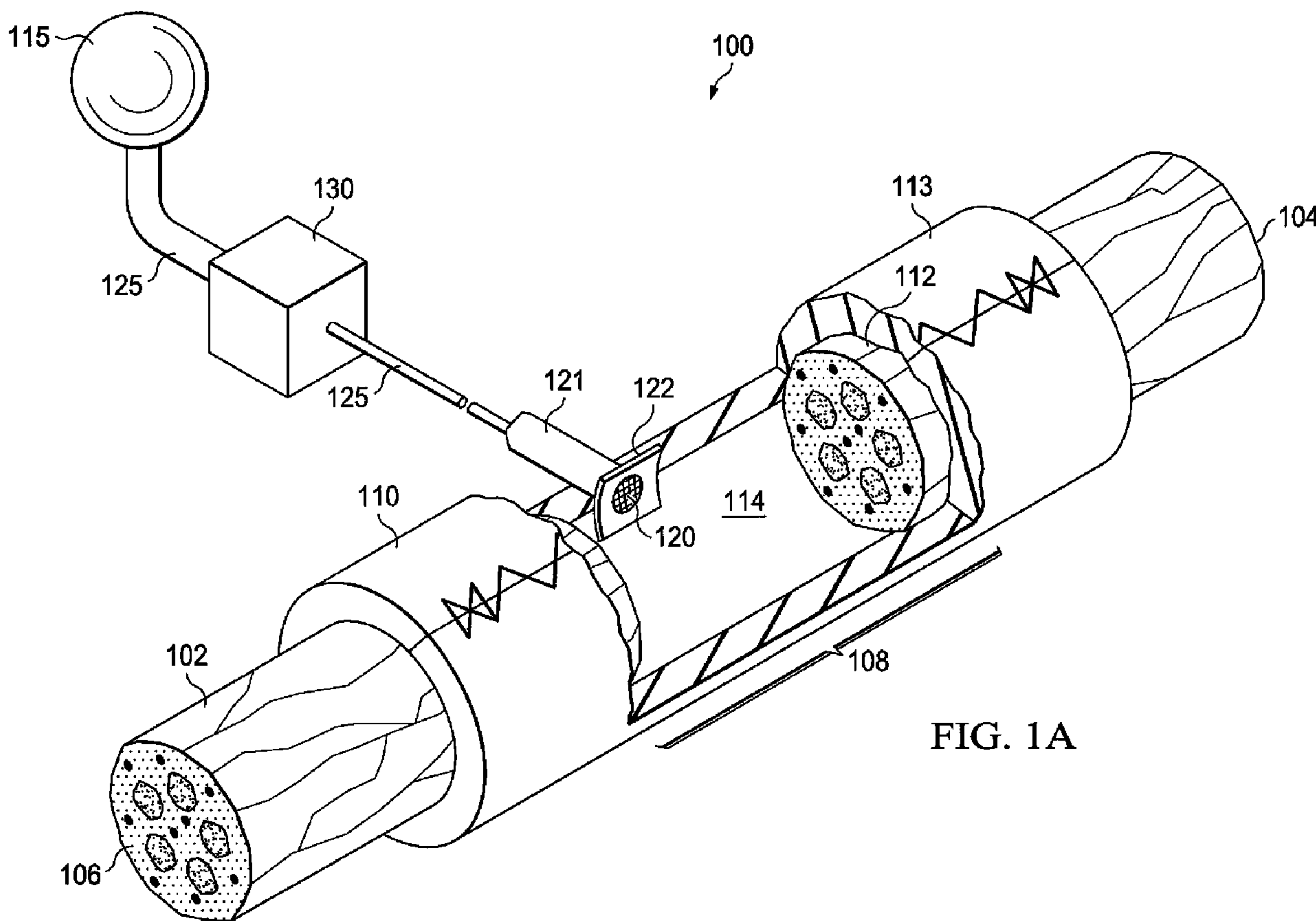


FIG. 1A

(57) Abrégé/Abstract:

Provided is an apparatus that includes a nerve conduit, a manifold and a support structure for providing a reduced pressure. Also provided is a system that includes a source of reduced pressure, a nerve conduit, a manifold, a support structure and a conduit for

(57) **Abrégé(suite)/Abstract(continued):**

providing fluid communication between the manifold support and the source of reduced pressure. Additionally provided is a method that includes implanting the above nerve conduit, manifold and support structure at a site of damaged nerve tissue and applying a reduced pressure to the manifold thereby stimulating repair or regrowth of nerve tissue.

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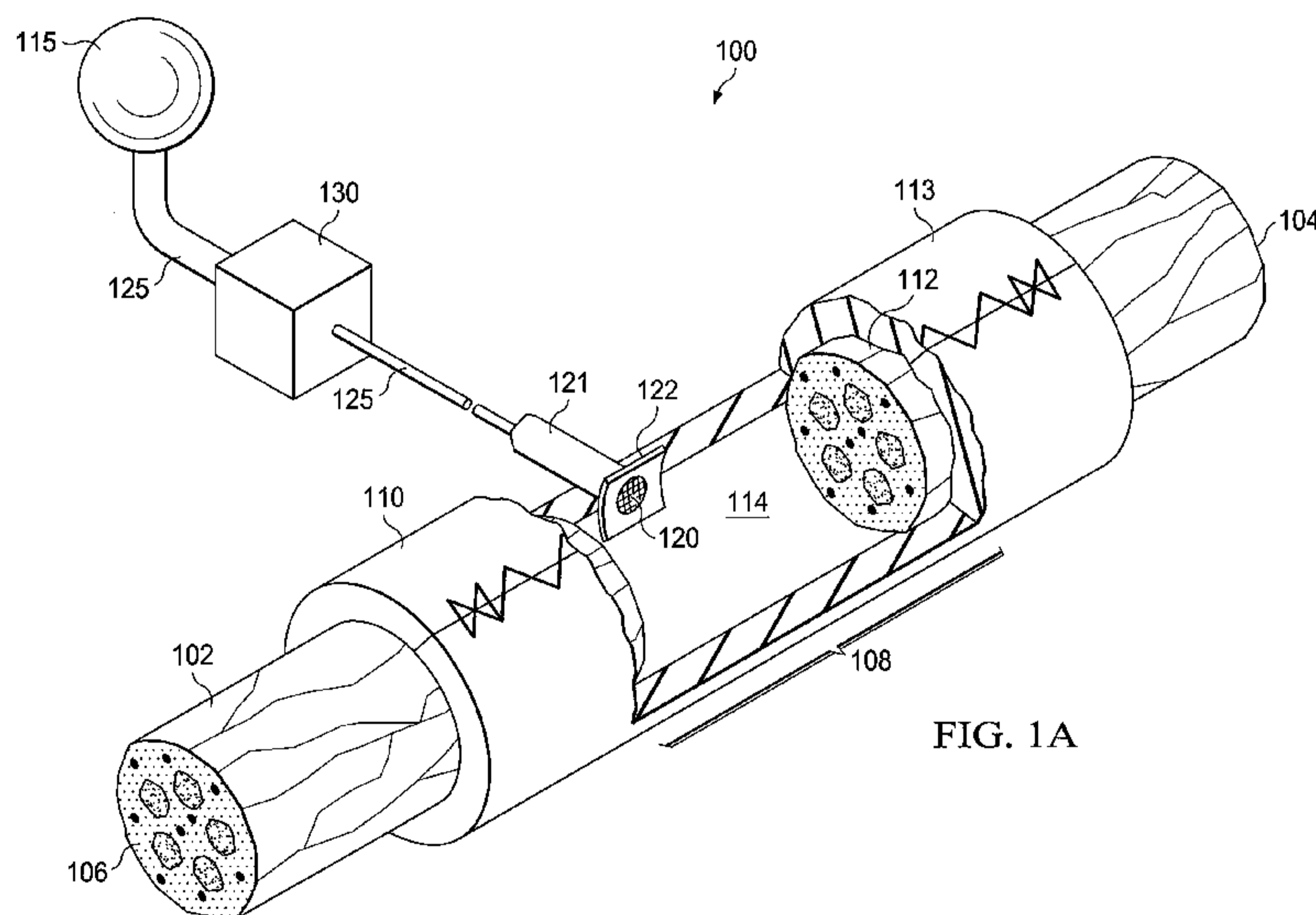


FIG. 1A

(57) Abstract: Provided is an apparatus that includes a nerve conduit, a manifold and a support structure for providing a reduced pressure. Also provided is a system that includes a source of reduced pressure, a nerve conduit, a manifold, a support structure and a conduit for providing fluid communication between the manifold support and the source of reduced pressure. Additionally provided is a method that includes implanting the above nerve conduit, manifold and support structure at a site of damaged nerve tissue and applying a reduced pressure to the manifold thereby stimulating repair or regrowth of nerve tissue.

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SYSTEM FOR PROVIDING FLUID FLOW TO NERVE TISSUES

[0001] This application claims priority to U.S. Provisional Application Nos. 61/142,053 and 61/142,065, each filed on December 31, 2008. This application also claims
5 priority to U.S. Provisional Application No. 61/234,692, filed on August 18, 2009 and U.S. Provisional Application No. 61/238,770, filed on September 1, 2009. Each of the foregoing applications is incorporated herein by reference in their entirety.

BACKGROUND

10 1. Field of the Invention

[0002] The present application relates generally to tissue engineering and in particular to apparatuses and systems suitable for use in treatment of damaged nerve tissue.

15 2. Description of Related Art

[0003] Clinical studies and practice have shown that providing a reduced pressure in proximity to a tissue site augments and accelerates the growth of new tissue at the tissue site. The applications of this phenomenon are numerous, but application of reduced pressure has
20 been particularly successful in treating wounds. This treatment (frequently referred to in the medical community as “negative pressure wound therapy,” “reduced pressure therapy,” or “vacuum therapy”) provides a number of benefits, including faster healing and increased formation of granulation tissue. Typically, reduced pressure has been applied to tissue through a porous pad or other manifold device. The porous pad contains pores that are capable of
25 distributing reduced pressure to the tissue and channeling fluids that are drawn from the tissue. The porous pad often is incorporated into a dressing having other components that facilitate treatment. A scaffold can also be placed into a defect to support tissue growth into the defect. The scaffold is usually bioabsorbable, leaving new tissue in its place.

[0004] Scaffolds for reduced pressure treatment are described in, *e.g.*, WO08/091521,
30 WO07/092397, WO07/196590, WO07/106594. The adequacy of current scaffolds for reduced pressure treatment can be evaluated in light of current knowledge of wound healing. Injury to body tissues results in a wound healing response with sequential stages of healing that include hemostasis (seconds to hours), inflammation (hours to days), repair (days to weeks), and

remodeling (weeks to months). A high level of homology exists across most tissue types with regards to the early phases of the wound healing process. However, the stages of healing for various tissues begin to diverge as time passes, with the involvement of different types of growth factors, cytokines, and cells. The later stages of the wound healing response are
5 dependent upon the previous stages, with increasing complexity in the temporal patterning of and interrelationships between each component of the response.

[0005] Strategies to facilitate normal repair, regeneration, and restoration of function for damaged tissues have focused on methods to support and augment particular steps within this healing response, especially the latter aspects of it. To this end, growth factors, cytokines,
10 extracellular matrix (ECM) analogs, exogenous cells and various scaffolding technologies have been applied alone or in combination with one another. Although some level of success has been achieved using this approach, several key challenges remain. One main challenge is that the timing and coordinated influence of each cytokine and growth factor within the wound healing response complicate the ability to add individual exogenous factors at the proper time
15 and in the correct coordination pattern. The introduction of exogenous cells also faces additional complications due to their potential immunogenicity as well as difficulties in maintaining cell viability.

[0006] Synthetic and biologic scaffolds have been utilized to provide three-dimensional frameworks for augmenting endogenous cell attachment, migration, and
20 colonization. To date nearly all scaffolds have been designed with the idea that they can be made to work with the biology. Traditional scaffolding technologies, however, rely on the passive influx of endogenous proteins, cytokines, growth factors, and cells into the interstitium of the porous scaffold. As such, the colonization of endogenous cells into the scaffold is limited by the distance away from vascular elements, which provide nutrient support within a
25 diffusion limit of the scaffold, regardless of tissue type. In addition, the scaffolds can also elicit an immunogenic or foreign body response that leads to an elongated repair process and formation of a fibrous capsule around the implant. Taken together, these complications can all lead to less than functional tissue regeneration at the injury site.

[0007] It would therefore be advantageous to provide additional systems for the repair
30 and remodeling of specialized tissues. The present invention provides such systems.

SUMMARY

[0008] The apparatuses, systems and methods of the illustrative embodiments described herein provide active guidance of nerve tissue repair and regeneration through an implanted manifold and nerve conduit. In one embodiment, an apparatus for providing
5 reduced pressure therapy and facilitating growth of nerve tissue in a patient is provided that includes a nerve conduit, a manifold and manifold support structure adaptable for implantation at a damaged nerve site, wherein the manifold provides and distributes a reduced pressure at the site of damaged nerve tissue. A manifold according to the invention may also serve as or
10 be coupled to a scaffold which further distributes reduced pressure and provides a structural matrix for growth of the tissue.

[0009] In certain embodiments an apparatus according to the invention comprises a nerve conduit, a manifold and at least a first support structure. A nerve conduit, in certain aspects, comprises a generally tubular shape having walls including an exterior wall and a luminal wall surrounding the tissue site to contain fluids within a luminal space between the
15 tissue site and the luminal wall. In some instances, a manifold according to the invention comprises a generally cylindrical body having surfaces including a side wall surface and two end wall surfaces, a first end wall surface of the two end wall surfaces for receiving reduced pressure, a fluid contact surface including a first portion of the surfaces of the cylindrical body other than the first end wall surface for fluid communication with the luminal space, and a
20 support surface including a second portion of the surface of the cylindrical body other than the first end wall surface and the fluid contact surface. A support structure according to the invention may comprise a generally tubular shape for enclosing the support surface, a first end portion for coupling the first end wall surface to the reduced-pressure source, and a second end portion for coupling the manifold to the nerve conduit in a generally radial direction with
25 respect to the luminal wall.

[0010] In another embodiment, a system for providing reduced pressure therapy and facilitating growth of nerve tissue in a patient is provided that comprises a source of reduced pressure for supplying reduced pressure and an apparatus including a nerve conduit, manifold and support structure adaptable for implantation at the tissue site, where the manifold is in
30 fluid communication with the source of reduced pressure. In a further embodiment, such a system may further comprise a canister for fluid capture and/or a valve for control of reduced pressure in fluid communication with, and positioned between, the manifold and the reduced pressure source. In still a further embodiment, a system according to the invention further

comprises a fluid source in fluid communication with the manifold and the damaged nerve tissue.

[0011] In still a further embodiment, a method of providing reduced pressure therapy and facilitating growth of nerve tissue at site of nerve tissue damage in a patient is provided that includes implanting a nerve conduit, manifold and support structure at the tissue site, where the manifold provides a reduced pressure to the damaged nerve tissue. The manifold may also serve as or be coupled to a scaffold material, wherein the scaffold material provides a structural matrix for the growth of the nerve tissue. In certain embodiments, the method further comprises providing a manifold in fluid communication with a fluid source, wherein the fluid source may be used to deliver a fluid to the manifold and the damaged nerve tissue. In yet a further embodiment, the fluid source may comprise a fluid comprising one or more bioactive compounds including, but not limited to, an antibiotic, an antiviral, a cytokine, a chemokine, an antibody and a growth factor.

[0012] Other objects, features, and advantages of the illustrative embodiments will become apparent with reference to the drawings and detailed description that follow.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] FIG. 1A-B is a schematic, perspective view of a reduced pressure treatment system for repairing a severed (FIG. 1A) or a pinched nerve (FIG. 1B) including a nerve conduit and a first embodiment of a manifold with a section of the nerve conduit removed to show the manifold;

[0014] FIG. 2 is a schematic of a reduced pressure treatment system for repairing a severed or partially severed nerve including a nerve conduit and a second embodiment of a manifold with a section of the nerve conduit removed to show the manifold;

[0015] FIG. 3 is a schematic of a reduced pressure treatment system for repairing a severed or partially severed nerve including a nerve conduit and a third embodiment of a manifold with a section of the nerve conduit removed to show the manifold; and

[0016] FIG. 4 is a schematic, perspective view of the system shown in FIGS. 1-3 showing the nerve conduit enclosing the damaged nerve; and

[0017] FIG. 5 is a schematic view of a fluid control system for the system shown in FIGS. 1-3.

DETAILED DESCRIPTION

[0018] In the following detailed description of the illustrative embodiments, reference is made to the accompanying drawings that form a part hereof. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention, and it is understood that other embodiments may be utilized and that logical structural, mechanical, electrical, and chemical changes may be made without departing from the spirit or scope of the invention. To avoid detail not necessary to enable those skilled in the art to practice the embodiments described herein, the description may omit certain information known to those skilled in the art. The following detailed description is, therefore, not to be taken in a limiting sense, and the scope of the illustrative embodiments are defined only by the appended claims.

[0019] Referring to FIG. 1A-B, a reduced pressure therapy system 100 for applying reduced pressure at a tissue site in the body of a patient to repair a defect such as, for example, a damaged nerve is disclosed. The damaged nerve may have been pinched, partially disconnected or severed, or partially degenerated as a result of disease. For example, the damaged nerve in FIG. 1A is a severed nerve 102 having a proximal segment 104 and a distal segment 106 relative to the central nervous system (CNS) of the patient. FIG. 1B illustrates a reduced pressure therapy system and in this case the damaged nerve is a pinched nerve 103 that has been damaged at a nerve damage site 108. In this case, the nerve has been pinched, partially severed or partially degenerated, but has not been completely severed. The nerve may be branched or unbranched at the nerve damage site 108. The term “nerve damage site” as used herein refers to a wound or defect located on or within any nerve tissue, including, but not limited to, a disconnected or partially disconnected nerve, a degenerated or partially degenerated nerve, and a compressed or pinched nerve. For example, reduced pressure tissue treatment may be used to enhance repair or regrowth of existing nerve tissue or to facilitate growth or grafted or transplanted nerve tissue and/or cells.

[0020] The reduced pressure therapy system 100 comprises a nerve conduit 110 that surrounds the pinched nerve 103 at the nerve damage site 108 with a section of the nerve conduit 110 removed to show the nerve damage site 108. The nerve conduit 110 is substantially tubular in shape and closes the nerve damage site 108 and a portion of the proximal segment 104 and the distal segment 106 that has not been damaged. The nerve conduit 110 has an exterior surface 113 and an inner surface 112 that forms a nerve gap 114 with the surface of the nerve damage site 108, *i.e.*, a luminal space between the inner surface 112 of the nerve conduit 110 and the surface of the nerve damage site 108. The reduced

pressure therapy system 100 also comprises a reduced pressure source 115 for providing a reduced pressure and a manifold 120 fluidly coupled to the pressure source 115 via a first conduit 125. The manifold 120 is contained within a manifold chamber 121 having a flange 122 extending from one end of the manifold chamber 121 for securing the manifold chamber 121 to the nerve conduit 110. The other end of the manifold chamber 121 is connected to the first conduit 125 so that the manifold 120 is held in fluid communication with the first conduit 125. The manifold chamber 121 may be constructed of any biocompatible material that is substantially impermeable to preserve the manifold's 120 fluid communication between the nerve gap 114 and the first conduit 125. The manifold chamber 121 is secured to the nerve conduit 110 by the flange 122 such that the manifold 120 is in fluid communication with the nerve gap 114 surrounding the surface of the nerve damage site 108, but positioned outside of the nerve gap 114. In certain aspects, the flange 122 is secured to the nerve conduit 110 with an adhesive. Moreover, in some applications, the flange 122 is detachably secured to the nerve conduit 110 such that the flange 122 and manifold chamber 121 can be removed from the nerve conduit 110 after reduced pressure therapy is complete. In one embodiment, the manifold 120 extends through the wall of the nerve conduit 110 in direct fluid contact with the nerve gap 114. In another embodiment, where the nerve conduit 110 is porous, the flange 122 is secured to the exterior surface 113 of the nerve conduit 110 so that the manifold 120 is positioned adjacent to the exterior surface 113 to be in fluid communication with the nerve gap 114 via the porous wall of the nerve conduit 110.

[0021] The manifold 120 may have a variety of shapes depending on the type of nerve damage, and depending on how the manifold is positioned in fluid contact with the nerve gap 114 around the nerve damage site 108. The manifold may also be coupled with a flange 122 that is in turn coupled to the exterior surface of the nerve conduit 113. The flange 122 forms a seal between the exterior surface of the nerve conduit 113 and the manifold 120 to prevent reduced pressure from being applied outside of the nerve conduit 110. The lumen of the nerve conduit and the nerve gap 114 may also contain a scaffold material (not shown) that provides a structure for tissue growth and repair. The reduced pressure therapy system 100 further comprises a canister 130 fluidly coupled between the reduced pressure source 115 and the manifold 120 via the conduit 125 to collect bodily fluids such as blood or exudate that are drawn from the nerve gap 114. In one embodiment, the reduced pressure source 115 and the canister 130 are integrated into a single housing structure.

[0022] As used herein, the term “coupled” includes direct coupling or indirect coupling via a separate object. The term “coupled” also encompasses two or more components that are continuous with one another by virtue of each of the components formed from the same piece of material. Also, the term “coupled” may include chemical, mechanical, thermal, or electrical coupling. Fluid coupling means that fluid is in communication with designated parts or locations.

[0023] In the context of this specification, the term “reduced pressure” generally refers to a pressure that is less than the ambient pressure at a tissue site that is subjected to treatment. In most cases, this reduced pressure will be less than the atmospheric pressure of the location at which the patient is located. Although the terms “vacuum” and “negative pressure” may be used to describe the pressure applied to the tissue site, the actual pressure applied to the tissue site may be significantly greater than the pressure normally associated with a complete vacuum. Consistent with this nomenclature, an increase in reduced pressure or vacuum pressure refers to a relative reduction of absolute pressure, while a decrease in reduced pressure or vacuum pressure refers to a relative increase of absolute pressure. The term “ $-\Delta p$ ” means change in reduced pressure. As used herein, a greater (*i.e.*, more negative) $-\Delta p$ means increased negative pressure (*i.e.*, a greater change in pressure from ambient pressure). Reduced pressure treatment typically applies reduced pressure at -5 mm Hg to -500 mm Hg, more usually -5 to -300 mm Hg, including but not limited to -50, -125 or -175 mm Hg. Reduced pressure may be constant at a particular pressure level or may be varied over time. For example, reduced pressure may be applied and stopped periodically or ramped-up or -down over time.

[0024] As indicated above, a nerve damage site may be a wound or defect located on or within any nerve tissue including, for example, a completely severed nerve 102 having a proximal segment 104 and a distal segment 106 relative to the CNS of the patient as shown in FIG. 2. The severed nerve 102 has been damaged at a nerve damage site 108 that has been completely severed. Another reduced pressure therapy system 200 for applying reduced pressure at the nerve damaged site 108 comprises similar components as the reduced pressure therapy system 100 as indicated by the same reference numerals. The reduced pressure therapy 200 comprises the nerve conduit 110 that surrounds the nerve damage site 108 and the severed ends of the severed nerve 102. The inner surface 112 of the nerve conduit 110 forms a nerve gap 114 between the severed ends of the severed nerve 102 within the nerve damage site 108, *i.e.*, a luminal space between the inner surface 112 of the nerve conduit 110 and the

surface of the nerve damage site 108. The reduced pressure therapy system 200 also comprises a manifold 220 fluidly coupled to the pressure source 115 via the first conduit 125 and to the nerve gap 114. The manifold 220 is also partially contained with-in a manifold chamber 221 having a flange 222 for securing the manifold chamber 221 to the nerve conduit 110 and otherwise the same as the manifold chamber 121. Unlike the manifold 120, the manifold 220 comprises a manifold protrusion 225 that extends into the nerve gap 114. The manifold 220 and manifold protrusion 225 may have a variety of shapes depending on the type of nerve damage, and depending on how the manifold is positioned in fluid contact with the nerve gap 114 around the nerve damage site 108. The flange 222 forms a seal between the exterior surface of the nerve conduit 113 and the manifold chamber 221 to prevent reduced pressure from being applied outside of the nerve conduit 110. In certain aspects, the flange 222 is secured to the nerve conduit 110 with an adhesive. Moreover, in some applications, the flange 222 is detachably secured to the nerve conduit 110 such that the flange 222 and manifold chamber 221 can be removed from the nerve conduit 110 after reduced pressure therapy is complete. The manifold protrusion 225 may be formed of a material so that the manifold protrusion also functions as a scaffold that provides a structure for tissue growth and repair. The reduced pressure therapy system 200 further comprises a canister 130 fluidly coupled between the reduced pressure source 115 and the manifold 220 via the conduit 125 to collect bodily fluids such as blood or exudate that are drawn from the nerve gap 114. In one embodiment, the reduced pressure source 115 and the canister 130 are integrated into a single housing structure.

[0025] Still another reduced pressure therapy system 300 for applying reduced pressure at the nerve damaged site 108 is illustrated in FIG. 3. A completely severed nerve 102 is shown having a proximal segment 104 and a distal segment 106 relative to the CNS. The severed nerve 102 has been damaged at a nerve damage site 108 that has been completely severed. The reduced pressure therapy 300 comprises the nerve conduit 110 that surrounds the nerve damage site 108 and the severed ends of the severed nerve 102. The inner surface 112 of the nerve conduit 110 forms a nerve gap 114 between the severed ends of the severed nerve 102 within the nerve damage site 108, *i.e.*, a luminal space between the inner surface 112 of the nerve conduit 110 and the surface of the nerve damage site 108. The reduced pressure therapy system 300 also comprises a manifold 320 fluidly coupled to the pressure source 115 via the first conduit 125 and to the nerve gap 114. The manifold 320 is also partially contained with-in manifold chambers 321 each having a flange 322 for securing the manifold

chambers 321 to the nerve conduit 110 and otherwise the same as the manifold chamber 121 and 221. Unlike the manifold 220, the manifold 320 extends into and through the nerve gap 114 and is secured on both sides of the nerve conduit 110 by a manifold chamber 321 and flange 322. The manifold 320 may have a variety of shapes depending on the type of nerve damage, and depending on how the manifold is positioned in fluid contact with the nerve gap 114 around the nerve damage site 108. The flanges 322 form a seal between the exterior surface of the nerve conduit 113 and the manifold chambers 321 to prevent reduced pressure from being applied outside of the nerve conduit 110. In certain aspects, the flanges 322 are secured to the nerve conduit 110 with adhesive. In some applications, one or both flanges 322 are detachably secured to the nerve conduit 110 such that the flange(s) 322 and manifold chamber(s) 321 can be removed from the nerve conduit 110 after reduced pressure therapy is complete. The manifold 320 may be formed of material so that the manifold also functions as a scaffold that provides a structure for tissue growth and repair. The reduced pressure therapy system 300 further comprises a canister 130 fluidly coupled between the reduced pressure source 115 and the manifold 320 via the conduit 125 to collect bodily fluids such as blood or exudate that are drawn from the nerve gap 114. In one embodiment, the reduced pressure source 115 and the canister 130 are integrated into a single housing structure. The reduced pressure therapy system 300 further comprises a fluid source 150 in fluid communication with the manifold 320 via a second conduit 325. Accordingly, in a certain aspect fluid flows from the fluid source 150 into the manifold 320 and the nerve gap 114 and ultimately is captured by the canister 130. Fluid flow through the manifold transversing the site of nerve damage 108 may help to prevent clogging of the manifold.

[0026] As indicated above, the nerve conduit 110 is shown in FIGS. 1-3 with a section removed, but shown as completely surrounding the nerve damage sites 108 as a closed nerve conduit 410 in FIG. 4. After the manifolds 120, 220, 320 are inserted in the nerve gap 114 or attached to the nerve conduit 110 adjacent to the nerve gap 114, the nerve conduit 110 may be sealed by utilizing one or more stitches 415 or any other fastening device known in the art. The nerve conduit 110 may be composed of a bioabsorbable or a bioinert material. Materials that may be used for nerve conduits include, without limitation, polylactic acid (PLA), polyglycolic acid (PGA), polylactide-co-glycolide (PLGA), polyvinylpyrrolidone, polycaprolactone, polycarbonates, polyfumarates, caprolactones, polyamides, polysaccharides (including alginates (*e.g.*, calcium alginate) and chitosan), hyaluronic acid, polyhydroxybutyrate, polyhydroxyvalerate, polydioxanone, polyorthoesters, polyethylene

glycols, poloxamers, polyphosphazenes, polyanhydrides, polyamino acids, polyacetals, polycyanoacrylates, polyurethanes, polyacrylates, ethylene-vinyl acetate polymers and other acyl substituted cellulose acetates and derivatives thereof, polystyrenes, polyvinyl chloride, polyvinyl fluoride, poly(vinylimidazole), chlorosulphonated polyolefins, polyethylene oxide, polyvinyl alcohol, Teflon[®], and nylon. In certain aspects, biological (*e.g.*, purified or recombinant) materials may be used form nerve conduits including, but not limited to, fibrin, fibronectin or collagen (*e.g.*, DURAMATRIX[™]).

[0027] A nerve conduit 110 may be an unbroken substantially tubular structure fitted across a gap between a proximal and distal nerve stump such as depicted in FIG. 3. Examples of such substantially tubular nerve conduits, also referred to as nerve guides, include without limitation NEURAGEN[®] and NEUROFLEX[™] collagen conduits. A nerve conduit may also be formed from a wrap that is positioned around a disconnected or damaged (*e.g.*, pinched) nerve and sealed with a closure, such as a suture. Specific examples of wrap-type nerve conduits include, without limitation, NEUROMEND[™] and NEURAWRAP[™] collagen conduits. In certain aspects, the nerve conduit is made of a material that encloses the damaged nerve, so as to exclude infiltration of non-nerve cells, such as glia. In some embodiments, the nerve conduit material is permeable, thereby allowing fluid and protein factors to diffuse through the conduit. For example, the pores in a nerve conduit may be sufficiently small so as to exclude the entry of cells into the conduit lumen (*e.g.*, pores having an interior diameter or average interior diameter of between about 5 μm and 50 μm , 10 μm and 30 μm or 10 μm and 20 μm). Thus, when reduced pressure is applied to the interior of the conduit fluid and proteins may be drawn to the lumen of the conduit by the pressure gradient. The skilled artisan will recognize that the dimensions of the conduit may be adjusted for any particular nerve application. Generally, the conduits comprise an internal diameter of less than about 6.0 mm, such as about 5, 4, 3, 2.5 or 2 mm.

[0028] Referring to FIG. 5, the reduced pressure therapy system 100, 200 or 300 may further comprise a pressure sensor 140 operably connected to the first conduit 125 to measure the reduced pressure being applied to the manifolds 120, 220, 320. The system further includes a control unit 145 electrically connected to the pressure sensor 140 and the reduced pressure source 115. The pressure sensor 140 measures the reduced pressure within the nerve gap 114, and also may indicate whether the first conduit 125 is occluded with blood or other bodily fluids. The pressure sensor 140 also provides feedback to control unit 145 which

regulates the reduced pressure therapy being applied by the reduced pressure source 115 through the first conduit 125 to the manifolds 120, 220, 320.

[0029] The reduced pressure therapy system 100, 200 or 300 may also comprise a fluid supply 150 fluidly coupled to the first conduit 125 via a second conduit 152 and operatively connected to the control unit 145. The fluid supply 150 may be used to deliver growth and/or healing agents to the nerve damage site 108 including, without limitation, an antibacterial agent, an antiviral agent, antibody, a cell-growth promotion agent, an irrigation fluid, or other chemically active agents. The system 100, 200, 300 further comprises a first valve 154 positioned in the second conduit 152 to control the flow of fluid therethrough, and a second valve 156 positioned in the first conduit 125 between the reduced pressure supply 115 and the juncture between the first conduit 125 and the second conduit 152 to control the flow of reduced pressure. In the case of a reduced pressure therapy system 300, the fluid supply 150 is directly coupled to the manifold 320 at the nerve tissue damage site 108 via the second conduit 325 as represented by the dashed lines. The control unit 145 is operatively connected to the first and second valves 154, 156 to control the delivery of reduced pressure and/or fluid from the fluid supply 150, respectively, to the manifolds 120, 220, 320 as required by the particular therapy being administered to the patient. The fluid supply 150 may deliver the liquids as indicated above, but may also deliver air to the manifolds 120, 220, 320 to promote healing and facilitate drainage at the site of the nerve damage site 108.

[0030] As used herein, the term “manifold” refers to a substance or structure that is provided to assist in directing reduced pressure to, delivering fluids to, or removing fluids from a tissue site. A manifold can include a plurality of flow channels or pathways that are interconnected to improve distribution of fluids provided to and removed from the area of tissue around the manifold. Examples of manifolds may include without limitation devices that have structural elements arranged to form flow channels, cellular foams such as open-cell foam, porous tissue collections, and liquids, gels and foams that include or cure to include flow channels. A detailed description of manifolds and their use according to the invention is provided below. In embodiments wherein the manifold protrudes into the nerve gap 114 or extends through the nerve gap 114 manifold materials that are bioabsorbable may be employed as detailed below.

[0031] The term “scaffold” as used herein refers to a substance or structure applied to or in a wound or defect that provides a structural matrix for the growth of cells and/or the formation of tissue. A scaffold is often a three dimensional porous structure. The scaffold can

be infused with, coated with, or comprised of cells, growth factors, extracellular matrix components, nutrients, integrins, or other substances to promote cell growth. A scaffold can take on characteristics of a manifold by directing flow through the matrix. A manifold can transmit flow to the scaffold and tissue; in the context of reduced pressure treatment, the manifold can be in fluid communication with the scaffold. A detailed description of scaffolds and their use according to the invention is provided below.

[0032] As such, the invention disclosed here discloses methods and apparatuses for controlling cellular-level based patterns of fluid flow that allow for control of patterned protein organization at a microscopic, nanoscopic, or mesoscopic scale amenable to provide a structured manifold and, optionally, a scaffold material for cellular migration, differentiation, and like behavior necessary for functional regeneration of tissues. In comparison to the passive nature of the current state of the art with regards to tissue repair and regeneration, the methods, scaffolds, manifolds, flow sources and systems disclosed herein provide an active mechanism by which to promote the endogenous deposition of proteins and organization of the provisional matrix with biochemical and physical cues to direct cellular colonization of a scaffold or tissue space. The present invention thus enhances current technology by exploiting the active force of directed fluid flow, providing a framework upon which to design manifolds and scaffolds based upon the need of the biology under the influence of fluid flow. Flow vectors and pathways are utilized to enhance protein deposition and cellular colonization. The systems provided herein are designed to promote establishment of a provisional matrix network with a seamless transition from the healthy tissue edges through a scaffold or tissue site to promote a functional tissue continuum.

[0033] Thus, the apparatuses, methods and systems disclosed herein provide a means for active guidance of tissue regeneration through an implanted scaffold or within a tissue site to promote functional recovery. This active guidance occurs through mechanisms of controlled fluid flow, which can be used to initiate or augment the early stages of the body's own natural healing process; a manifold can provide the active guidance necessary to create a controlled fluid flow. Specifically, the controlled flow vectors that the manifolds provide can be used to facilitate the directed influx of cells and proteins into a scaffold. Creation of specific flow pathways within a tissue site or scaffold can lead to patterned deposition of proteins, such as collagen and fibrin within the manifold, scaffold or tissue space. Biochemical cues from cytokines, growth factors, and cells bound within the provisional matrix can work in conjunction with the natural physical cues of the provisional matrix and

extracellular matrix to guide the subsequent migration of endogenous cells during the repair stages of healing. These cues act as a form of track or gradient that emanates from surrounding healthy tissues and passes through the scaffolding or tissue space to facilitate a continuous guidance pathway for organized tissue regeneration.

5 **[0034]** To that end, this disclosure provides unique manifolding technologies designed for specific biological needs based upon principles of fluid and gradient flow. In certain aspects, the invention concerns a new approach to wound healing, flow (or gradient) activated tissue engineering. In rudimentary form, this approach involves a source or generator of flow that forms a gradient for controlled movement of either endogenous or exogenous fluids into, 10 out of, or through a tissue space for the organized deposition of proteins and/or spatial concentration of cytokines and growth factors, with subsequent formation of a directionally oriented provisional matrix. The tissue space being defined here includes, but is not limited to, the region surrounding a site of nerve tissue damage.

[0035] Fluid flow into, through, or out of the nerve tissue space can be refined and 15 directed through the inclusion of additional elements to the system including manifolds and/or scaffolds. The coordinated elements of the system are designed to create flow parameters, pathways, and patterns sufficiently detailed in scale as to be able to influence and direct the controlled adsorption of proteins, the organization of matrix, and organized colonization of specific cell types. Individual elements of the system are as follows.

20 **[0036]** Source or generator of flow. Flow is induced into, through, or out of the nerve tissue space by methods or apparatuses that introduce changes in mechanical, chemical, and/or electrical potentials. These generators of flow provide either a gradient or a change in potential from the site or reservoir of endogenous or exogenous fluids to the placement position of the flow generator or its extension element (*i.e.*, manifold or scaffold). In one 25 embodiment, the source of flow comprises a source of reduced pressure. Systems and apparatuses according to the invention may also comprise valves or arrays of valves that control the application and amount of negative pressure applied to the manifold. In certain aspects, nerve conduits and/or manifolds described herein comprise a pressure sensor. Thus, in some embodiments, the amount of negative pressure applied by a source is regulated based 30 on the amount of negative pressure that is sensed in the manifold or nerve conduit or at the site of tissue damage.

[0037] Manifold. The flow generators are the driving force for stimulating the flow of fluids. Manifolds are apparatuses for refining the pattern of flow between the source or

generator of flow and the tissue space. The macroscale level of flow is refined by specialized manifolds utilized for directed localization to a single point or to a plurality of selectively positioned points for creating initiation sites for microscale flow pathways within the manifold/scaffold and, ultimately, the tissue space. The manifold may also serve as a conduit
5 for the removal of fluids from and as an apparatus for the delivery of exogenous fluids to the tissue space.

[0038] A manifold generally refers to a physical substance or structure that serves to assist in applying and translating a mechanical, chemical, electrical or similar alterations into changes in the flow of a fluid, herein defined as the movement of liquids, gases, and other
10 deformable substances such as proteins, cells, and other like moieties. As such, this physical device includes a single point or plurality of points for the egress or evacuation of pressure, fluids, and like substances capable of translating the movement of fluids in a scaffold, as defined above. This can include, but is not limited to, the introduction of exogenous factors such as cells and/or therapeutic moieties into the scaffold through the lumen or plurality of
15 lumens present in the manifold. In addition, as used herein, a manifold includes a single point or plurality of points for the ingress or introduction of fluid from the scaffold back towards the point source of flow.

[0039] Flow distributed by the manifold can direct the movement of endogenous proteins, growth factors, cytokines, and cells from their resident locations within the host to
20 the tissue space or scaffold in an organized manner. The establishment of flow along these pathways leads to the deposition of proteins and provisional matrix that creates an interfacial endogenous network connecting the host to the scaffold. Extensions of this matrix can be established within the scaffold through selective positioning of the manifold flow initiation sites with flow promoting scaffolding designs. The organized protein deposition and
25 provisional matrix provide a biochemical and physical framework that stimulates the attachment and migration of cells along directed pathways throughout the scaffold and the tissue space. The resulting endogenous network of proteins, growth factors, and cells provides a foundation upon which subsequent phases of the body's own tissue repair and regeneration mechanisms can build.

[0040] When in place, the manifold works in conjunction with a flow generating source and a scaffold, if present. Flow generating sources include, but are not limited to generators of negative pressure; generators of positive pressure; and generators of osmotic flow. The flow gradient established in the manifold may be further refined through the
30

scaffold, to deliver a flow gradient to the scaffold to optimize flow through the scaffold as needed for the particular defect. Many of the embodiments disclosed herein are manifolds capable of translating changes in pressure and the like into controlled movement of fluids, optionally through a physical scaffold, for the purposes of directed tissue regeneration. These
5 embodiments are generally specified for a particular application in the regeneration of specific tissues, but are not limited to a particular tissue therein.

[0041] In order to realize the goal of inducing flow for the purpose of tissue regeneration, alterations in the aforementioned mechanical, chemical, or electrical impetus must be translated from the singular gradient source toward a physical substrate or scaffold to
10 elicit cellular-level changes in protein adsorption, matrix organization, cell migration, and other tissue regeneration-related behaviors. These alterations are multivariate in nature and can include mechanical changes that elicit a physical change in pressure applied to the scaffold as applied to the site of the wound or desired site of tissue regeneration, chemical changes that elicit a gradient in protein and/or ion concentrations, which result in the creation of osmotic
15 gradients capable of inducing flow, or electrical changes that create a gradient of current/ion exchange allowing for propagation of electrical signals from the point source. It is to be understood, however, that the applicants are not bound by any particular mechanism through which gradients and fluid flow induce advantageous results in tissue repair or growth. In order to advantageously transmit these gradients to the tissue, a physical device is needed to direct
20 the path of flow from its source to the scaffold or tissue site and vice versa.

[0042] In some embodiments, the manifold comprises a physical structure in close apposition to or within the contents of a scaffold and serves to propagate an alteration in a physical parameter, whether it be mechanical, chemical, electrical, or something similar in nature, for the means of directing these changes from its point source to the scaffolding
25 material. The placement of this manifold with respect to its location with regard to that of the scaffold may be of crucial importance for facilitating controlled and directed regeneration of specific tissue types. For example, in peripheral nerve where regeneration primarily occurs in a unidirectional manner from the proximal to distal nerve stumps, it may be important to place the manifold along the length of a nerve conduit more towards its distal end to help direct
30 regeneration towards that end. However, it may also be important to not place the manifold at the most distal aspect of the scaffold/conduit as soluble factors derived from the distal stump have been shown to be important for directing nerve regeneration towards its source.

[0043] Manifolds may be composed of a bioabsorbable or bioinert material. Examples include non-bioabsorbable materials such as medical grade silicone polymers, metals, polyvinylchloride (PVC), and polyurethane. Bioabsorbable polymers such as collagen, polylactic acid (PLA), polyglycolic acid (PGA), polylactide-co-glycolide (PLGA), a polysaccharide, a hydroxyapatite, or a polyethylene glycol, or combinations thereof, can also be used. Some manifolds are also a mix of non-bioresorbable and bioresorbable materials. In general material used for a scaffold may also be used to compose a manifold and such materials are further detailed below. In certain aspects, manifold materials are structured to include a high void fraction for improved bioabsorption properties.

[0044] Support. Manifold support structures may be composed of any acceptable biocompatible material. A support structure will typically be impermeable and surround the manifold so as to maintain manifold pressure.

[0045] A portion of the support, such as a flange, couples the manifold and the nerve conduit. In certain aspects, a flange is attached to the exterior surface of a nerve conduit with an adhesive such as a fibrin glue, cyanoacrylate, or other biologically derived adhesive. A support may also be connected to a nerve conduit via reversible mechanisms other than an adhesive, such as chemical, thermal, osmotic, mechanical (snap or other interference fit, threaded, etc), magnetic, and electrostatic mechanisms. The manifold may be used to deliver agents that reverse the action of the binding mechanism in order to detach the support from the nerve conduit (*e.g.*, upon completion of therapy). For example, electrostatic binding may be released through introduction of salt solutions or biocompatible solvents may be used to release adhesives.

[0046] Scaffold. Biologic and synthetic scaffolds are used in the field of tissue engineering to support protein adhesion and cellular ingrowth for tissue repair and regeneration. The current state of the art in scaffold technology relies upon the inherent characteristics of the surrounding tissue space for the adsorption of proteins and migration of cells. A scaffold for use according to the invention is coupled to a manifold, provides physical guidance to direct the pathway of fluid flow in the tissue site, creating avenues for the movement and migration of adhesive proteins and cells, respectively, which are in turn integral to the establishment of a provisional matrix in predetermined patterns of organization within the tissue space. The methods and apparatuses described for fluid flow-induced and gradient-induced generation of tissues have direct implications in the design of the scaffolds. Within this context, scaffolds serve to refine the pathways of fluid flow within the tissue space to

cellular level patterns from the fluid source to the point(s) of flow initiation within the manifold. A scaffold may embody characteristics of a manifold or be combined in conjunction with a manifold for refinement of the flow pathways within the tissue site. In certain aspects, a scaffold is a reticulated structure comprising high void fraction for improved
5 bioabsorption properties.

[0047] Nonlimiting examples of suitable scaffold materials include extracellular matrix proteins such as fibrin, collagen or fibronectin, and synthetic or naturally occurring polymers, including bioabsorbable or non-absorbable polymers, such as polylactic acid (PLA), polyglycolic acid (PGA), polylactide-co-glycolide (PLGA), polyvinylpyrrolidone,
10 polycaprolactone, polycarbonates, polyfumarates, caprolactones, polyamides, polysaccharides (including alginates (*e.g.*, calcium alginate) and chitosan), hyaluronic acid, polyhydroxybutyrate, polyhydroxyvalerate, polydioxanone, polyorthoesters, polyethylene glycols, poloxamers, polyphosphazenes, polyanhydrides, polyamino acids, polyacetals, polycyanoacrylates, polyurethanes, polyacrylates, ethylene-vinyl acetate polymers and other
15 acyl substituted cellulose acetates and derivatives thereof, polystyrenes, polyvinyl chloride, polyvinyl fluoride, poly(vinylimidazole), chlorosulphonated polyolefins, polyethylene oxide, polyvinyl alcohol, Teflon[®], and nylon. The scaffold can also comprise ceramics such as hydroxyapatite, coralline apatite, calcium phosphate, calcium sulfate, calcium carbonate or other carbonates, bioglass, allografts, autografts, xenografts, decellularized tissues, or
20 composites of any of the above. In particular embodiments, the scaffold comprises collagen, polylactic acid (PLA), polyglycolic acid (PGA), polylactide-co-glycolide (PLGA), a polyurethane, a polysaccharide, an hydroxyapatite, or a polytherylene glycol. Additionally, the scaffold can comprise combinations of any two, three or more materials, either in separate or multiple areas of the scaffold, combined noncovalently, or covalently (*e.g.*, copolymers
25 such as a polyethylene oxide-polypropylene glycol block copolymers, or terpolymers), or combinations thereof. Suitable matrix materials are discussed in, for example, Ma and Elisseeff, 2005, and Saltzman, 2004.

[0048] Bioactive agents

[0049] In certain aspects, the apparatuses and methods according to the invention
30 concern bioactive agents. Bioactive agents may, in some cases, be incorporated directly onto a manifold or scaffold material (*i.e.*, to generate a bioactive manifold and/or scaffold). For example, agents that facilitate tissue growth such as collagen or fibrin may be directly incorporated onto or into a manifold or scaffold material. Likewise, in applications where

aberrant immune response need be avoided (*e.g.*, tissue grafts) immune regulator agents such as rapamycin may be incorporated into manifold or scaffold structures.

[0050] In further aspects, soluble bioactive agents may be introduced at a site of tissue damage by virtue of the flow through the tissue site. For example, a manifold may be in fluid communication with a fluid source and a bioactive agent may be introduced into the fluid source and thereby into the manifold and damaged nerve tissue.

[0051] Nonlimiting examples of bioactive growth factors for various applications are growth hormone (GH), a bone morphogenetic protein (BMP), transforming growth factor- α (TGF- α), a TGF- β , a fibroblast growth factor (FGF), granulocyte-colony stimulating factor (G-CSF), granulocyte/macrophage-colony stimulating factor (GM-CSF), epidermal growth factor (EGF), platelet derived growth factor (PDGF), insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), hepatocyte growth factor/scatter factor (HGF/SF), an interleukin, tumor necrosis factor- α (TNF- α) or nerve growth factor (NGF).

[0052] Nerve tissue repair and engineering. The apparatuses and systems disclosed herein can be used for nerve tissue repair and engineering in various contexts including the following.

[0053] Repair and regeneration of lost tissue. A generator of flow may be combined with manifolds and/or scaffolds to direct the regeneration of lost tissue at a site of injury or compromised function. Tissues lost from traumatic injury, surgery, burns, or other causes (*e.g.*, infection or autoimmune disease) can be led to regenerate using the methods, scaffolds, manifolds, flow sources and systems of the invention. Functional nerve tissue is directed to regenerate.

[0054] Retard the progression of a tissue disease state. A generator of flow may be combined with manifolds and/or scaffolds to retard disease progression of an affected nerve tissue such as occurs, *e.g.*, in autoimmune disease.

[0055] Maintenance of tissue viability. A generator of flow may be combined with manifolds and/or scaffolds to maintain the viability of explanted tissues either for *in vitro* study, *ex vivo* scaffold or implant preparation, or *in vivo* transplant. A generator of flow combined with a manifold may be used to provide nutrient flow to the tissue and to control waste removal from the tissue.

[0056] Expansion of tissue. A generator of flow may be combined with manifolds and/or scaffolds to promote the expansion of existing tissues. The methods, scaffolds,

manifolds, flow sources and systems of the invention can be used to direct the growth of tissues where additional tissue quantity is needed or desired.

[0057] Acceleration of tissue formation. A generator of flow may be combined with manifolds and/or scaffolds to accelerate the rate of tissue formation within a natural healing response. The methods, scaffolds, manifolds, flow sources, and systems of the invention may be used to accelerate tissue growth by augmenting formation of provisional matrices, facilitating its stable positioning, and aiding in recruitment of cells to the tissue space.

[0058] Stimulating the differentiation of stem cells along specific pathways. A generator of flow may be combined with manifolds and/or scaffolds to stimulate the differentiation of stem cells or other pluripotent cells into specific lineages. Application of flow using the methods, scaffolds, manifolds, flow sources and systems of the invention may be used to direct pluripotent cells into specific cell lineages needed to foster growth in the tissue space.

[0059] Introducing proteins, matrix, cells, or pharmaceuticals into the *in vivo* environment. A generator of flow may be combined with manifolds and/or scaffolds to introduce exogenous growth factors, proteins, cells, or pharmaceutical agents into the tissue space to augment tissue repair, regeneration, and/or maintenance.

[0060] Creating matrices *in vitro* for implantation *in vivo*. A generator of flow may be combined with manifolds and/or scaffolds to facilitate formation of matrices *in vitro* that may subsequently be used for *in vivo* transplantation.

[0061] Promoting integration of transplanted tissue. A generator of flow may be combined with manifolds and/or scaffolds to promote integration of transplanted tissue into the host environment. This can be applied to autograft, allograft, or xenograft transplants.

[0062] Directing extracellular matrix (ECM) deposition and orientation *in vitro*. A flow generator may be combined with manifolds and/or scaffolds to guide the directed deposition and orientation of ECM expressed by cells and tissues. The directed orientation of ECM has an impact in organizing and directing the attachment and colonization of subsequent cell layers and tissues.

[0063] References

U.S. Patent No. 4,787,906
U.S. Patent No. 6,103,255
U.S. Patent No. 6,135,116
U.S. Patent No. 6,365,146

- U.S. Patent No. 6,695,823
U.S. Patent No. 6,696,575
U.S. Patent No. 6,767,334
U.S. Patent No. 6,814,079
5 U.S. Patent No. 6,856,821
U.S. Patent No. 6,936,037
U.S. Patent No. 6,951,553
U.S. Patent No. 6,994,702
U.S. Patent No. 7,004,915
10 U.S. Patent No. 7,070,584
U.S. Patent No. 7,077,832
U.S. Patent No. 7,108,683
U.S. Patent No. 7,160,553
U.S. Patent No. 7,186,244
15 U.S. Patent No. 7,214,202
U.S. Patent No. 7,279,612
U.S. Patent No. 7,316,672
U.S. Patent No. 7,346,945
U.S. Patent No. 7,351,250
20 U.S. Patent No. 7,384,786
U.S. Patent Publn. 2003/0225347
U.S. Patent Publn. 2005/0260189
U.S. Patent Publn. 2007/0123895
U.S. Patent Publn. 2008/0033324
25 U.S. Patent Publn. 2008/0208358
U.S. Provisional Patent Appln. 61/142,053
U.S. Provisional Patent Appln. 61/142,065
Anderson et al., Tissue Eng., 13:2525-38, 2007.
Brody et al., J. Biomed. Mater. Res. B: Appl. Biomater., 83:16-43, 2007.
30 *Gemmiti et al., Tissue Eng., 12:469-79, 2006.*
Lago et al., IEEE Trans. Biomed. Eng., 54:1129-37, 2007.
Ma et al., Scaffolding in Tissue Engineering, 2005.
Manwaring et al., Biomaterials, 22:3155-3168, 2001.

Manwaring *et al.*, *Biomaterials*, 25:3631-3638, 2004.

Mercier *et al.*, *Biomaterials*, 26:1945-1952, 2005.

Mikos *et al.*, *J. Biomed. Mater. Ref.*, 27:183-189, 2004.

Norman *et al.*, *Ann Biomed Eng.*, 34:89-101, 2006.

5 PCT Appln. WO 00/38755A2

PCT Appln. WO 00/61206A1

PCT Appln. WO 03/018098A2

PCT Appln. WO 03/092620A2

PCT Appln. WO 04/060148A2

10 PCT Appln. WO 04/105576A2

PCT Appln. WO 05/009488A2

PCT Appln. WO 05/033273A2

PCT Appln. WO 06/004951

PCT Appln. WO 06/127853

15 PCT Appln. WO 07/067685A2

PCT Appln. WO 07/092397A2

PCT Appln. WO 07/106589A2

PCT Appln. WO 07/106590A2

PCT Appln. WO 07/106591A2

20 PCT Appln. WO 07/106592A2

PCT Appln. WO 07/106594A2

PCT Appln. WO 07/133555A2

PCT Appln. WO 07/133556A2

PCT Appln. WO 07/143060A2

25 PCT Appln. WO 07/196590

PCT Appln. WO 08/013896A2

PCT Appln. WO 08/036162A2

PCT Appln. WO 08/036359A2

PCT Appln. WO 08/036361A2

30 PCT Appln. WO 08/042481A2

PCT Appln. WO 08/091521A2

Pfister *et al.*, *Neurosurgery*, 60:137-41, 2007.

Saltzman, *Tissue Engineering: Engineering Principles for the Design of Replacement Organs and Tissues*, 2004.

Sachlos *et al.*, *Cells and Mat.*, 5:29-40, 2003.

Segvich *et al.*, *J. Biomed. Mater. Res. B: Appl. Biomater.*, 84B:340-349, 2008.

5 Shimko *et al.*, *J Biomed Mater. Res. B: Appl. Biomater.*, 73:315-24, 2005.

Takahashi *et al.*, *Cell*, 126:663-76, 2006.

Tan *et al.*, *Bone*, 41:745-751, 2007.

Tan *et al.*, *Biochem. Biophys. Res. Comm.*, 369:1150-1154, 2008.

Walsh *et al.*, *Tissue Eng.*, 11:1085-1094, 2005.

10 Wen *et al.*, *Handbook of Nanostructured Biomaterials and Their Applications in Nanobiotechnology*, 1-23, 2005.

[0064] All references cited in this specification are hereby incorporated by reference. The discussion of the references herein is intended merely to summarize the assertions made by the authors and no admission is made that any reference constitutes prior art. Applicants
15 reserve the right to challenge the accuracy and pertinence of the cited references.

[0065] In view of the above, it will be seen that the advantages of the invention are achieved and other advantages attained. As various changes could be made in the above methods and compositions without departing from the scope of the invention, it is intended that all matter contained in the above description and shown in the accompanying drawings
20 shall be interpreted as illustrative and not in a limiting sense.

CLAIMS

We claim:

- 5 Claim 1. An apparatus for providing reduced pressure from a reduced-pressure source to a defect at a tissue site of a nerve, the apparatus comprising:
- a nerve conduit having a generally tubular shape having walls including an exterior wall and a luminal wall surrounding the tissue site to contain fluids within a luminal space between the tissue site and the luminal wall;
- 10 a manifold having a generally cylindrical body having surfaces including a side wall surface and two end wall surfaces, a first end wall surface of the two end wall surfaces for receiving reduced pressure, a fluid contact surface including a first portion of the surfaces of the cylindrical body other than the first end wall surface for fluid communication with the luminal space, and a support surface including a second portion of the surface of the cylindrical
- 15 body other than the first end wall surface and the fluid contact surface; and a first support structure having a generally tubular shape for enclosing the support surface, a first end portion for coupling the first end wall surface to the reduced-pressure source, and a second end portion for coupling the manifold to the nerve conduit in a generally radial direction with respect to the
- 20 luminal wall.
- Claim 2. The apparatus of claim 1, wherein the fluid contact surface comprises a second end wall surface of the two end wall surfaces positioned adjacent the luminal wall to fluidly communicate with the luminal space.
- Claim 3. The apparatus of claim 2, wherein the nerve conduit comprises a material
- 25 generally impermeable to fluids from tissue surrounding the nerve conduit.

Claim 4. The apparatus of claim 1, wherein the nerve conduit is porous and the fluid contact surface comprises a second end wall surface of the two end wall surfaces positioned adjacent the exterior surface of the nerve conduit to fluidly communicate with the luminal space through the walls of the nerve conduit.

5 Claim 5. The apparatus of claim 4, wherein the nerve conduit comprises a material generally impermeable to fluids from tissue surrounding the nerve conduit.

10 Claim 6. The apparatus of claim 1, wherein the fluid contact surface comprises a second end wall surface of the two end wall surfaces and a portion of the side wall surface adjacent the second end wall surface extending from the luminal wall into the luminal space.

15 Claim 7. The apparatus of claim 1, wherein the fluid contact surface comprises a portion of the side wall surface extending from a first side of the luminal wall through the luminal space to a second side of the luminal wall, and a second end wall surface of the two end wall surfaces for receiving a fluid from a fluid source, the apparatus further comprising:
a second support structure having a generally tubular shape for enclosing the support surface adjacent the second end wall surface, a first end portion for coupling the second end wall surface to the fluid source, and a second end portion for coupling the manifold to the nerve conduit.

20 Claim 8. The apparatus of claim 1, wherein the defect is a severed, partially severed, pinched, or degenerated nerve.

Claim 9. The apparatus of claim 1, wherein the second end portion of the support structure comprises a flange.

25 Claim 10. The apparatus of claim 1, wherein the second end portion of the support structure provides a detachable coupling of the manifold to the nerve conduit.

- Claim 11. The apparatus of claim 1, wherein the second end portion of the support structure comprises an adhesive for coupling the manifold and the nerve conduit.
- Claim 12. The apparatus of claim 1, wherein the manifold comprises a porous structure wherein the pore size is sufficiently small to exclude cells from entering the manifold.
- 5 Claim 13. The apparatus of claim 1, wherein the manifold serves as a scaffold that facilitates tissue growth or regrowth.
- Claim 14. The apparatus of claim 1, wherein the nerve conduit comprises pores that are sufficiently small to exclude the entry of cells into the luminal space.
- Claim 15. The apparatus of claim 14, wherein the pores have an interior diameter of
10 between about 5 μm and 50 μm .
- Claim 16. The apparatus of claim 1, wherein the manifold is positioned on the distal side of the nerve conduit relative to the tissue site.
- Claim 17. The apparatus of claim 1, wherein the manifold provides reduced pressure preferentially to the distal side of the nerve relative to the tissue site.
- 15 Claim 18. The apparatus of claim 1, wherein the manifold or nerve conduit is composed of a bioinert material.
- Claim 19. The apparatus of claim 1, wherein the manifold or nerve conduit is composed of a bioabsorbable material.
- Claim 20. The apparatus of claim 1, wherein the luminal space of the nerve conduit
20 comprises a scaffold that facilitates tissue growth or regrowth.
- Claim 21. The apparatus of claim 20, wherein the scaffold is formed from a foam or gel material.
- Claim 22. The apparatus of claim 20, wherein the scaffold is biological material selected from fibrin or collagen.
- 25 Claim 23. The apparatus of claim 22, wherein the scaffold material comprises a bioactive agent.

Claim 24. The apparatus of claim 23, wherein the bioactive agent is at least one of an antibiotic, an antibody and a growth factor.

Claim 25. The apparatus of claim 24, wherein the bioactive agent is a growth hormone (GH), a bone morphogenetic protein (BMP), transforming growth factor- α (TGF- α), a
5 TGF- β , a fibroblast growth factor (FGF), granulocyte-colony stimulating factor (G-CSF), granulocyte/macrophage-colony stimulating factor (GM-CSF), epidermal growth factor (EGF), platelet derived growth factor (PDGF), insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), hepatocyte growth factor/scatter factor (HGF/SF), an interleukin, tumor necrosis factor- α (TNF- α) or nerve growth factor (NGF).

10 Claim 26. The apparatus of claim 1, wherein the nerve conduit comprises a slice along its length that forms an opening whereby the nerve conduit is implantable around the tissue site and sealable with one or more closure elements.

Claim 27. A system for providing reduced pressure to a defect at a tissue site of a nerve, the system comprising:

- 15 a pressure source for supplying the reduced pressure;
a nerve conduit having a generally tubular shape having walls including an exterior wall and a luminal wall surrounding the tissue site to contain fluids within a luminal space between the tissue site and the luminal wall;
- 20 a manifold having a generally cylindrical body having surfaces including a side wall surface and two end wall surfaces, a first end wall surface of the two end wall surfaces in fluid communication with the pressure source, a fluid contact surface including a first portion of the surfaces of the cylindrical body other than the first end wall surface for fluid communication with the luminal space, and a support surface including a second portion of the
25 surface of the cylindrical body other than the first end wall surface and the fluid contact surface; and
- 30 a first support structure having a generally tubular shape for enclosing the support surface, a first end portion for coupling the first end wall surface to the reduced-pressure source, and a second end portion for coupling the manifold to the nerve conduit in a generally radial direction with respect to the luminal wall.

Claim 28. The system of claim 27, further comprising a fluid source in fluid communication with the manifold for supplying a fluid to the luminal space.

Claim 29. The system of claim 27, wherein the fluid contact surface comprises a second end wall surface of the two end wall surfaces positioned adjacent the luminal wall to fluidly communicate with the luminal space.

Claim 30. The system of claim 29, wherein the nerve conduit comprises a material generally impermeable to fluids from tissue surrounding the nerve conduit.

Claim 31. The system of claim 27, wherein the nerve conduit is porous and the fluid contact surface comprises a second end wall surface of the two end wall surfaces positioned adjacent the exterior surface of the nerve conduit to fluidly communicate with the luminal space through the walls of the nerve conduit.

Claim 32. The system of claim 31, wherein the nerve conduit comprises a material generally impermeable to fluids from tissue surrounding the nerve conduit.

Claim 33. The system of claim 27, wherein the fluid contact surface comprises a second end wall surface of the two end wall surfaces and a portion of the side wall surface adjacent the second end wall surface extending from the luminal wall into the luminal space.

Claim 34. The system of claim 27, wherein the fluid contact surface comprises a portion of the side wall surface extending from a first side of the luminal wall through the luminal space to a second side of the luminal wall, and a second end wall surface of the two end wall surfaces for receiving a fluid from a fluid source, the apparatus further comprising:
a second support structure having a generally tubular shape for enclosing the support surface adjacent the second end wall surface, a first end portion for coupling the second end wall surface to the fluid source, and a second end portion for coupling the manifold to the nerve conduit.

- Claim 35. The system of claim 27, wherein the defect is a severed, partially severed, pinched, or degenerated nerve.
- Claim 36. The system of claim 27, wherein the second end portion of the support structure comprises a flange.
- 5 Claim 37. The system of claim 27, wherein the second end portion of the support structure provides a detachable coupling of the manifold to the nerve conduit.
- Claim 38. The system of claim 27, wherein the second end portion of the support structure comprises an adhesive for coupling the manifold and the nerve conduit.
- 10 Claim 39. The system of claim 27, wherein the manifold comprises a porous structure wherein the pore size is sufficiently small to exclude cells from entering the manifold.
- Claim 40. The system of claim 27, wherein the manifold serves as a scaffold that facilitates tissue growth or regrowth.
- Claim 41. The system of claim 27, wherein the nerve conduit comprises pores that are sufficiently small to exclude the entry of cells into the luminal space.
- 15 Claim 42. The system of claim 41, wherein the pores have an interior diameter of between about 5 μm and 50 μm .
- Claim 43. The system of claim 27, wherein the manifold is positioned on the distal side of the nerve conduit relative to the tissue site.
- 20 Claim 44. The system of claim 27, wherein the manifold provides reduced pressure preferentially to the distal side of the nerve relative to the tissue site.
- Claim 45. The system of claim 27, wherein the manifold or nerve conduit is composed of a bioinert material.
- Claim 46. The system of claim 27, wherein the manifold or nerve conduit is composed of a bioabsorbable material.
- 25 Claim 47. The system of claim 27, wherein the luminal space of the nerve conduit comprises a scaffold that facilitates tissue growth or regrowth.

Claim 48. The system of claim 47, wherein the scaffold is formed from a foam or gel material.

Claim 49. The system of claim 47, wherein the scaffold is biological material selected from fibrin or collagen.

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Claim 50. The system of claim 47, wherein the scaffold material comprises a bioactive agent.

Claim 51. The system of claim 50, wherein the bioactive agent is at least one of an antibiotic, an antibody and a growth factor.

10 Claim 52. The system of claim 51, wherein the bioactive agent is a growth hormone (GH), a bone morphogenetic protein (BMP), transforming growth factor- α (TGF- α), a TGF- β , a fibroblast growth factor (FGF), granulocyte-colony stimulating factor (G-CSF), granulocyte/macrophage-colony stimulating factor (GM-CSF), epidermal growth factor (EGF), platelet derived growth factor (PDGF), insulin-like growth factor (IGF), vascular
15 endothelial growth factor (VEGF), hepatocyte growth factor/scatter factor (HGF/SF), an interleukin, tumor necrosis factor- α (TNF- α) or nerve growth factor (NGF).

Claim 53. The system of claim 27, wherein the nerve conduit comprises a slice along its length that forms an opening whereby the nerve conduit is implantable around the tissue site and sealable with one or more closure elements.

Claim 54. A method for providing reduced pressure to a defect at a tissue site of a nerve, the method comprising:

implanting a nerve conduit having a generally tubular shape having walls including an exterior wall and a luminal wall;

5 sealing the nerve conduit around the tissue site to contain fluids within the luminal space between the tissue site and the luminal wall;

implanting a manifold and a support structure at the tissue site wherein the manifold has a generally cylindrical body having surfaces including a side wall surface and two end wall surfaces, a first end wall surface of the two end wall surfaces for receiving reduced pressure, a fluid contact surface including a first portion of the surfaces of the cylindrical body other than the first end wall surface for fluid communication with the luminal space, and a support surface including a second portion of the surface of the cylindrical body other than the first end wall surface and the fluid contact surface and wherein the support structure has a generally tubular shape for enclosing the support surface, a first end portion for coupling the first end wall surface to the reduced-pressure source, and a second end portion for coupling the manifold to the nerve conduit in a generally radial direction with respect to the luminal wall; and

20 applying reduced pressure through the manifold to the tissue site.

Claim 55. The method of claim 54, wherein implanting a manifold and support structure at the tissue site comprises attaching the second end portion of the support structure to the exterior wall of the nerve conduit.

Claim 56. A method for repairing or regenerating a defect at a tissue site of a nerve, the method comprising:

implanting a nerve conduit having a generally tubular shape having walls including an exterior wall and a luminal wall;

5 sealing the nerve conduit around the tissue site to contain fluids within the luminal space between the tissue site and the luminal wall;

implanting a manifold and a support structure at the tissue site wherein the manifold has a generally cylindrical body having surfaces including a side wall surface and two end wall surfaces, a first end wall surface of the two end wall surfaces for receiving reduced pressure, a fluid contact surface including a first portion of the surfaces of the cylindrical body other than the first end wall surface for fluid communication with the luminal space, and a support surface including a second portion of the surface of the cylindrical body other than the first end wall surface and the fluid contact surface and
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15 wherein the support structure has a generally tubular shape for enclosing the support surface, a first end portion for coupling the first end wall surface to the reduced-pressure source, and a second end portion for coupling the manifold to the nerve conduit in a generally radial direction with respect to the luminal wall;

20 applying reduced pressure through the manifold to the tissue site; and wherein the application of reduced pressure facilitates the repair or regeneration of the defect.

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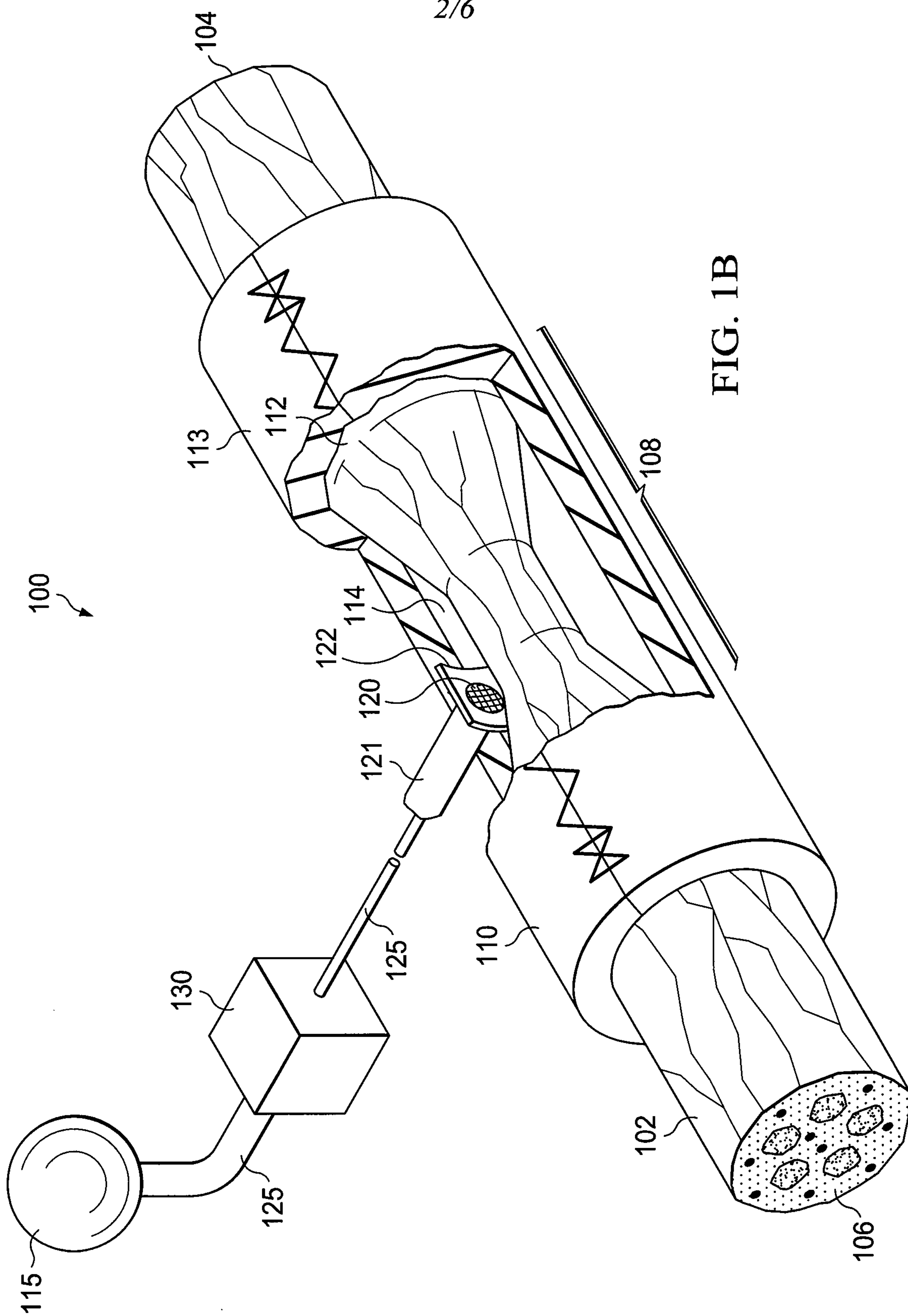


FIG. 1B

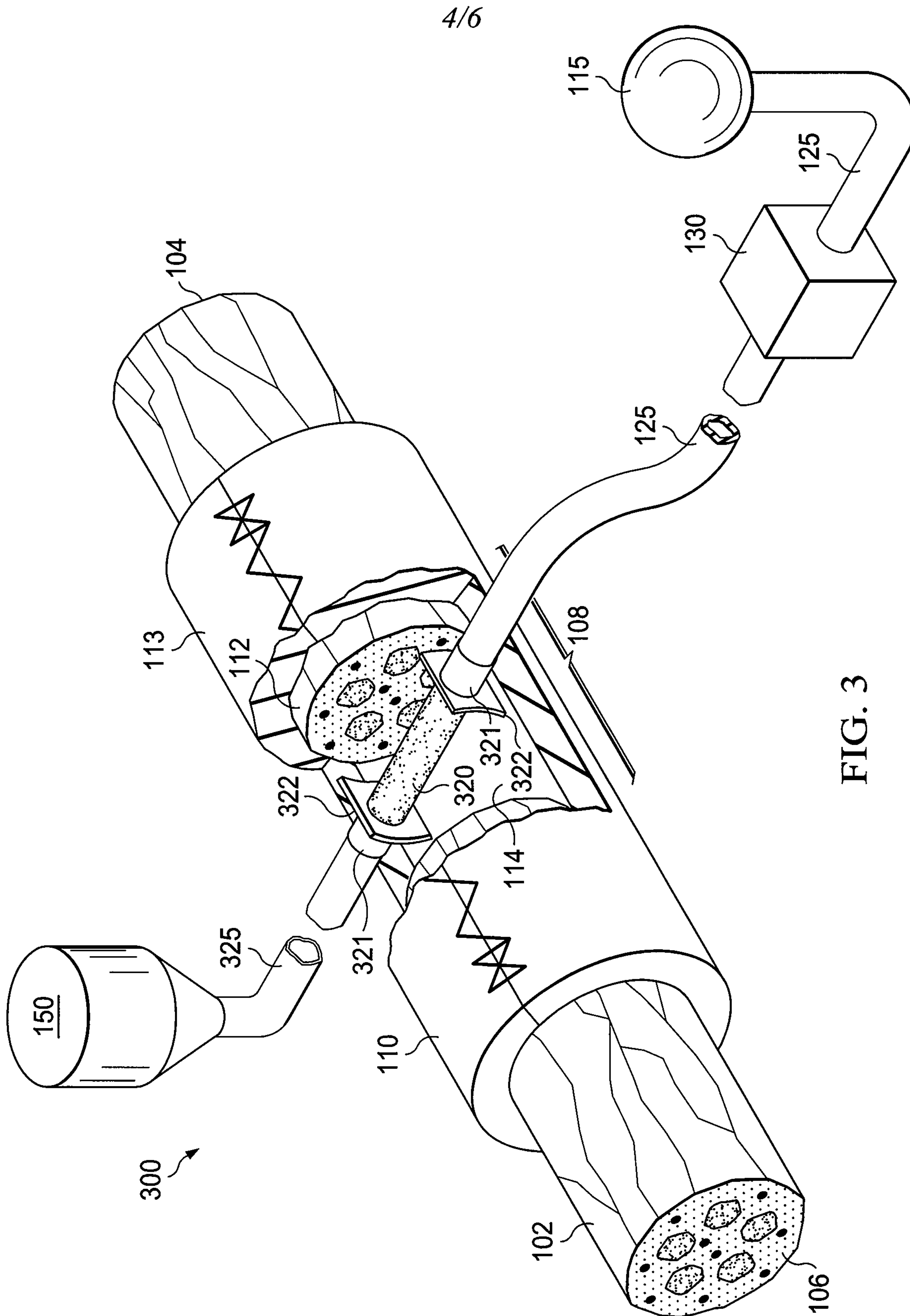


FIG. 3

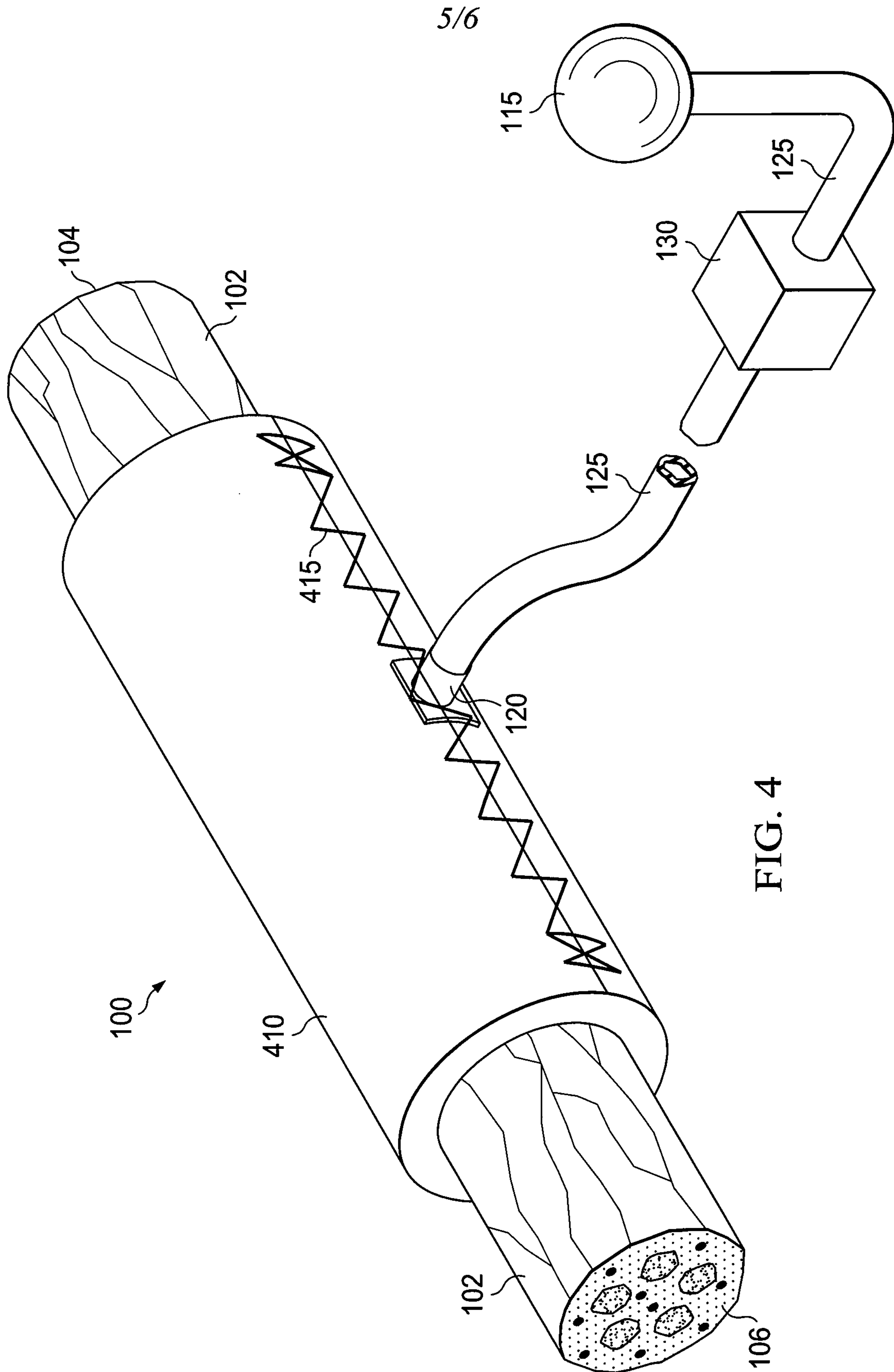
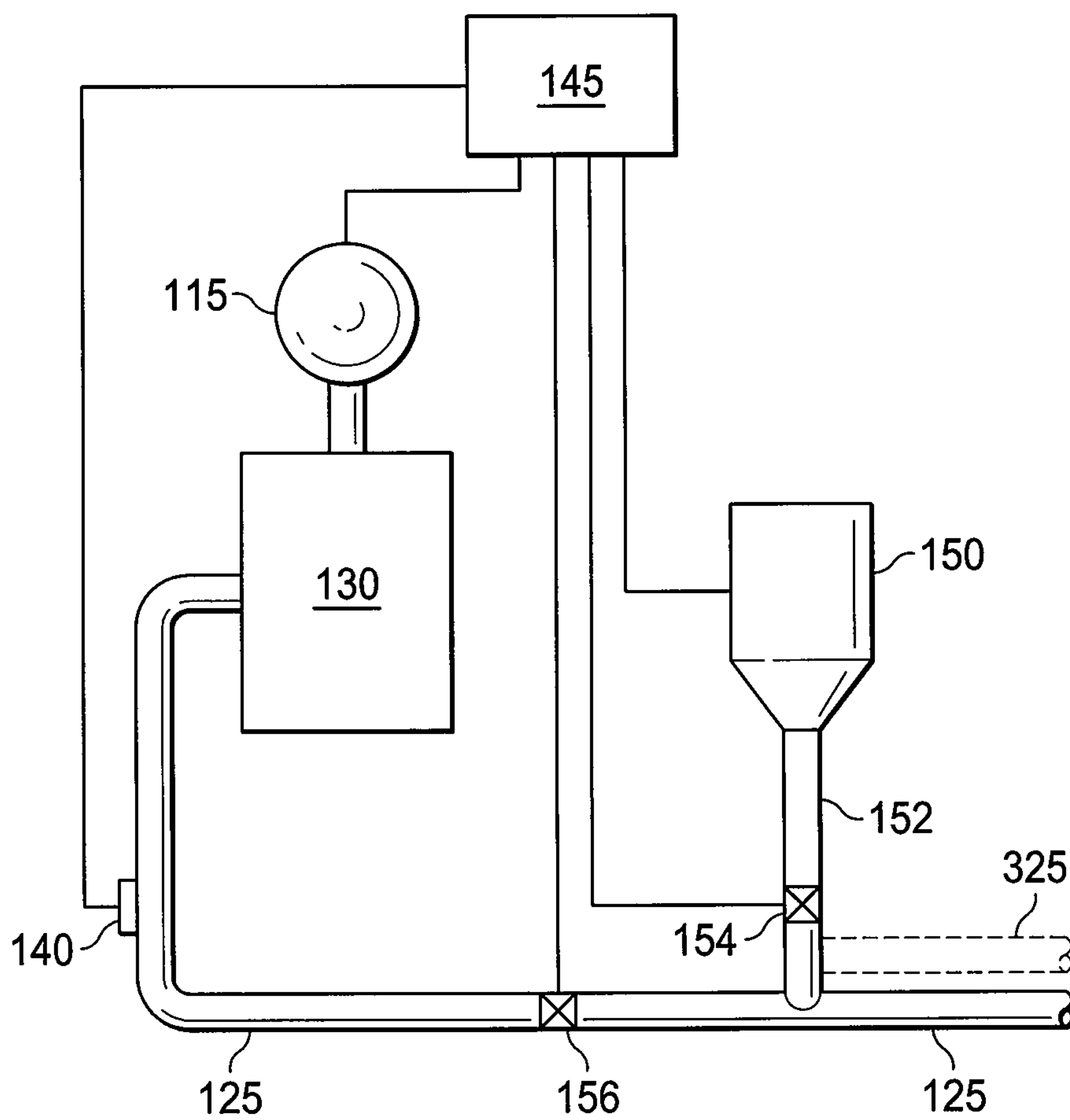


FIG. 4

FIG. 5



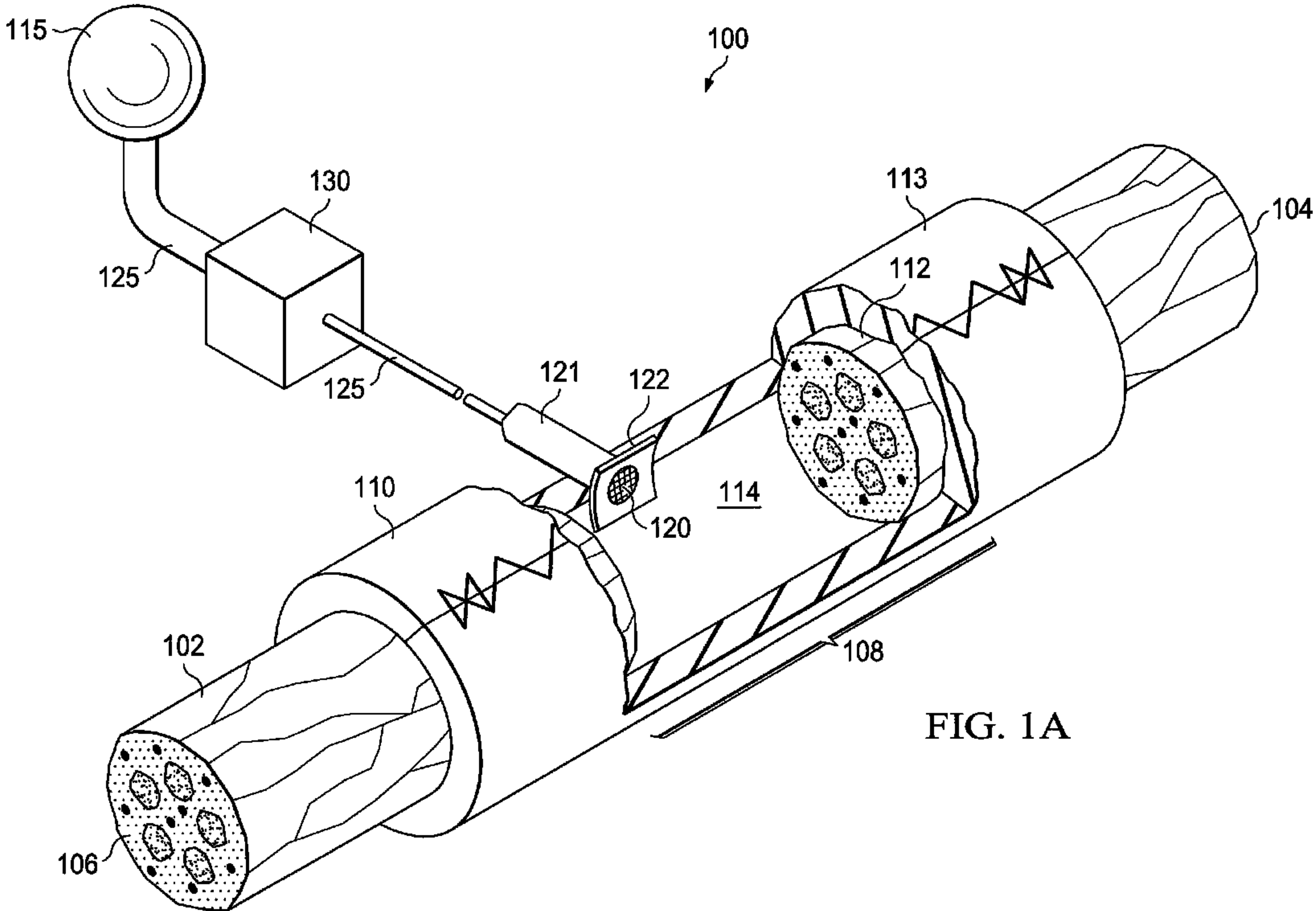


FIG. 1A