(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 August 2006 (31.08.2006)

PCT

(10) International Publication Number
WO 2006/090362 A2

(51) International Patent Classification:
A61F 7/02 (2006.01)

(21) International Application Number:
PCT/IL2006/000188

(22) International Filing Date:
14 February 2006 (14.02.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/654,505 22 February 2005 (22.02.2005) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2006/090362 A2

(54) Title: VASCULAR GRAFT FOR IN VIVO HEMODYALISIS AND/OR TARGETED DELIVERY OF A DRUG

(57) Abstract: A vascular graft having two lumens which are in fluid communication therebetween via a membrane disposed along at least a portion of a wall separating the two lumens is provided. Also provided are methods of performing in vivo hemodialysis and/or targeted drug delivery by implanting the vascular graft and administering a dialysate and/or drug fluid, respectively, therein. In addition, the vascular graft can be used for low invasiveness sampling of components of a biological fluid (e.g., plasma) for diagnostic purposes.

VASCULAR GRAFT FOR *IN VIVO* HEMODYALISIS AND/OR TARGETED DELIVERY OF A DRUG

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to a vascular graft which can be used for *in vivo* hemodialysis, targeted delivery of a drug to the tissue-of-interest and/or low invasiveness sampling of components of a biological fluid (e.g., plasma) for diagnostic purposes.

Patients suffering from end-stage renal failure, a condition characterized by less than 10 % of the normal functioning of the kidneys, rely on artificial dialysis to control their blood pressure and maintain proper balance of salts and minerals. However, due to dialysis-related complications, many dialysis-depended patients are candidate for kidney transplantation. In the U.S.A. more than 400,000 people are on long-term dialysis and more than 20,000 have a functioning transplanted kidney.

In artificial dialysis, the waste from the patient's blood, including salts, minerals, toxins and extra fluid is removed and the substantially waste-free blood is returned to the body. Two common types of dialysis are employed, peritoneal dialysis and hemodialysis. Peritoneal dialysis is based on filling the abdominal cavity with a dialysate solution via a catheter and following a dwell time of 4 to 6 hours the waste-containing dialysate solution is drained outside of the body. In hemodialysis, the blood is filtered through an artificial kidney machine. Traditional hemodilaysis procedures involve withdrawal of relatively large quantities of blood from a patient by means of a needle inserted into one blood vessel, dialyzing the blood against a dialysate solution and returning the substantially waste-free blood into the patient by means of a needle inserted into another blood vessel.

Over the past decade, various devices have been developed in order to provide permanent or semi-permanent means of extracorporeal access to the blood vessels. These include implantable access ports in a form of a catheter or tube having one end at the blood vessel and another end at the skin (see for example, U.S. Pat. Nos. 5,476,451, 5,556,381 and 5,792,123 to Ensminger et al.; U.S. Pat. No. 5,728,103 to Picha, et al.; U.S. Pat. No. 5,741,228 to Lambrecht et al.; and U.S. Pat. No. 6,319,226 to Sherry),

implantable dialysis access port assembly for connection of a dialysis machine to a patient (e.g., U.S. Pat. No. 5,944,688 to Lois), and implanted single or dual lumen device for repeated accessing of a vessel within a body, especially for hemodialysis and plasmapheresis (U.S. Pat. No. 6,206,851 to Prosl). These devices are usually implanted below the skin to prevent infection, contamination and/or mishandling. However, all of these devices rely on performing the hemodialysis outside of the patient's body, a procedure associated with high infection rate, damage to blood vessels, hemorrhage associated with heparin administration during dialysis and general deterioration of the patient's health.

Recently, a method of performing hemodialysis *in vivo* (*i.e.*, within the blood vessel of the patient) has been suggested (U.S. Pat. No. 6,561,996 to Gorsuch). According to this method a catheter-like filter device is implanted into the vena cava and dialysis of blood is performed by administering a substantially pure dialysate solution into the device and retrieving the waste-containing dialysate solution into a collecting bag. However, due to the risk of inserting a "free-floating" device into a main blood vessel of the patient, such a method is not clinically practiced.

Targeted delivery of drugs to a tissue-of-interest (*e.g.* a tissue which exhibits a pathology treatable by the drug) is preferred over systemic administration since low and therapeutically effective amounts of the drug can be locally introduced to the tissue without causing unwanted side effects. Various methods and devices have been developed for targeted delivery of drugs. For example, various inhalers which release drugs in aerosol-form were developed for treating lung diseases; insulin pumps which measure the level of glucose in the blood and release insulin are used for diabetes control; for various brain tumors, poly(lactide-co-glycolide) microspheres which release chemotherapeutic agents were developed; in addition, various drug-eluting vascular grafts (e.g., drug-eluting stents) were developed. These comprise drug molecules, which are impregnated or covalently attached to the vascular grafts and are designed for constant release into the blood stream. However, many drug molecules are not suitable for slow release or exhibit short-half life and thus cannot be impregnated or covalently attached to the currently available vascular grafts.

There is thus a widely recognized need for, and it would be highly advantageous to have, a method and a device capable of *in vivo* hemodialysis and/or targeted drug delivery devoid of the above limitations.

SUMMARY OF THE INVENTION

According to one aspect of the present invention there is provided a vascular graft comprising two lumens being in fluid communication therebetween via a membrane disposed along at least a portion of a wall separating the two lumens.

According to another aspect of the present invention there is provided a method of performing *in vivo* hemodialysis in a subject, comprising: (a) implanting in the subject a vascular graft comprising two lumens being in fluid communication therebetween via a membrane disposed along at least a portion of a wall separating the two lumens, wherein a first lumen of the two lumens is designed capable of supporting blood flow and whereas a second lumen of the two lumens is designed for containing a dialysate fluid; and (b) administering the dialysate fluid into the second lumen; thereby performing the *in vivo* hemodialysis in the subject.

According to yet another aspect of the present invention there is provided a method of administering a drug into a tissue-of-interest of a subject, comprising: (a) implanting in the subject a vascular graft comprising two lumens being in fluid communication therebetween via a membrane disposed along at least a portion of a wall separating the two lumens, wherein a first lumen of the two lumens is designed capable of supporting blood flow and whereas a second lumen of the two lumens is designed for containing the drug; and (b) administering the drug into the second lumen; thereby administering the drug into the tissue-of-interest of the subject.

According to still another aspect of the present invention there is provided a method of sampling a component of a biological fluid of a subject, comprising: (a) implanting in the subject a graft comprising two lumens being in fluid communication therebetween via a membrane disposed along at least a portion of a wall separating the two lumens, wherein a first lumen of the two lumens is designed capable of supporting biological fluid flow and whereas a second lumen of the two lumens is designed for containing the component of the biological fluid; and (b) retrieving a sample of the

component of the biological fluid from the second lumen; thereby sampling the component of the biological fluid of the subject.

According to an additional aspect of the present invention there is provided a method of controlling a level of a drug administered to a subject, comprising: (a) implanting in the subject a graft comprising two lumens being in fluid communication therebetween via a membrane disposed along at least a portion of a wall separating the two lumens, wherein a first lumen of the two lumens is designed capable of supporting biological fluid flow and whereas a second lumen of the two lumens is designed for containing a component of the biological fluid of the subject and the drug; (b) administering the drug into the second lumen; (c) retrieving a sample of the component of the biological fluid from the second lumen; and (d) monitoring the sample of the component of biological fluid for presence and/or level of a marker indicative of an effect of the drug; thereby controlling the level of the drug administered to the subject.

According to further features in preferred embodiments of the invention described below, a first lumen of the two lumens is designed capable of supporting blood flow.

According to still further features in the described preferred embodiments a second lumen of the two lumens comprises a port for providing a fluid to the second lumen.

According to still further features in the described preferred embodiments, the vascular graft further comprising a tube selected of a length such that when the vascular graft is implanted in a subject a proximal end of the tube is connected to the port and a distal end of the tube is under or at an outer surface of a skin of the subject.

According to still further features in the described preferred embodiments the second lumen further comprises a second port for outflow of the fluid contained in the second lumen.

According to still further features in the described preferred embodiments the vascular graft further comprising a second tube selected of a length such that when the vascular graft is implanted in the subject a proximal end of the second tube is connected to the second port and a distal end of the second tube is under or at an outer surface of the skin of the subject.

According to still further features in the described preferred embodiments the fluid is a dialysate fluid.

According to still further features in the described preferred embodiments the fluid is a drug-containing fluid.

According to still further features in the described preferred embodiments the membrane is characterized by a Molecular Weight Cut Off (MWCO) in the range between about 1 x 10^3 to about 5 x 10^4 daltons.

According to still further features in the described preferred embodiments the vascular graft further comprising a third lumen, the third lumen being in fluid communication with the first lumen via an additional membrane disposed along at least a portion of a wall separating the first lumen and the third lumen.

According to still further features in the described preferred embodiments the additional membrane is designed for ultrafiltration.

According to still further features in the described preferred embodiments the additional membrane is characterized by an MWCO of about 5.8 x 10^3 daltons.

According to still further features in the described preferred embodiments the first lumen is disposed within the second lumen.

According to still further features in the described preferred embodiments the first lumen is disposed within the third lumen.

According to still further features in the described preferred embodiments an inner diameter of the first lumen is selected from the range of 1-30 mm.

According to still further features in the described preferred embodiments an inner diameter of the second lumen is selected from the range of 2-35 mm.

According to still further features in the described preferred embodiments the vascular graft is composed of a non-woven polymeric material.

According to still further features in the described preferred embodiments the vascular graft is composed of an electrospun polymer.

According to still further features in the described preferred embodiments step (b) is effected prior to step (a).

According to still further features in the described preferred embodiments step (b) is effected following step (a).

According to still further features in the described preferred embodiments step (a) is effected by connecting the first lumen to a vasculature of the subject.

According to still further features in the described preferred embodiments the second lumen comprises a port for providing the dialysate fluid to the second lumen.

According to still further features in the described preferred embodiments the vasculature feeds into the tissue-of-interest.

According to still further features in the described preferred embodiments the second lumen comprises a port for providing the drug to the second lumen.

According to still further features in the described preferred embodiments the membrane is characterized by an average pore size selected from the range of 1-100 Angstrom.

According to still further features in the described preferred embodiments the biological fluid is blood.

According to still further features in the described preferred embodiments the component of the biological fluid is plasma.

According to still further features in the described preferred embodiments step (a) is effected by connecting the first lumen to a urine vessel.

According to still further features in the described preferred embodiments step (a) is effected by connecting the first lumen to a lymphatic vessel.

According to still further features in the described preferred embodiments the second lumen comprises a port for retrieving the sample of the component of the biological fluid from the second lumen.

The present invention successfully addresses the shortcomings of the presently known configurations by providing a vascular graft suitable for *in vivo* hemodialysis, targeted drug delivery and/or low invasiveness sampling of components of biological fluid.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In case of conflict, the patent specification,

including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of the preferred embodiments of the present invention only, and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the invention. In this regard, no attempt is made to show structural details of the invention in more detail than is necessary for a fundamental understanding of the invention, the description taken with the drawings making apparent to those skilled in the art how the several forms of the invention may be embodied in practice.

In the drawings:

FIGs. 1a-d schematically depict four embodiments of the vascular graft of the present invention.

FIG. 2 is a midline section of one embodiment of the vascular graft of the present invention.

FIG. 3 is a schematic three-dimensional view of one embodiment of the vascular graft of the present invention.

FIG. 4 schematically depicts one embodiment of the vascular graft of the present invention.

FIG. 5 schematically depicts one embodiment of the vascular graft of the present invention.

FIG. 6 schematically depicts one embodiment of the vascular graft of the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is of a vascular graft which can be used for *in vivo* hemodialysis, targeted drug delivery and/or low invasiveness sampling of components of a biological fluid (e.g., plasma) for diagnostic purposes.

The principles and operation of the vascular graft and methods of using same according to the present invention may be better understood with reference to the drawings and accompanying descriptions.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details of construction and the arrangement of the components set forth in the following description or illustrated in the drawings. The invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

Hemodialysis is a procedure performed in patients suffering from end-stage renal disease and involves filtering the patient's blood to remove extra salts, minerals, toxins and fluid. Under currently practiced approaches, the patient's blood is withdrawn by tubes connected to implantable access ports and is filtered against a dialysate solution using an artificial kidney machine. Such a procedure can last several hours and is routinely performed 3-4 times per week. An alternative approach of treating end-stage renal disease is peritoneal dialysis, in which the dialysate solution is administered to the patient's abdominal cavity and following a dwell time of 4 to 6 hours, the "waste"-containing dialysate solution is drained outside of the body. However, in addition of being mostly inconvenient, both hemodialysis and peritoneal dialysis are associated with high infection rate, damage to blood vessels, hemorrhage associated with heparin administration during dialysis and general deterioration of the patient's health.

To overcome such limitations, prior art studies have suggested *in vivo* hemodialysis, *i.e.*, dialysis which is performed within the blood vessel of the patient. As described in U.S. Pat. No. 6,561,996 to Gorsuch, such *in vivo* hemodialysis can be effected via a catheter-like filter device which is implanted in the vena cava of the patient and filled with a dialysate solution via another catheter. However, due to the risk of

inserting a "free-floating" device into a main blood vessel of the patient, such a method is not clinically practiced.

While reducing the present invention to practice, the present inventor has devised a vascular graft which can be used for *in vivo* hemodialysis, targeted delivery of a drug into the vasculature feeding the tissue-of-interest and low invasiveness sampling of components of biological fluid (such as plasma) for diagnostic purposes.

Thus, according to one aspect of the present invention, there is provided a vascular graft. The vascular graft of the present invention includes two lumens which are in fluid communication therebetween via a membrane disposed along at least a portion of a wall separating the two lumens.

As used herein the phrase "vascular graft" refers to any tubular structure which is suitable for implantation into a vasculature of a subject. The vascular graft of the present invention is preferably sutured to an excised blood vessel to thereby enable blood flow therethrough.

Several configurations of such a double-lumen graft are envisioned by the present invention. For example, the two lumens can be positioned side by side (e.g., parallel) effectively forming a figure eight cross section. In such a configuration, the lumens share a side wall. Another configuration can be that one lumen is placed on the top of the other lumen as a piggy-back reservoir. In such a configuration the top lumen can have a ball-like shape or it can be of a tubular structure with a main axis being non-parallel with respect to the main axis of the other lumen (e.g., the angle formed between these two axis is > 0 °, e.g., 45° or 90°). Alternatively, the graft can be designed such that one lumen is disposed within a second lumen such that part of the wall forming the inner lumen is shared between the two lumens. Examples of several configurations are described in greater detail below with reference to Figures 1a-d.

Preferably, one lumen of the vascular graft is designed capable of supporting flow of a biological fluid such as blood (referred to as "first lumen" hereinafter) and the other lumen is designed for containing a fluid [e.g. components of the biological fluid, saline, blood (or blood components, e.g., plasma), a dialysate solution, a drug-containing solution and the like] (referred to as "second lumen" hereinafter).

The biological fluid used according to the present invention can be any fluid of a subject such as blood, urine and the like, which is capable of flowing through the first lumen of the graft of the present invention.

The fluid contained within the second lumen can be a biological fluid or components thereof (e.g., plasma) which are present near the vascular graft when implanted in the body, can be from an external source (extracorporeal) or it can be blood components (e.g., plasma) which flow (e.g., by diffusion) from the first lumen to the second lumen via the membrane disposed therebetween. The fluid can be filled prior to and/or following implantation of the graft within the vasculature of the subject. For example, such a fluid can be provided to the second lumen via a syringe needle which is inserted through the graft into the second lumen. It will be appreciated that the second lumen is preferably made such that it can be replenished with fluids without leaking.

Additionally or alternatively, the second lumen can include a port for providing the fluid to the second lumen (referred to as "inport" hereinafter).

According to one preferred embodiment of the present invention, the fluid is provided from an external source (extracorporeal) following implantation of the vascular graft of the present invention. Thus, to enable communication of the fluid to the second lumen (via the inport), the vascular graft further includes a tube or a catheter (further referred to as "inflow tube" hereinafter). Such a tube is designed such that when the vascular graft is implanted in a subject the proximal end of the tube is connected to the inport and the distal end of the tube is under or at an outer surface of a skin of the subject. In various exemplary embodiments of the present invention the inflow tube has a closure element at its distal end.

Preferably, the second lumen of the vascular graft of the present invention further includes a second port for outflow of the fluid contained in the second lumen (further referred to as "outport" hereinafter). Such an outport is preferably connected to the external part of the subject's body via a second tube or catheter (further referred to as "outflow tube" hereinafter). The fluid that is contained within the second lumen can be for example, "waste"-containing dialysate solution (*i.e.*, a dialysate solution following hemodialysis which contains extra salts, minerals, urea and the like), or component(s) of a biological fluid (e.g., part of the blood plasma) which passes (or flows) through the

membrane. Both the inflow and outflow tubes are preferably adapted for placement between an internal location within a subject's body to a selected location within or external to the skin of the subject.

It will be appreciated that the second tube can be used to retrieve a sample of the fluid contained in the second lumen in order, for example, to monitor the presence or the level of non-cellular components of the blood of the subject (e.g., blood levels of glucose, urea and the like).

According to one preferred embodiment of the present invention, the vascular graft is designed to enable low invasiveness sampling of component(s) of a biological fluid (e.g., plasma, serum) for monitoring the presence and/or level of molecules (e.g., salts, protein, viruses) present in such components (for diagnostic purposes) in chronic patients in need thereof (e.g., in diabetic patients). In this case, the second lumen, which contains the component of the biological fluid (e.g., plasma) that flows through the membrane disposed between the first and second lumens, is used solely for sampling such components and thus does not include an inport or an inflow tube. On the other hand, for retrieval of samples of such components of biological fluid, the second lumen preferably includes an outport and preferably also an outflow tube connected thereto as described hereinabove. A non-limiting example of such a graft is described with reference to Figure 5.

As is mentioned above, fluid communication between the two lumens of the vascular graft of the present invention is enabled via a membrane. Such a membrane enables the passage (e.g., flow) of fluid from one lumen to another, *e.g.*, from the first lumen to the second lumen and/or from the second lumen to the first lumen.

The membrane is disposed along at least a portion of the wall separating the two lumens (shared by the lumens). It will be appreciated that the portion of the wall which includes the membrane is selected according to the overall size of the wall shared by the two lumens and the desired amount and rate of fluid that is intended to pass from one lumen to another and it is within the capabilities of those skilled in the art to determine the size of such wall and the relative portion which includes the membrane.

The membrane is used to enable selective passage of particles such as blood components, drugs and fluid from one lumen to the other and its selectivity is depended on the porosity and pore size of the material used for constructing the membrane.

Preferably, the vascular graft is designed such that the membrane contained therein can be washed or even replaced if needed (e.g., in case the membrane is clogged or damaged). For example, for maintenance cleaning, the outflow tube can be closed and a biologically compatible cleansing reagent can be introduced under a certain hydrostatic pressure through the inflow tube. It will be appreciated that membrane replacement can be performed under surgery using techniques known in the art.

The vascular graft can further include a third lumen, which is in fluid communication with the first lumen via an additional membrane disposed along at least a portion of a wall separating the first lumen and the third lumen. Such third lumen preferably includes ports and tubes (or catheters), which connect the third lumen to the external skin of the subject.

It will be appreciated that various configurations can be used to construct the vascular graft with more than two lumens (e.g., three lumens). For example, the third lumen can be designed such that it is placed side by side or on the top of the first and/or second lumen(s), as long as the first and third lumen share a wall, of which at least a portion comprises the additional membrane. For example, part of the first lumen can be disposed within the third lumen, while another part can be disposed within the second lumen (see for example Figure 4); the first lumen can be in parallel to the second lumen and form an angle (e.g., of 90 °) with respect to the third lumen; the first lumen can form an angle (e.g., of 90 °) with respect to the second lumen and be parallel with respect to the third lumen.

The vascular graft of the present invention can further include a pump for administering the fluid into the second lumen (via the inflow tube). The pump can be electrically or mechanically driven and can pump the fluid into the second lumen via the inflow tube. Preferably, the vascular graft of the present invention includes two pumps, for pumping the fluid to and from the second lumen. Such pumps are preferably reciprocating pumps such as peristaltic pumps well known to those skilled in the art. The

pump can be connected to a processing unit, which is programmed to control the delivery of the fluid (via the pump) according to a pre-determined schedule.

Referring now to the drawings, Figures 1a-d schematically illustrate four exemplary configurations of the vascular graft of the present invention which is referred to herein as vascular graft **100**. Graft **100** comprises a first lumen **102**, which is designed to enable flow of biological fluid (e.g., blood) therethrough and a second lumen **104**, which is in fluid communication with lumen **102**, and is designed to contain a fluid [e.g., component(s) of the biological fluid, drug]. Membrane **110**, which is disposed on wall **108**, is shared by lumens **102** and **104** and enables fluid communication therebetween. According to preferred embodiments of the present invention lumen **102** can be configured side by side with respect to lumen **104** effectively forming a figure eight cross section (Figure 1a), on the top of lumen **104** such that an angle **105**, which is greater than "0", is formed between the main axis of both lumens (e.g., angle **105** can be 90 ° as shown in Figure 1b), can be disposed within lumen **104** (Figure 1c) or can include lumen **104** therein (Figure 1d).

Preferably, when placed within the subject (e.g., implanted) lumen **102** is sutured to an excised blood vessel(s) of the subject to enable blood flow therethrough and lumen **104**, which contains the fluid and is in fluid communication with lumen **102** via membrane **110**, is sealed at its ends. It will be appreciated that one or both of the sealed ends of lumen **104** can be also sutured to part of the excised blood vessel as long as such attachment does not hamper the flow of blood through lumen **102**. When the vascular graft is designed according to Figure 1d, lumen **104** preferably includes at least one spoke (e.g., a radial spoke) capable of connecting lumen **104** to outer lumen **102** and/or to at least one of the excised end(s) of the blood vessel(s). Preferably, lumen **104** includes 2-4 radial spokes at each end of its sealed ends capable of securing lumen **104** in its position within lumen **102** even when blood flows therethrough.

Figure 2 illustrates in greater detail one configuration of graft **100**. Graft **100** comprises lumen **102** which is disposed within lumen **104**. Lumen **102** is sutured at its proximal end to feeding blood vessel **118** and at its distal end to receiving blood vessel **120** to thereby enable blood flow therebetween. Lumen **104** is connected to inflow tube **132** via inport **138** and to outflow tube **134** via outport **136**. Inport **138** and outport **136**

enable fluid flow in and out of lumen **104**. Non-limiting examples of such ports are the PORT-A-CATH® Systems provided from Smiths Medical MD, Inc. (Deltec products), St. Paul, Minnesota, USA. Inflow tube **132** is designed to provide fluid (e.g., extracorporeal fluid) into lumen **104**. Outflow tube **134** is designed to enable flow of fluid from lumen **104** to the external part of the subject's body. For example, outflow tube **134** can be for retrieving a sample of the fluid contained in lumen **104** (e.g., subject's plasma) into a collecting tube or bag outside of the subject's body (not shown). Inflow tube **132** and outflow tube **134** are adapted to constitute long-term penetration between implanted vascular graft **100** and a selected location adjacently external to a skin of the subject via dermal adapters **128**. Dermal adapters **128** are generally of a flexible planar geometry, which allows them to be sutured to a surface of a skin of the subject. External shell **146** encompasses lumen **104** and lumen **102**.

Figure 3 schematically depicts a three-dimensional view of vascular graft **100**. Lumen **102** is disposed within lumen **104**. Inport tube **132** is connected at the proximal end to lumen **104** and at the distal end to dermal adapter **128** (shown on the surface of the subject's skin **130**). Outflow tube **134** is connected at the proximal end to lumen **104** and at the distal end to dermal adapter **128**. Feeding blood vessel **118** is connected to a proximal end of lumen **102** and receiving blood vessel **120** is connected to a distal end of lumen **102**.

Figure 4 schematically depicts a three lumen embodiment of vascular graft **100**. In this embodiment lumen **102** is in fluid communication with lumen **104** via membrane **110**, and lumen **106** is in fluid communication with lumen **102** via membrane **142**. A portion of lumen **102** is disposed within lumen **104** and another portion of lumen **102** is disposed within lumen **106**. Wall **108** is shared between lumen **102** and lumen **104** and membrane **110** is disposed on a portion of wall **108**. Wall **140** is shared between lumen **102** and lumen **106** and membrane **142** is disposed on a portion of wall **140**.

Figure 5 schematically depicts one embodiment of the graft of the present invention which can be used for low invasiveness sampling of components of a biological fluid (e.g., for monitoring samples of the components of the biological fluid, such as glucose, urea, salts and the like). Lumen **102** is designed to enable flow of a biological fluid (e.g., blood) and is disposed within lumen **104**. Lumen **104** and lumen **102** are in

fluid communication via membrane **110**, which is disposed on wall **108**. Membrane **110** enables the flow of components of the biological fluid (e.g., plasma, serum) from lumen **102** to lumen **104**. Outport **136** and outflow **134** are designed such that fluid contained in lumen **104** can be retrieved using a low invasive procedure (via dermal adapter **128**) from the outside of the subject's body.

Figure 6 schematically depicts an ambulatory or less stationary configuration of graft **100** forming a close-loop circulation devise. In this embodiment inflow tube **132** and outflow tube **134** are connected to portable reservoir **148**. Specifically, the proximal ends of inflow tube **132** and outflow tube **134** are connected to lumen **104** (preferably via inport **138** and outport **136**, respectively) while the distal ends of inflow tube **132** and outflow tube **134** are connected to portable reservoir **148**. Portable reservoir **148** can include a dialysate solution or a drug-containing fluid as well as "contaminated" dialysate solution (e.g., a dialysate solution following hemodialysis) or components of the biological fluid that were contained in lumen **104**. Fluid contained in portable reservoir **148** can flow through inflow tube **132** and preferably inport **138** to lumen **104**. Fluid contained in lumen **104** can flow via membrane **110** (which is disposed on wall **108**) to lumen **102**. On the other hand, components of the biological fluid, which flows in lumen **102** (e.g., blood), can flow to lumen **104** (via membrane **110**) and further, preferably via outport **136** through outflow **134** to portable reservoir **148**. Dermal adapters **128** connect between the parts of inflow tube **132** and outflow **134** that are implanted in the subject and the parts of these tubes which are placed outside the subject's skin. When used for hemodialysis, portable reservoir **148** is periodically flushed (e.g., every 1-2 days, depending on the size of such reservoir) and the fluid contained therein is replaced with a clean (e.g., substantially pure) dialysate solution. Alternatively, when portable reservoir **148** is used for drug administration, reservoir **148** can be replenished periodically with drug-containing fluid.

The vascular graft of the present invention can be fabricated from a biodegradable polymer, a biostable polymer or a combination of biodegradable and biostable polymers.

Suitable biostable polymers which can be used in the present embodiments include, without limitation, polycarbonate based aliphatic polyurethanes, silicon modificated polyurethanes, polydimethylsiloxane and other silicone rubbers, polyester,

polyolefins, polymethyl- methacrylate, vinyl halide polymer and copolymers, polyvinyl aromatics, polyvinyl esters, polyamides, polyimides and polyethers.

Suitable biodegradable polymers which can be used in the present embodiments include, without limitation, poly (L-lactic acid), poly (lactide-co-glycolide), polycaprolactone, polyphosphate ester, poly (hydroxy- butyrate), poly (glycolic acid), poly (DL-lactic acid), poly (amino acid), cyanocrylate, some copolymers and biomolecules such as collagen, DNA, silk, chitozan and cellulose.

The vascular graft of the present invention can be formed from knitted, woven or non-woven continuous polymeric filament fibers (see for example, U.S.; 6,454,796 to Barkman et al.; US Pat. Appl. No. 20050004664; U.S. Pat. No. 4,323,525; U.S. Pat. No. 4,552,707, which are fully incorporated herein by reference). It will be appreciated that each lumen of the vascular graft of the present invention can include one or more layers of such knitted, woven or non-woven polymeric filaments and each of such layers can have specific properties (e.g., thickness, porosity, pore size) and can be conjugated or impregnated to specific agents or drugs as is further described hereinbelow.

Preferably, the polymeric fibers used to manufacture the vascular graft of the present invention have a diameter in the range between about 50 nm and 1000 nm, more preferably, between about 100 nm and 500 nm.

For example, the vascular graft of the present invention can be made from expanded polytetrafluoroethylene (ePTFE), a woven form of PTFE (made of a carbon and fluorine based synthetic polymer) that creates a mesh-like structure, essentially as described in U.S. Pat. No. 6,719,783 to Lentz, et al.

Alternatively, the polymeric fibers of the vascular graft of the present invention are fabricated using an Electrospinning technique. The Electrospinning steps may be performed using any Electrospinning apparatus known in the art. Suitable Electrospinning techniques are disclosed, e.g., in International Patent Application, Publication Nos. WO 2002/049535, WO 2002/049536, WO 2002/049536, WO 2002/049678, WO 2002/074189, WO 2002/074190, WO 2002/074191, WO 2005/032400 and WO 2005/065578, the contents of which are hereby incorporated by reference. Other spinning techniques are disclosed in, e.g., U.S. Patent Nos., 3,737,508, 3,950,478, 3,996,321, 4,189,336, 4,402,900, 4,421,707, 4,431,602, 4,557,732, 4,643,657, 4,804,511,

5,002,474, 5,122,329, 5,387,387, 5,667,743, 6,248,273 and 6,252,031 the contents of which are hereby incorporated by reference.

It will be appreciated that using the Electrospinning technique one can easily control the porosity and pore size of the electrospun element used to fabricate the vascular graft. For example, a suitable electrospun element which can be used for fabricating the vascular graft of the present invention can have a porosity exceeding 90 % and an average pore size in the range between 1-100 Angstrom. As used herein the phrase "pore size" refers to the nominal dimensions of a particle that cannot traverse the graft wall, namely – a filtration cutoff point, above which the graft wall serves as a barrier.

The vascular graft of the present is preferably characterized by enhanced physical, mechanical and biological properties to support blood flow. Such vascular graft can posses any combination of the following characteristics: (a) inner diameter expandable by at least 10 % under a pulsatile pressure characterizing a mammalian blood system; (b) capable of maintaining the inner diameter while bent at a bent diameter of twice the inner diameter; (c) having a porosity of at least 60 %; (d) preventing leakage of blood passing therethrough; (e) characterized by tissue ingrowth and cell endothelization over at least 90 % of the vascular graft within at least 10 days from implantation in a mammal; and (f) having a self-sealing properties so as to minimize blood leakage following piercing.

The graft designed according to the teachings of the present invention can be implanted in a subject. As used herein the term "subject" refers to any animal subject e.g., a mammal, e.g., a human being at any age who suffers from a pathology or a condition requiring implantation of the graft of the present invention. Such graft can be used for example, to perform *in vivo* hemodialysis, targeted delivery of a drug to the vasculature feeding a tissue-of-interest and/or low invasiveness sampling of components of biological fluid of a subject.

It will be appreciated that the dimensions and membrane selectivity of the vascular graft of the present invention can vary depending on the intended use and the site of implantation. Following is a non-limiting description of membrane selectivity and dimensions which can be used to construct the vascular graft of the present invention.

When the vascular graft of the present invention is used for *in vivo* hemodialysis, the membrane is adapted to enable preferred diffusion of toxins and/or other blood borne molecules between the first lumen (e.g., lumen **102** as shown in Figures 1-4) and the second lumen (e.g., lumen **104** as shown in Figures 1-4), which serves as a dialysis compartment. For this purpose, the membrane (e.g., membrane **110** as shown in Figures 1-4) is preferably characterized by a dialyser Molecular Weight Cut Off (MWCO) in the range between about 1 x 10^3 to about 5 x 10^4 daltons. A comparison of the blood and plasma components passing through these respective cut-off sizes is further shown in Table I of U.S. Pat. No. 5,980,481 which is fully incorporated herein by reference. Such membrane selectivity can be achieved using, for example, an average pore size of about 1–100 Angstrom (Reviewed by Clark WR and Ronco C, 2001, Nephrol. Dial. Transplant 16(Suppl. 5):56-60, which is fully incorporated herein by reference].

When the vascular graft of the present invention is used to deliver a drug into the vasculature feeding the tissue-of-interest (e.g., brain) and/or for low invasiveness sampling of components of a biological fluid, the membrane (e.g., membrane **110** as shown in Figures 1-4) is selected so as to enable the passage of a drug-containing fluid from the second lumen (e.g., lumen **104** as shown in Figures 1-4) to the first lumen (e.g., lumen **102** as shown in Figures 1-4) and/or to enable the flow of component(s) of biological fluid from the first lumen to the second and preferably, to prevent passage of cellular blood components from the first lumen to the second lumen. Such membrane can have an average pore size of about 1–100 Angstrom.

The dimensions of the membrane disposed between the first and second lumens (e.g., membrane **110** as shown in Figures 1-4) depend on the dimension of the wall separating these lumens (e.g., wall **108** as shown in Figures 1a-d, 2, and 4) and of the combination of porosity, average pore size, type of fluid intended to pass therethrough and flow rate of such fluid. A non-limiting example of such dimensions which can be used for *in vivo* hemodialysis are: length 0.5–10 cm, width 1–5 cm and thickness 0.1–1 mm. A non-limiting example of such dimensions which can be used for targeted drug delivery and/or for sampling of components of a biological fluid (e.g., plasma) are: length 0.1–5 cm, width 1–5 cm and thickness 0.1-1 mm.

The dimensions of the first lumen of the vascular graft of the present invention (e.g., lumen **102** as shown in Figures 1-4) are selected so as to enable blood flow therein and are compatible with the flow of blood at the targeted blood vessel when implanted in the subject. Preferably, the inner diameter of the first lumen (e.g., diameter **114** as shown in Figure 2) is from about 1 mm to about 30 mm, more preferably from about 2 mm to about 20 mm, more preferably from about 2 mm to about 10 mm, more preferably, in the range of 3-8 mm (e.g., 6 mm). The thickness of the first lumen (e.g., thickness **116** shown in Figure 2) is preferably selected from the range of about 20 μm to about 2 mm, more preferably, from about 100 μm to about 1.5 mm, more preferably, from about 0.2 mm to about 1.5 mm, even more preferably, from about 0.6 mm to about 1.2 mm.

The length of the first lumen (length **112** as shown in Figure 2) can be from about 1 cm to about 50 cm, depending on the intended use and the target of implantation. For example, for *in vivo* hemodialysis which is performed by implanting the vascular graft in the forearm vein, such a length can be from about 1 cm to about 15 cm (e.g., 8 cm). Alternatively, for targeted drug delivery of a drug into the carotic artery and/or sampling of component(s) of biological fluid (e.g., plasma) such a length can be from about 1 cm to about 5 cm (e.g., 3 cm).

The dimensions of the second lumen of the vascular graft of the present invention (e.g., lumen **104** as shown in Figures 1-4) are selected according to the relative configuration of the second lumen with respect to the first lumen and the intended use of the vascular graft of the present invention. For example, when used for *in vivo* hemodialysis with the configuration depicted in Figure 1c or Figure 2, the second lumen contains dialysate solution and exhibits the following preferred dimensions: the length of the second lumen (length **122** as shown in Figure 2) is from about 4 to about 15 cm, the inner diameter (diameter **124** as shown in Figure 2) is from about 2 to about 35 mm (e.g., from 5-10 mm) and thickness of lumen wall (thickness **126** as shown in Figure 2) is from about 0.5 to about 1 mm.

When the vascular graft of the present invention is configured as shown in Figure 1c or Figure 2 and is used for targeted delivery of a drug into the vasculature feeding tissue and/or organ-of-interest, the second lumen contains drug fluid and the preferred dimensions of the second lumen are as follows: length **122** is from about 1 to about 5 cm,

inner diameter **124** is from about 2 to about 35 mm (e.g., 2-10 mm, 4-10 mm) and thickness of lumen wall **126** is from about 0.5 to about 1 mm.

The dimensions of the inflow (e.g., inflow tube **132** as shown in Figures 2 and 3) and outflow (e.g., outflow tube **134** as shown in Figures 2 and 3) tubes of the vascular graft of the present invention depend on the type (e.g., degree of fluid viscosity) and rate of fluid flow which are selected according to the intended use of the vascular graft.

For example, when the vascular graft is used for *in vivo* hemodialysis (*i.e.*, when the external fluid is a dialysate solution), the inflow/outflow tubes may have the following dimensions: inner diameter from about 0.5 mm to about 10 mm, more preferably, from about 1 mm to about 6 mm, even more preferably, from about 1.5 to about 3 mm (e.g., 2 mm); thickness of the wall of the inflow/outflow tubes can be from about 200 μm to about 1000 μm, more preferably, from about 350 μm to about 800 μm.

When the vascular graft is used for targeted drug delivery, the inflow/outflow tubes may have the following dimensions: inner diameter from about 0.5 mm to about 7 mm, more preferably, from about 1 mm to about 6 mm, even more preferably, from about 1 to about 2 mm (e.g., 1.5 mm); thickness of the wall of the inflow/outflow tubes can be from about 200 μm to about 1000 μm, more preferably, from about 300 μm to about 600 μm.

The length of the inflow/outflow tubes depend on the distance between the site of implantation within the blood vessel and the access site of the tube under or on the subject's skin. Preferably, such distance can be from about 1 cm to about 30 cm.

The dimension of the inport (e.g., inport **138** as shown in Figure 2) and the outport (e.g., outport **136** as shown in Figure 2) of the vascular graft of the present invention are also depended on the type and rate of fluid flow and it is within the capabilities of those skilled in the art to adjust such dimensions to the inflow and outflow tubes and to the thickness of the shell (or wall) surrounding the second lumen.

For example, when the vascular graft is used for hemodialysis, the inport and outport may exhibit the following dimensions: port diameter 13 mm, thickness of port wall 0.3–1.5 mm.

When used for targeted drug delivery, the vascular graft may include only an inport and such an inport can be significantly smaller in size than the one used for *in vivo*

hemodialysis. For example, the inport used for targeted delivery of a drug may exhibit the following dimensions: port diameter 0.2-2 mm, thickness of port wall 0.2-1 mm. Alternatively, when used for sampling of components of biological fluid, the vascular graft can include only the outflow tube which may have the following dimensions: port diameter 0.1-1 mm, thickness of port wall 0.1-1 mm.

It will be appreciated that for both *in vivo* hemodialysis and targeted delivery of drug the inport preferably includes a valve capable of preventing passage of fluid from the second lumen to the inflow tube. Similarly, the outport may also include a valve capable of preventing passage of fluid from the outflow tube to the second lumen. Non-limiting examples of such valves are described in US Pat. No. 6953444 to Rosenberg M., which is fully incorporated herein by reference.

Additionally or alternatively, the wall of the second lumen and/or the port(s) enabling the administration of fluid into the second lumen (e.g., the inport or outport) can be designed so as to enable self-sealing following a needle puncture hole. For example, the wall of the second lumen and/or the ports can be manufactured by electrospinning to include more than one layer, of which one or more layers (e.g., a non-luminal or external layer) contain a thrombogenic agent (e.g., thrombin), such that upon needle extraction, a localized coagulation process would be triggered at the periphery of the needle hole, thereby enhancing the self sealing properties of the vascular graft.

Methods of implanting the vascular graft in the subject are well-known in the art. The site of implantation can be any blood vessel such as a vein or an artery of the hand, forearm, leg, upper abdominal area, carotid artery and the like, depending on the intended use (e.g., the therapeutic application). For example, the vascular graft can be implanted such that it connects an artery (as the feeding blood vessel) with a vein (as the receiving blood vessel), similar to an AV fistula, by techniques known in the art. Briefly, implantation takes place by excising a portion of the targeted blood vessel(s), replacing such portion with the vascular graft and connecting the graft to the excised ends of the feeding and receiving blood vessels to thereby allow blood flow through the first lumen. It will be appreciated that the internal diameter of the feeding blood vessel should be roughly equal or larger than the internal diameter of the proximal end of the first lumen of the vascular graft and the internal diameter of the receiving blood vessel should be

roughly equal or larger than the internal diameter of the distal end of the first lumen of the vascular graft. Following implantation, the distal ends of the inflow and outflow tubes (which are connected to the inport and outport of the second lumen) are connected to dermal adapters placed under the skin and connected to a subcutaneous port or alternatively constitute direct interface with the outside environment of the subject's skin.

Thus, the vascular graft of the present invention can be implanted in a subject in need of hemodialysis, e.g., a subject who suffers from end-stage renal disease. In this case, a dialysate solution is administered prior to or following implantation of the vascular graft in the subject. For hemodialysis, the distal end of the inflow tube (e.g., tube **132** in Figures 2 and 3) is connected to a source of dialysate solution and the "waste"-containing dialysate solution is disposed through the distal end of the outflow tube (e.g., tube **134** in Figures 2 and 3) outside of the subject's body into a collecting bag. The dialysate solution can be administered periodically (according to a pre-programmed schedule) or can be provided as a bolus administration by the subject or a health-care giver. Similarly, the "waste"-containing dialysate solution can be collected (or drained) into a collecting bag placed outside the body in an outflow rate that is coordinated with the inflow rate of the dialysate solution. It will be appreciated that in order to determine whether the treatment session has reached sufficient physiological effect, routine analysis of selected characteristics of blood is performed. In addition, routine maintenance sessions of the dialysis compartment of the vascular graft (*i.e.*, the second lumen) can be performed by compressing the hemodialysis compartment with a cleansing agent at a predetermined hydrostatic pressure for a predetermined duration of time.

Alternatively, when a vascular graft capable of close-loop circulation (according to the embodiment described with reference to Figure 6) is implanted in the subject, the distal ends of the inflow tube and the outflow tube (e.g., tubes **132** and **134**, respectively in Figure 6) are connected to a portable reservoir (reservoir **148**, Figure 6) which is preferably placed outside the subject's skin. The dialysate solution in this case is periodically flushed and replaced in order to control efficient hemodialysis.

It will be appreciated that for hemodialysis the vascular graft of the present invention can be configured to include three lumens as schematically depicted in Figure 4. Thus, blood which flows from a feeding blood vessel towards a receiving blood vessel

(see direction of blood flow marked by arrow **144** in Figure 4) is subject to a first dialysis by a dialysate solution that is provided to the second lumen (lumen **104** in Figure 4). Such dialysis is performed via the first membrane (membrane **110** in Figure 4) that is characterized by a MWCO in the range of 1×10^3 - 5×10^4 daltons. The blood then continues to flow within the first lumen of the vascular graft and is further subjected to ultrafiltration by a second dialysate solution suitable for ultrafiltration that is provided to the third lumen (lumen **106** in Figure 4). Such dialysis is performed via the second membrane (membrane **142** shown in Figure 4) which enables the passage of particles up to 5.8×10^4 daltons. Membrane **142** is characterized by an effective pore size in the range between 20 and 500 Angstrom.

Additionally or alternatively, ultrafiltration for hemodialysis can be controlled by modulating (e.g., decreasing) the hydrostatic pressure in the dialysate compartment of the vascular graft of the present invention (e.g., the second and/or third lumen of the vascular graft) to thereby promote the removal of fluid and middle-sized molecules from the blood stream into the dialysate compartment. As used herein the phrase "middle-sized molecules" refers to molecules having a size in the range between 20 and 58 kilo Daltons. It will be appreciated that such middle-sized molecules include cytokines involved in sepsis and molecules considered to cause uremia.

Thus, by implanting the vascular graft of the present invention in the subject hemodialysis and preferably also ultrafiltration of the blood is performed without exposing the subject to un-necessary blood withdrawal and risk of blood coagulation and contamination.

Additionally or alternatively, the vascular graft of the present invention can be implanted in a subject in need of targeted delivery of a drug to the vasculature feeding the tissue-of-interest (*e.g.*, a tissue which exhibits a pathology treatable by the drug). In this case, the first lumen of the vascular graft of the present invention is preferably connected to a vasculature of the subject that feeds into the tissue-of-interest and the second lumen can be connected to an inflow tube which provides the drug. For example, in order to introduce chemotherapy agents into a subject's brain, the first lumen of the vascular graft can be connected to the carotic artery which feeds the brain. Alternatively, in order to

introduce a drug molecule to the liver (e.g., a chemotherapy drug), the first lumen of the vascular graft can be connected to the hepatic artery.

Thus, by implanting the vascular graft of the present invention in the subject a drug, which may have a short half-life or alternatively, which may be extremely expensive such as a chemotherapy agent, can be administered to the tissue or organ-of-interest without exposing the subject to unwanted side-effects. It will be appreciated that the use of the vascular graft of the present invention as a drug delivery system is advantageous over existing drug delivery systems. For example, the Medtronic's IsoMed™ constant flow infusion system uses gas-compressed means for intra-arterial delivery of a chemotherapeutic agent into the hepatic artery. In contrast to prior art systems, the drug delivery system of the present invention is based on a simple to implant and operate system, which may use passive administration of a drug, for prolonged drug delivery into a tissue or organ-of-interest (e.g., the liver via the hepatic artery).

The graft of the present invention (e.g., as described in reference to Figure 5 hereinabove) can be also used for sampling a component of a biological fluid of a subject. For example, in case the biological fluid that flows in the first lumen is blood, then a component which can be sampled using the graft of the present invention can be for example plasma, serum and the like.

As used herein, the term "sampling" refers to the removal of a portion of the component of the biological fluid (e.g., plasma) of the subject for examination or analysis. Thus, a graft according to the teachings of the present invention can be implanted in a subject and a fluid contained in the second lumen (e.g., plasma) can be retrieved via for example, the outport and the outflow tube. The graft can be implanted in any vessel of the subject (e.g., a blood vessel, a urine vessel and/or a lymphatic vessel) such that the first lumen is sutured to excised ends of the vessel (essentially as described hereinabove). Samples of the components of the biological fluid (e.g., plasma) can be further monitored for the presence of markers of interest, e.g., glucose level, platelet count, urea, salts and the like.

In addition, the vascular graft of the present invention can be used for controlling a level of a drug administered to a subject. Thus, the vascular graft of the present invention is implanted in the subject as described hereinabove and the drug is

administered into the second lumen, preferably via the inflow tube and preferably also the inport. In order to control the level of the drug administered to the subject a sample of the plasma contained within the second lumen is retrieved (e.g., by the outport and the outflow tube conected to the second lumen) and monitored for the presence and/or level of a marker(s) indicative for the effect of the drug. For example, if the drug administered to the subject is insulin, the marker, which presence and/or level is monitored can be glucose. Alternatively, if the drug administered to the subject is a chemotherapy drug, the marker which presence and/or level is detected in the sample of the plasma can be a cancer related marker such as the prostate-specific antigen (PSA).

Thus, the teachings of the present invention can be used for controlling the administration of a drug-of-interest by detecting the effect of the drug simultaneously or following predetermined time periods of drug administration, without exposing the subject to un-necessary invasive and repeated puncturing. For example, when a gene therapy – based agent (e.g., adenovirus-mediated agent) is administered to the brain of a subject having a brain tumor, the level of the gene therapy agent being administered to the vasculature feeding the brain can be carefully controlled by monitoring the presence and/or level of markers in the plasma that are indicative of the drug effect.

It will be appreciated that the vascular graft of the present invention can further include drug molecules or agents which are impregnated or covalently attached to the polymers used to fabricate the graft. Such drug molecules can be slowly released from the graft to the blood stream and/or the tissues present near the site of implantation to thereby provide an additional therapeutic effect. For example, to prevent blood coagulation or re-stenosis following implantation of the graft, the graft of the present invention can include anti-coagulation factors, antithrombotic or trombolytic agents (e.g., antiplatelet, heparin, tridodecylmethylammonium-heparin, ticlopidine, caumadin), anti-inflammatory agent (e.g., dexamethasone). In addition, the graft can include various hormones (e.g., estrogen, corticosteroid), vasodilator agents, antimicrobial drugs, antibiotic, anti-cancer agents (e.g., cytostatic agent, antimitotic or antiproliferative agents such as epothilone A, epothilone B), antisecretory, nonsterodial anti-inflammatory agents, growth factor antagonist, free radical scavenger, antioxidant and/or immunosuppressive agent. The agents, which can be impregnated or covalently attached to the graft can be

for example an imaging agent (e.g., a radioopaque agent, a radiolabeled agent) which is used to monitor the graft following implantation within the body.

In addition, as is mentioned before, the vascular graft can include factors which promote blood coagulation (e.g., thrombin, collagen, von Willebrand Factor, Thrombospondin, Tissue Factor, phospholipids, platelet activating factor or an analogue thereof, fibrin, factor V, factor IX, an Antiphospholipid antibody or a portion thereof, copper or an alloy thereof and platinum or an alloy thereof) and which assist in suture of puncture holes. Such agents are preferably attached to non-luminal layers (e.g., middle layer or outer layer) of a vascular graft as described in PCT/IL2006/000102 to the present inventor which is fully incorporated herein by reference.

As used herein the term "about" refers to ± 10 %.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims. All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention.

WHAT IS CLAIMED IS:

1. A vascular graft comprising two lumens being in fluid communication therebetween via a membrane disposed along at least a portion of a wall separating said two lumens.

2. The vascular graft of claim 1, wherein a first lumen of said two lumens is designed capable of supporting blood flow.

3. The vascular graft of claim 2, wherein a second lumen of said two lumens comprises a port for providing a fluid to said second lumen.

4. The vascular graft of claim 3, further comprising a tube selected of a length such that when the vascular graft is implanted in a subject a proximal end of said tube is connected to said port and a distal end of said tube is under or at an outer surface of a skin of said subject.

5. The vascular graft of claim 4, wherein said second lumen further comprises a second port for outflow of said fluid contained in said second lumen.

6. The vascular graft of claim 5, further comprising a second tube selected of a length such that when the vascular graft is implanted in said subject a proximal end of said second tube is connected to said second port and a distal end of said second tube is under or at an outer surface of said skin of said subject.

7. The vascular graft of claim 3, wherein said fluid is a dialysate fluid.

8. The vascular graft of claim 3, wherein said fluid is a drug-containing fluid.

9. The vascular graft of claim 2, wherein said membrane is characterized by a Molecular Weight Cut Off (MWCO) in the range between about 1 x 10^3 to about 5 x 10^4 daltons.

10. The vascular graft of claim 2, further comprising a third lumen, said third lumen being in fluid communication with said first lumen via an additional membrane disposed along at least a portion of a wall separating said first lumen and said third lumen.

11. The vascular graft of claim 10, wherein said additional membrane is designed for ultrafiltration.

12. The vascular graft of claim 11, wherein said additional membrane is characterized by an MWCO of about 5.8 x 10^3 daltons.

13. The vascular graft of claim 3, wherein said first lumen is disposed within said second lumen.

14. The vascular graft of claim 10, wherein said first lumen is disposed within said third lumen.

15. The vascular graft of claim 2, wherein an inner diameter of said first lumen is selected from the range of 1-30 mm.

16. The vascular graft of claim 13, wherein an inner diameter of said second lumen is selected from the range of 2-35 mm.

17. The vascular graft of claim 1, wherein the vascular graft is composed of a non-woven polymeric material.

18. The vascular graft of claim 1, wherein the vascular graft is composed of an electrospun polymer.

19. A method of performing *in vivo* hemodialysis in a subject, comprising:

(a) implanting in the subject a vascular graft comprising two lumens being in fluid communication therebetween via a membrane disposed along at least a portion of a wall separating said two lumens, wherein a first lumen of said two lumens is designed capable of supporting blood flow and whereas a second lumen of said two lumens is designed for containing a dialysate fluid; and

(b) administering said dialysate fluid into said second lumen;

thereby performing the *in vivo* hemodialysis in the subject.

20. The method of claim 19, wherein step (b) is effected prior to step (a).

21. The method of claim 19, wherein step (b) is effected following step (a).

22. The method of claim 19, wherein step (a) is effected by connecting said first lumen to a vasculature of the subject.

23. The method of claim 19, wherein said second lumen comprises a port for providing said dialysate fluid to said second lumen.

24. The method of claim 23, wherein said vascular graft further comprises a tube selected of a length such that when said vascular graft is implanted in the subject a proximal end of said tube is connected to said port and a distal end of said tube is under or at an outer surface of a skin of the subject.

25. The method of claim 24, wherein said second lumen further comprises a second port for outflow of a fluid contained in said second lumen.

26. The method of claim 25, wherein said vascular graft further comprises a second tube selected of a length such that when said vascular graft is implanted in the subject a proximal end of said second tube is connected to said second port and a distal end of said second tube is under or at an outer surface of said skin of the subject.

27. The method of claim 19, wherein said membrane is characterized by a Molecular Weight Cut Off (MWCO) in the range between about 1×10^3 to about 5×10^4 daltons.

28. The method of claim 19, wherein said vascular graft further comprises a third lumen, said third lumen being in fluid communication with said first lumen via an additional membrane disposed along at least a portion of a wall separating said first lumen and said third lumen.

29. The method of claim 28, wherein said additional membrane is designed for ultrafiltration.

30. The method of claim 29, wherein said additional membrane is characterized by an MWCO of about 5.8×10^3 daltons.

31. The method of claim 19, wherein said first lumen is disposed within said second lumen.

32. The method of claim 28, wherein said first lumen is disposed within said third lumen.

33. The method of claim 19, wherein an inner diameter of said first lumen is selected from the range of 1-30.

34. The method of claim 31, wherein an inner diameter of said second lumen is selected from the range of 2-35 mm.

35. The method of claim 19, wherein said vascular graft is composed of a non-woven polymeric material.

36. The method of claim 19, wherein the vascular graft is composed of an electrospun polymer.

37. A method of administering a drug into a tissue-of-interest of a subject, comprising:

(a) implanting in the subject a vascular graft comprising two lumens being in fluid communication therebetween via a membrane disposed along at least a portion of a wall separating said two lumens, wherein a first lumen of said two lumens is designed capable of supporting blood flow and whereas a second lumen of said two lumens is designed for containing the drug; and

(b) administering the drug into said second lumen;

thereby administering the drug into the tissue-of-interest of the subject.

38. The method of claim 37, wherein step (b) is effected prior to step (a).

39. The method of claim 37, wherein step (b) is effected following step (a).

40. The method of claim 37, wherein step (a) is effected by connecting said first lumen to a vasculature of the subject.

41. The method of claim 40, wherein said vasculature feeds into the tissue-of-interest.

42. The method of claim 37, wherein said second lumen comprises a port for providing the drug to said second lumen.

43. The method of claim 42, wherein said vascular graft further comprises a tube selected of a length such that when said vascular graft is implanted in the subject a proximal end of said tube is connected to said port and a distal end of said tube is under or at an outer surface of a skin of the subject.

44. The method of claim 43, wherein said second lumen further comprises a second port for outflow of a fluid contained in said second lumen.

45. The method of claim 44, wherein said vascular graft further comprises a second tube selected of a length such that when said vascular graft is implanted in the subject a proximal end of said second tube is connected to said second port and a distal end of said second tube is under or at an outer surface of said skin of the subject.

46. The method of claim 37, wherein said membrane is characterized by an average pore size selected from the range of 1-100 Angstrom.

47. The method of claim 37, wherein said first lumen is disposed within said second lumen.

48. The method of claim 37, wherein an inner diameter of said first lumen is selected from the range of 1-30 mm.

49. The method of claim 47, wherein an inner diameter of said second lumen is selected from the range of 2-35 mm.

50. The method of claim 37, wherein said vascular graft is composed of a non-woven polymeric material.

51. The method of claim 37, wherein said vascular graft is composed of an electrospun polymer.

52. A method of sampling a component of a biological fluid of a subject, comprising:

(a) implanting in the subject a graft comprising two lumens being in fluid communication therebetween via a membrane disposed along at least a portion of a wall separating said two lumens, wherein a first lumen of said two lumens is designed capable of supporting biological fluid flow and whereas a second lumen of said two lumens is designed for containing the component of the biological fluid; and

(b) retrieving a sample of the component of the biological fluid from said second lumen;

thereby sampling the component of the biological fluid of the subject.

53. The method of claim 52, wherein said biological fluid is blood.

54. The method of claim 52, wherein the component of the biological fluid is plasma.

55. The method of claim 52, wherein step (b) is effected following step (a).

56. The method of claim 52, wherein step (a) is effected by connecting said first lumen to a vasculature of the subject.

57. The method of claim 52, wherein step (a) is effected by connecting said first lumen to a urine vessel.

58. The method of claim 52, wherein step (a) is effected by connecting said first lumen to a lymphatic vessel.

59. The method of claim 52, wherein said second lumen comprises a port for retrieving said sample of the component of the biological fluid from said second lumen.

60. The method of claim 52, wherein said vascular graft further comprises a tube selected of a length such that when said vascular graft is implanted in the subject a proximal end of said tube is connected to said port and a distal end of said tube is under or at an outer surface of a skin of the subject.

61. The method of claim 52, wherein said membrane is characterized by an average pore size selected from the range of 1-100 Angstrom.

62. The method of claim 52, wherein said vascular graft is composed of a non-woven polymeric material.

63. The method of claim 52, wherein said vascular graft is composed of an electrospun polymer.

64. A method of controlling a level of a drug administered to a subject, comprising:

(a) implanting in the subject a graft comprising two lumens being in fluid communication therebetween via a membrane disposed along at least a portion of a wall separating said two lumens, wherein a first lumen of said two lumens is designed capable of supporting biological fluid flow and whereas a second lumen of said two lumens is designed for containing a component of said biological fluid of the subject and the drug;

(b) administering the drug into said second lumen;

(c) retrieving a sample of said component of said biological fluid from said second lumen; and

(d) monitoring said sample of said component of biological fluid for presence and/or level of a marker indicative of an effect of the drug;

thereby controlling the level of the drug administered to the subject.

65. The method of claim 64, wherein said biological fluid is blood.

66. The method of claim 64, wherein said component of said biological fluid is plasma.

67. The method of claim 64, wherein step (b) is effected prior to step (a).

68. The method of claim 64, wherein step (b) is effected following step (a).

69. The method of claim 64, wherein step (a) is effected by connecting said first lumen to a vasculature of the subject.

70. The method of claim 69, wherein said vasculature feeds into a tissue-of-interest.

71. The method of claim 64, wherein said second lumen comprises a port for providing the drug to said second lumen.

72. The method of claim 64, wherein said graft further comprises a tube selected of a length such that when said graft is implanted in the subject a proximal end of said tube is connected to said port and a distal end of said tube is under or at an outer surface of a skin of the subject.

73. The method of claim 64, wherein said second lumen further comprises a second port for retrieving said sample of said component of biological fluid from said second lumen.

74. The method of claim 73, wherein said graft further comprises a second tube selected of a length such that when said graft is implanted in the subject a proximal end of said second tube is connected to said second port and a distal end of said second tube is under or at an outer surface of said skin of the subject.

75. The method of claim 64, wherein said membrane is characterized by an average pore size selected from the range of 1-100 Angstrom.

76. The method of claim 64, wherein said graft is composed of a non-woven polymeric material.

77. The method of claim 64, wherein said graft is composed of an electrospun polymer.

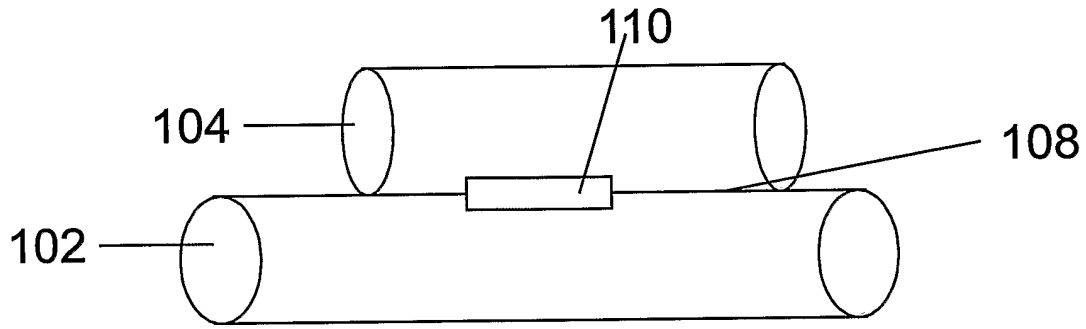

Fig. 1a

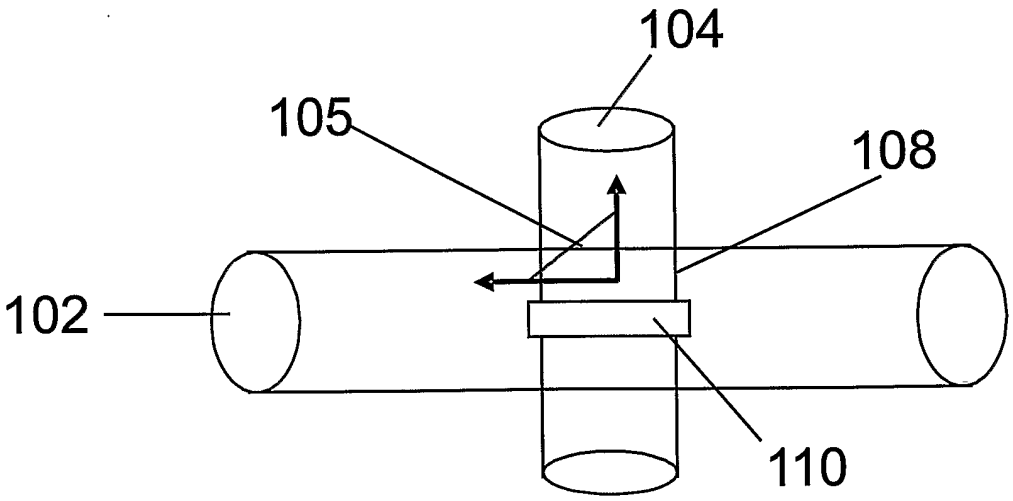

Fig. 1b

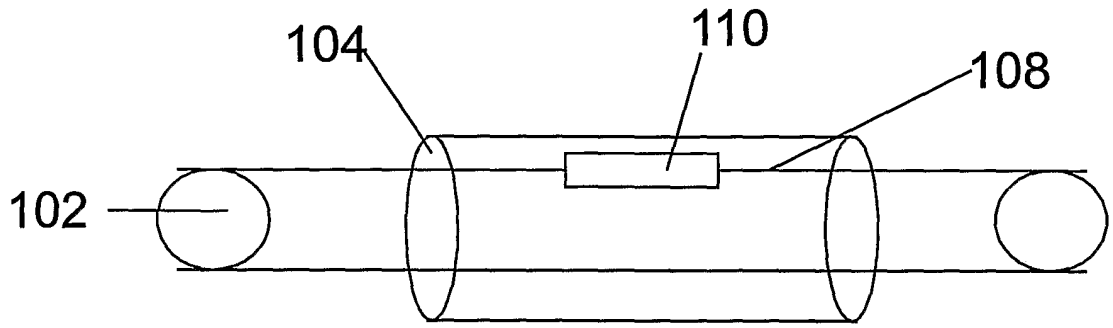

Fig. 1c

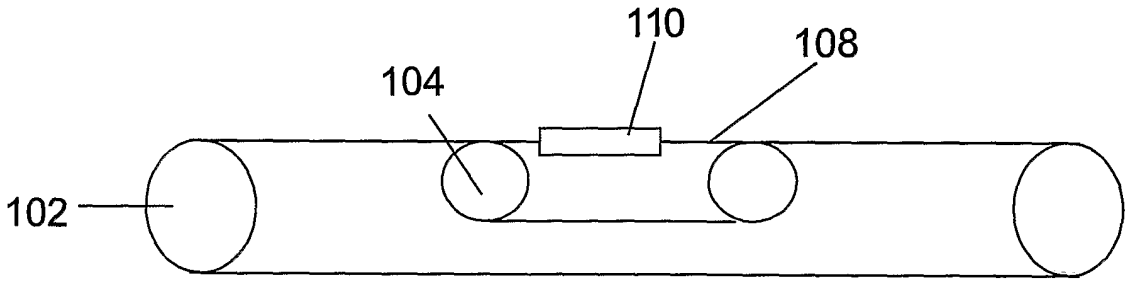

Fig. 1d

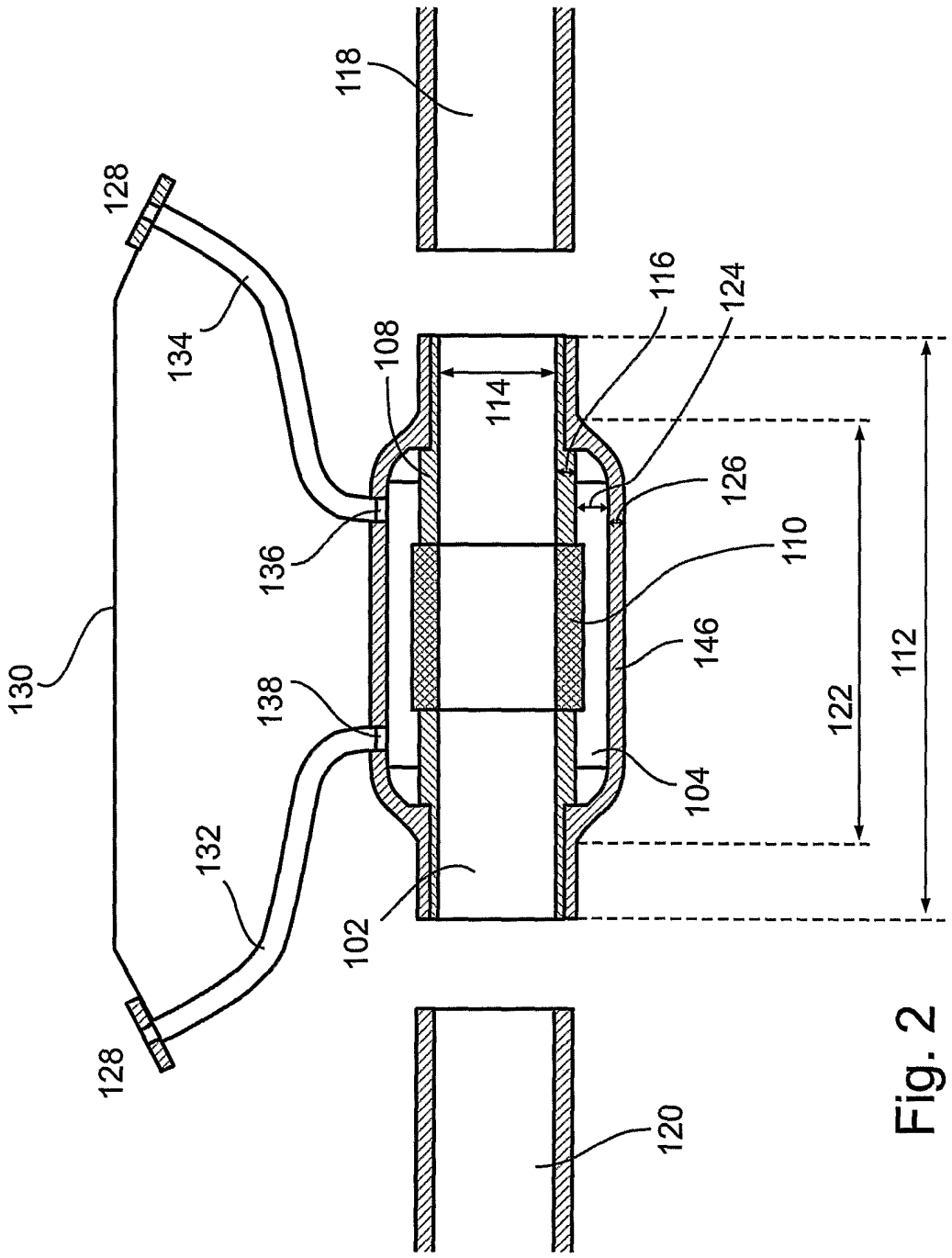
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Fig. 2

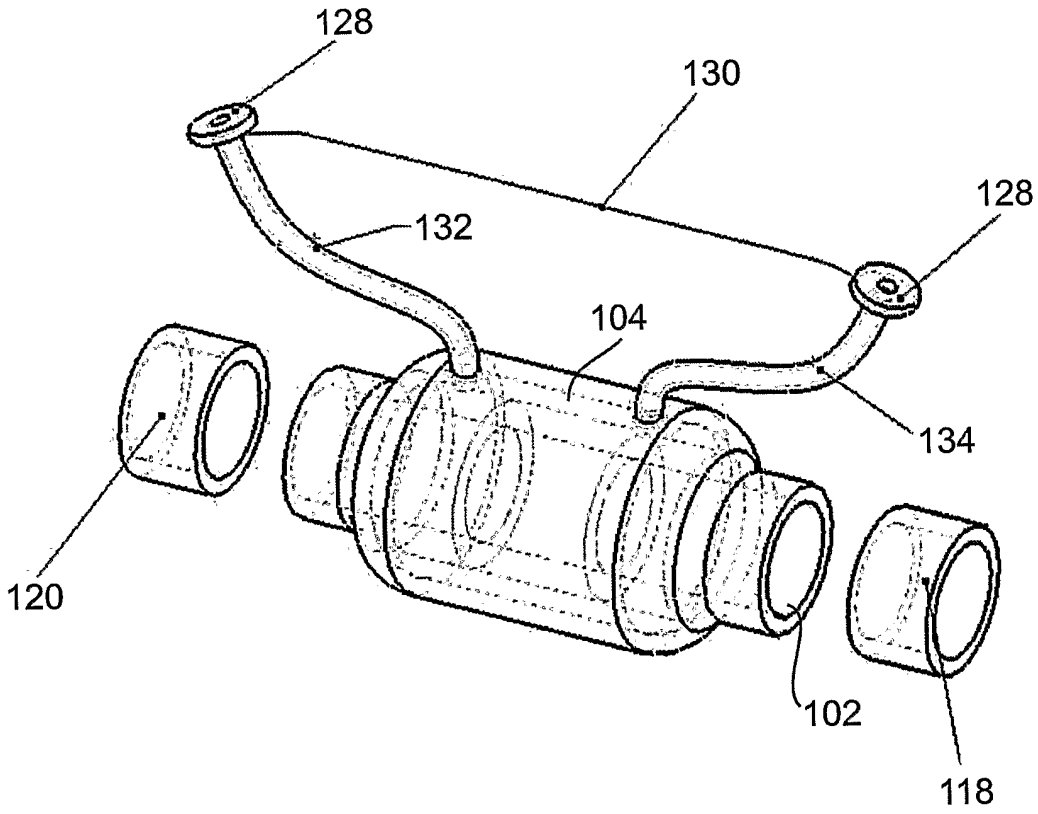

Fig. 3

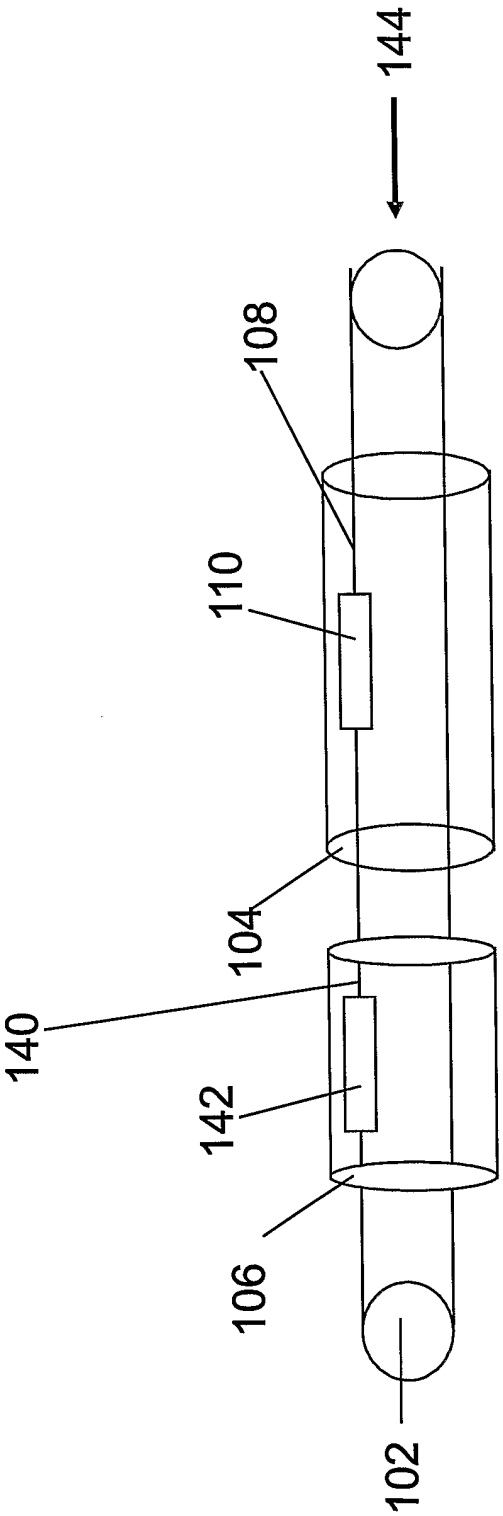

Fig. 4

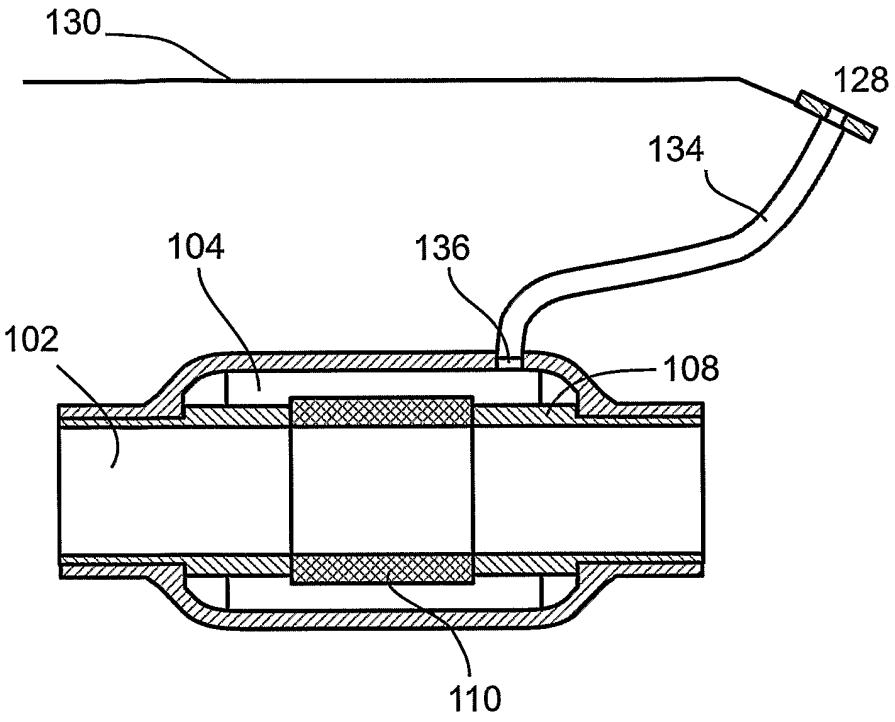
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Fig. 5

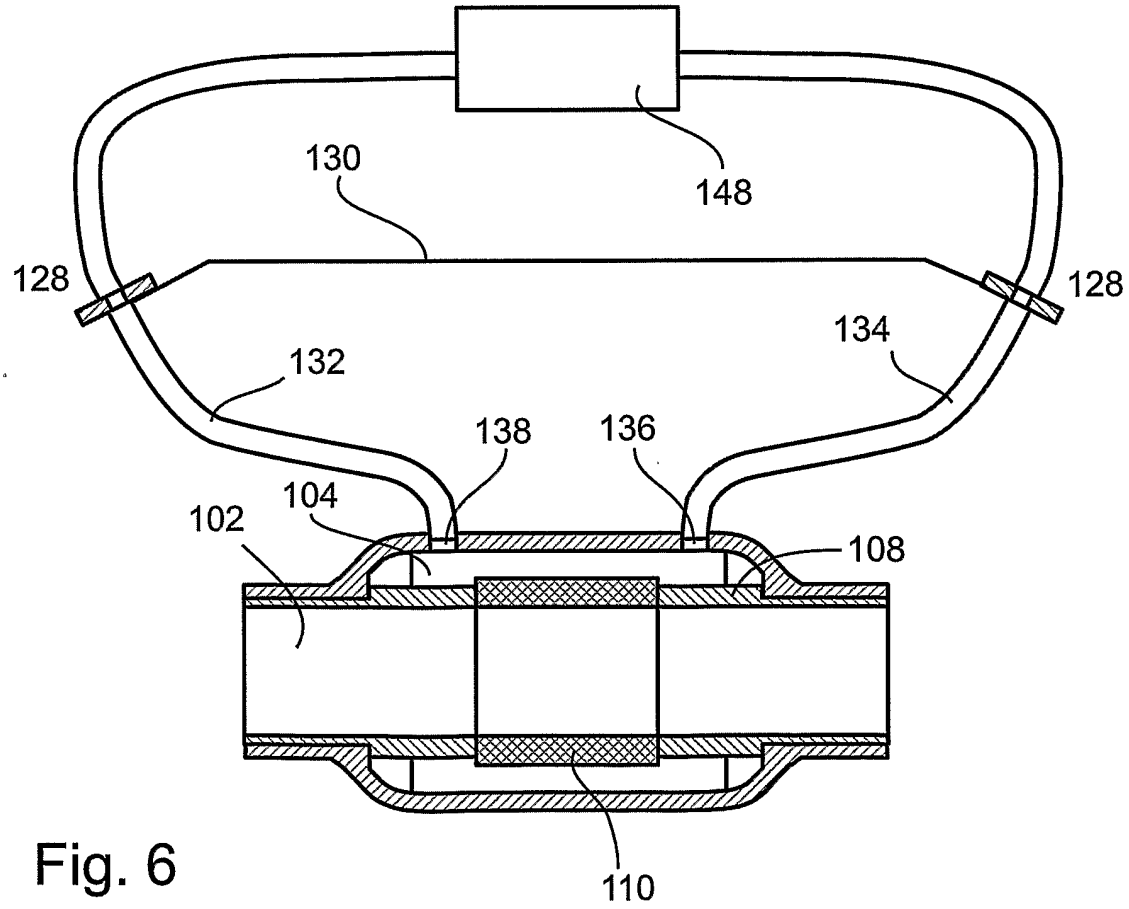
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Fig. 6