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(54) Title: WEARABLE HEMOPERFUSION DEVICE

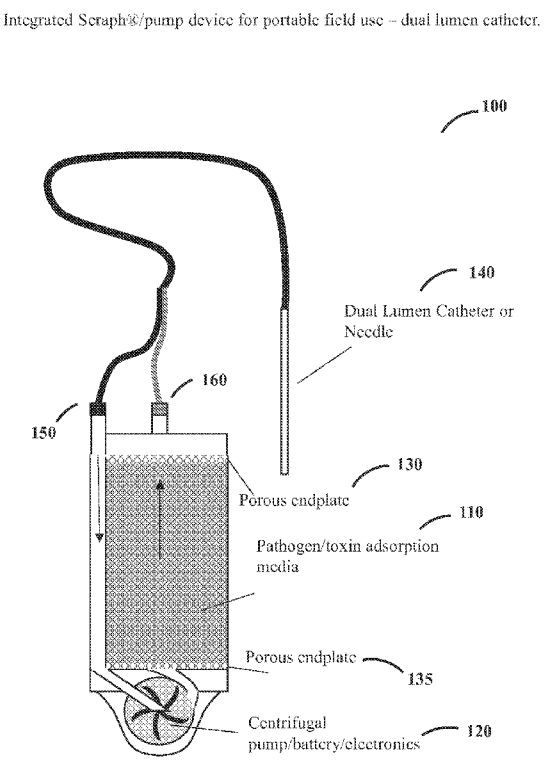

FIG. 1

(57) Abstract: The present technology relates to methods and devices for the removal of toxins and pathogens from infected blood of patients. In particular, devices are designed to be portable, wearable, disposable and self-contained extracorporeal devices that can be easily assembled from a kitln one embodiment, the present invention provides a portable and/or wearable device for extracorporeal removal of a toxin and/or pathogen from blood of an individual infected with a toxin and/or pathogen.

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WEARABLE HEMOPERFUSION DEVICE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Patent Application No. 62/117,108, filed February 17, 2015 and to U.S. Provisional Application No. 62/053,706, filed September 22, 2014, the teachings of which are hereby incorporated by reference in their entireties for all purposes.

BACKGROUND OF THE INVENTION

[0002] With urgent threats of drug resistant organisms, untreatable viral outbreaks, and both known and unknown biological weapons, new countermeasures are required for domestic and military use. While significant research is being performed to develop new antibiotics and vaccines, less effort is being invested in other potential countermeasures, such as broad-spectrum extracorporeal therapies.

[0003] A device that can safely remove a very broad spectrum of pathogens and toxins can be used for many different types of threats. Additional advantages include rapid performance, reduced risk of side-effects and associated toxicity. However, a potential disadvantage of extracorporeal technologies is device portability, mass scale storage, and a requirement of significant technical training to deploy or respond to a mass casualty event. While drugs may not suffer from these limitations, the process of drug discovery and approval is very slow, and the drug industry simply cannot respond quickly enough to severe outbreaks if a drug is unavailable.

[0004] There is a need in the art for an effective self-contained, wearable extracorporeal device that can remove toxins and pathogens from the bloodstream of exposed or infected patients. The devices and methods of the present invention meet this need and provide additional advantageous as well.

BRIEF SUMMARY OF THE INVENTION

[0005] In one embodiment, the present invention provides a portable and/or wearable device for extracorporeal removal of a toxin and/or pathogen from blood of an individual

infected with a toxin and/or pathogen. The portable and/or wearable device includes a cartridge, the cartridge comprising an adsorption media, wherein the adsorption media is a solid substrate of high surface area having at least one polysaccharide adsorbent on the surface thereof with a binding affinity or binding site for the toxin and/or pathogen such that when the flowing blood is in contact with the adsorption media, the toxin and/or pathogen bind to the binding sites on the at least one polysaccharide adsorbent and become separated from blood. In some embodiments, the device includes a pump such as a rotary pump. In other aspects, the portable and/or wearable device also includes a power source, and optionally an electronic control module. In some aspects, the power source is detachable. The electronic control module can optionally be detachable.

[0006] In another embodiment, the present invention provides a portable and/or wearable extracorporeal hemoperfusion device, the device comprising:

a cartridge comprising adsorption media, the cartridge having a first endplate and a second endplate;

a blood influx port to allow blood to flow into the device; and

a blood efflux port to allow blood to flow out of the device, wherein the blood flows through the first endplate through the adsorption media and out the blood efflux port.

[0007] In yet another embodiment, the present invention provides an *ex vivo* method of reducing and/or removing a toxin and/or pathogen in the blood of an individual infected with the toxin and/or pathogen. The extracorporeal method comprises: a) passing blood from the individual through a portable or wearable device comprising an adsorption media, wherein the adsorption media and toxins and/or pathogens in the blood form an adhering complex; b) separating the resulting blood from the adhering complex to produce blood with a reduced level of the toxin and/or pathogen; and c) infusing or returning the blood with the reduced level of the toxin and/or pathogen (back) into the individual.

[0008] In some aspects, the blood is selected from the group consisting of whole blood, serum and plasma. In preferred aspects, the blood is whole blood. In some aspects, the adsorption media is a solid substrate of high surface area having at least one polysaccharide adsorbent. In some instances, the at least one polysaccharide adsorbent is selected from the group consisting of heparin, heparan sulfate, hyaluronic acid, sialic acid, carbohydrates with mannose sequences, chitosan, and a combination thereof. The solid substrate can include a

plurality of rigid polymer bead. The rigid polymer bead can be selected from the group consisting of polyurethane, polymethylmethacrylate, polyethylene or co-polymers of ethylene and other monomers, polyethylene imine, polypropylene, and polyisobutylene. Alternatively, the solid substrate can include one or a plurality of hollow fibers. In some aspects, the device used in the method also includes a pump.

[0009] In some aspects, the portable and/or wearable device is a blood bag.

[0010] In some aspects, by performing the method described herein the toxin or pathogen in the blood is reduced by about 10% to about 100%, e.g., about 10%, about 15%, about 20%, about 25%, about 30%, about 35% about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95% or about 100%. In some aspects, the pathogen in the blood is reduced by about 10% to about 100%, e.g., about 10%, about 15%, about 20%, about 25%, about 30%, about 35% about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95% or about 100%.

[0011] In some aspects, the toxin is selected from the group consisting of *Clostridium botulinum* toxin, ricin toxin from *Ricinus communis*, epsilon toxin of *Clostridium perfringens*, Shiga toxin, and a combination thereof. In some aspects, the pathogen is selected from the group consisting of Ebola virus, Marburg virus, Lassa virus, Junin virus, Machupo virus, Guanarito virus, Chapare virus, Lugo virus, Dengue virus, Garis virus, Ilesha virus, Rift Valley Fever virus, Kyasanur Forest disease virus, Yellow Fever virus, Seoul virus, Crimean-Congo hemorrhagic fever virus, Scandinavian nephropathia epidemica virus, hantavirus, smallpox virus, *Bacillus anthracis*, *Yersinia pestis*, and *Francisella tularenis*, and a combination thereof. In other aspects, the pathogen is Ebola virus, Marburg virus, Lassa virus, Dengue virus, smallpox virus, *Bacillus anthracis*, *Yersinia pestis*, *Francisella tularenis*, and a combination thereof.

[0012] In some aspects, the least one polysaccharide adsorbent is selected from the group consisting of heparin, heparan sulfate, hyaluronic acid, sialic acid, carbohydrates with mannose sequences, chitosan, and a combination thereof. The solid substrate can include a plurality of rigid polymer bead. The rigid polymer bead can be selected from the group consisting of polyurethane, polymethylmethacrylate, polyethylene or co-polymers of ethylene and other monomers, polyethylene imine, polypropylene, and polyisobutylene. Alternatively, the solid substrate can include one or a plurality of hollow or solid fibers.

[0013] Also provided herein is a kit including the portable and/or wearable device described herein and an instruction manual. In some aspects, the kit includes sterile saline. The kit can also include an anti-coagulant agent, *e.g.*, heparin or a pharmaceutically effective therapeutic agent, *e.g.*, an antiviral drug, an antibacterial drug, or anti-toxin drug.

[0014] These and other aspects, objects and embodiments will become more apparent when read with the detailed description which follows.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] FIG. 1 is a schematic illustration of an exemplary embodiment of an integrated Seraph® pump device with a dual lumen catheter.

[0016] FIG. 2 is a schematic illustration of an exemplary embodiment of an integrated Seraph® pump device with separate arterial (supply) and venous (return) blood access.

[0017] FIG. 3 is a schematic illustration of an exemplary embodiment of a wearable Seraph® pump device with no external pump. The blood flow is driven by differential pressure between arterial and venous pressure.

[0018] FIG. 4 is a schematic illustration of an exemplary embodiment of an integrated Seraph® pump device with separate arterial and venous blood access. The device has a remote power source and electronic controls.

[0019] FIG. 5 is a schematic illustration of an exemplary embodiment of an integrated Seraph® pump device w with a dual lumen catheter. The device has a remote power source and electronic controls.

[0020] FIG. 6 is a schematic illustration of exemplary embodiments of the filtration cartridge containing the pathogen and toxin adsorption media. The cartridge can be cylindrical 610, contoured 620 or brick-shaped 630.

[0021] FIGS. 7A-B illustrate an inventive device and treatment without hardware or instrumentation. FIG. 7A illustrates a blood collection through a filter. FIG. 7B shows autologous transfusion of purified blood through an inventive filter.

DETAILED DESCRIPTION OF THE INVENTION

[0022] The present invention relates in-part to a portable and/or wearable extracorporeal device and methods for removing toxins and/or pathogens from infected or contaminated blood. The methods include using an adsorption media that binds to the toxins and/or pathogens which can be separated from the subject's blood. The toxin- and/or pathogen-free blood can be continuously or intermittently reinfused into the subject.

I. Definitions

[0023] As used herein, the following terms have the meanings ascribed to them unless specified otherwise.

[0024] The term "extracorporeal therapy" refers to a medical procedure that is conducted outside the body. In some instances, extracorporeal therapies include methods in which a bodily fluid such as blood is taken from the individual and desired products such as, but not limited to, oxygen, blood-anticoagulants, anesthetics, and the like are *added* to the body fluid before it is returned to the individual. In other instances, an extracorporeal therapy includes *removing* undesired products like naturally occurring toxins or poisons from the body or body fluids.

[0025] The term "adsorption media" refers to a material to which a cell, organism, virus, toxin, pathogen, polypeptide, polynucleotide, chemical molecule, small molecule, biological molecule or fragment thereof can adhere to the surface thereof.

[0026] The term "adhering complex" refers to a complex of at least two molecules wherein the first molecule is attached (*e.g.*, linked, coupled or bound) to the surface of a substrate and the second molecule is attached to the first molecule.

[0027] The term "high surface area" refers to the property of having a large specific surface area to volume ratio.

[0028] The term "adsorbent" refers to a solid substrate with a chemical compound, a biological molecule, or a material that is attached (*e.g.*, linked, coupled or bound) thereto. In certain instances, the adsorbent is the solid substrate itself. In one embodiment, an adsorbent is a polymer resin with a polysaccharide bound thereto.

[0029] The term "rigid polymer bead" refers to a bead, granule, pellet, sphere, particle, microcapsule, sphere, microsphere, nanosphere, microbead, nanobead, microparticle, nanoparticle, and the like that is made from a polymer resin.

[0030] The term "carbohydrate" refers to a molecule containing carbon, hydrogen and oxygen atoms, and usually with the empirical formula $C_x(H_2O)_y$, where x and y are different numbers. Examples of carbohydrates includes monosaccharides, disaccharides, oligosaccharides, and polysaccharides.

[0031] The term "polysaccharide" refers to a molecule of monosaccharide units joined together by glycosidic bonds, and having an empirical formula of $C_x(H_2O)_y$, where x is between 200 to about 3000.

[0032] The term "hydrophilic surface" includes a surface with a water contact angle less than 90° when the surface is flat.

[0033] The term "low affinity to heparan sulfate" in the context of a bacteria, refers to the low binding affinity of the bacteria for heparan sulfate. In some aspects, the binding affinity is determined using standard assays, such as an enzyme-linked immunosorbent assay (ELISA) for heparan sulfate. In other aspects, the binding affinity is determined based on a predictive analysis, such as an analysis of putative heparan sulfate binding proteins expressed by the pathogen, *e.g.*, bacteria.. The term "no affinity for heparan sulfate" refers to having no binding affinity for, or a lower than detectable affinity for heparan sulfate. In some instances, having no affinity for heparan sulfate includes having no predicted binding affinity for heparan sulfate.

II. Detailed Descriptions of the Embodiments

[0034] In one aspect, the wearable hemoperfusion device contains at least one adsorption media optimized for minimal pressure drop, in which arterial pressure is used to move whole blood across the adsorption bed, and returned to venous supply. In certain aspects, a blood pump is placed in series with the adsorption device to provide external pressure for increased blood flow across and/or through the adsorption media. The pump may optionally be integrated into the extracorporeal cartridge to reduce size and weight. Pumps such as centrifugal pumps that are integrated into the cartridge include, but are not limited to, Flow Forward Medical's The Arteriovenous Fistula Eligibility (AFE) System™ or the HeartWare®'s Circulite® Synergy Pocket Circulatory Assist Device (CAD). If used with veno-venous blood access, inlet flow can be controlled using established methods in order to prevent vein collapse.

[0035] A power source and computer control is optionally built into the pump module of the device. In other aspects, a separate, wearable power supply is used, and optionally, reused if connected to a subsequent device. For disposal purposes, a battery or power source and computer module can be ejected from the integrated device prior to disposal or incineration. For cartridges with an integrated rotary pump, the blood supply and return is provided by a dual lumen needle or catheter. Single lumen catheters are also used for arterial supply and venous return, or venous supply and venous return

[0036] In some aspects, the blood lines are pre-attached to the cartridge containing the adsorption media. The holdup volume of the device can be minimized, and a volume of sterile saline can be included into the integrated device for circuit priming and deairing. Additional safety features include, but are not limited to, a venous return line bubble trap, pressure sensors, and screen filters. Systemic anticoagulation control can also be added and controlled through Venturi liquid injection.

[0037] In another embodiment, the present invention provides a portable and/or wearable extracorporeal hemoperfusion device, the device comprising:

a cartridge comprising adsorption media, the cartridge having a first endplate and a second endplate;

a blood influx port to allow blood to flow into the device; and

a blood efflux port to allow blood to flow out of the device, wherein the blood flows through the first endplate through the adsorption media and out the blood efflux port.

[0038] With reference to FIG. 1, an embodiment of an extracorporeal hemoperfusion device 100 is described. The device 100 includes a dual lumen catheter or needle 140, a pathogen and toxin adsoption media 110 (*e.g.*, Seraph® Microbind® Affinity Blood Filter; ExThera Medical, Berkeley, CA) and porous endplates 130 and 135 at the top and bottom ends of the media, two blood ports 150 and 160 in fluid communication with an optional centrifugal pump 120. The unit that houses the centrifugal pump can also contain a battery and electronics that control the device. The inlet port 150 and the outlet port 160 are in fluid communication with the blood flow path. Typically, the blood enters the device and is contaminated and then leaves the device less contaminated, or decontaminated.

[0039] Turning now to FIG. 2, an embodiment of an integrated, extracorporeal hemoperfusion device 200 with arterial-venous blood access and a pathogen/toxin adsorption

media 210 is shown. The device 200 includes an arterial catheter 240 for the blood to enter the device and a venous catheter 250 for the toxin-free and/or pathogen-free blood to exit the device. Upon entering the device the blood travels to the centrifugal pump 220 and passes through a porous endplate 235 prior to contacting the pathogen/toxin adsorption media 210 of the cartridge. The blood is then pumped through a second porous endplate 230 and flows out through the venous catheter 250 and into the subject. It is comtemplated that the device can be used in the field, *e.g.*, outside a clinical or hospital setting if required.

[0040] FIG. 3 illustrates an embodiment of a wearable, extracorporeal hemoperfusion device 300 with no external pump. Blood flow through the device 300 is driven by differential pressure between arterial and venous pressure. The blood enters the device through the arterial catheter 340 and passes to the bottom of the device and then through the porous endplate 330 and into contact with the adsorption media 310. The purified blood flows through a second porous endplate 320 and then the exits the cartridge through the venous catheter 350 to re-enter the subject. In some aspects, such a device has no pump, power source or electronic controls.

[0041] Next, FIG. 4 provides an embodiment of a wearable, extracorporeal hemoperfusion device 400 with a dual lumen catheter 450 and a remote power source and electronics 430. The device contains a dual lumen catheter or needle 450, a centrifugal pump 420, an adsorption media 410, and an external battery pack and electronics 430. The infected or contaminated blood enters the device 400 through the catheter end and the inlet port 450. The blood passes to the centrifugal pump which is controlled and powered by the remote battery and electronics 430. The blood flows through the porous endplate 445 and comes into contact with the adsorption media 410. The adsorption media removes toxins and pathogens from the blood. The processed blood then passes through the second porous endplate 440 and the outlet port 470. The blood exits the cartridge and flows through the bloodline and re-enters to the subject through the dual lumen catheter or needle 450. The battery pack and electronics module 430 can be detached from the cartridge and pump device and assembled with an unused cartridge and pump device.

[0042] With reference to FIG. 5, an embodiment of an integrated, adsorption and pump device 500 with arterial and venous blood access 550, 560, respectively, and a remote power source and electronics module 530. The device includes an arterial catheter 550, a venous catheter 560, blood lines, a centrifugal pump 520, a pathogen and toxin adsorption media

510, and a external battery pack and electronics 530. The infected or contaminated blood enters through the arterial catheter and passes through the bloodline into the device. The centrifugal pump 520 passes the blood through the porous endplate 545 and into contact with the adsorption media 510. The processed blood flows through the second porous endplate 540 and then an outlet port. The toxin-free and/or pathogen-free blood re-enters the subject through the venous catheter 560. The cartridge containing the adsorption media and the pump is controlled by a battery pack and electronics module 530 that are separate from the adsorption and pump device. The battery pack and electronics module 530 can be detached from the other components of the device and used with other devices.

[0043] Turning to FIG. 6, as illustrated therein are several embodiments of the cartridge that are used in the extracorporeal wearable hemoperfusion device described in FIGS. 1-5. The cartridge contains the adsorption media that can remove toxins and pathogens from blood and in some instances, a pump. In some embodiments, the cartridge has a cylindrical shape 610. In other embodiments, the cartridge has a contoured shape that facilitates wearing the device on a leg or arm 620. In yet other aspects, the cartridge has a brick or rectangular block shape which can optimize storage volume 630.

A. Adsorption media

[0044] The adsorption media for small molecule toxins can be a microporous media such as activated carbon or size exclusion chromatography resin that has been rendered blood compatible. Adsorption media for pathogens, such as viruses, bacteria, fungi, or parasites, are preferably coated with at least one affinity ligand such as heparin, heparan sulfate, mannose, dextrose, other carbohydrates, antibodies, and other adhesins, such as opsonins. By including heparin ligands with other non-heparin affinity ligands, the blood compatibility of the device is greatly improved and the broad spectrum characteristics are significantly increased.

[0045] The adsorption media is selected according to the use of the device. For instance, a particular media is used to remove a pathogen of interest, including, but not limited to, a virus, *e.g.*, Ebola virus, Marburg virus, Lassa virus, Junin virus, Machupo virus, Guanarito virus, Chapare virus, Lugo virus, Dengue virus, Garis virus, Ilesha virus, Rift Valley Fever virus, Kyasanur Forest disease virus, Yellow Fever virus, Seoul virus, Crimean-Congo hemorrhagic fever virus, Scandinavian nephropathia epidemica virus, hantavirus, and smallpox virus; bacterium, *e.g.*, *Bacillus anthracis*, *Yersinia pestis*, and *Francisella tularenis*;

or toxin, *e.g.*, *Clostridium botulinum* toxin, ricin toxin from *Ricinus communis*, epsilon toxin of *Clostridium perfringens*, and Shiga toxin. Any pathogen or toxin that binds to the adsorption media contained within the disposable adsorption bed or cartridge can be removed by the device provided herein.

[0046] Various materials, in shape and composition, can be used as an adsorption media in the present invention. All suitable adsorbent substrates provide high surface area while promoting the conveyance of adsorbates to the adsorbent sites that bind them (primarily) by forced convective or diffusion transport. Useful substrates for creating the adsorption media include non-porous rigid beads, particles, or packing, reticulated foams, a rigid monolithic bed (*e.g.* formed from sintered beads or particles), a column packed with woven or non-woven fabric, a column packed with a yarn or solid or hollow mesoporous- or microporous-monofilament fibers, a spiral wound cartridge formed from flat film or dense membrane, or a combination of media such as a mixed bead/fabric cartridge. In some embodiments, a suitable substrate for use in the present invention is one that is initially mesoporous or microporous, but becomes essentially non-porous when the surface is treated before, during or after the creation of adsorption sites.

[0047] One useful substrate is in the form of solid beads or particles. The beads can be made of materials that are sufficiently rigid to resist deformation or compaction under the encountered flow rates and pressures. In some embodiments, sufficient substrate rigidity is the absence of a significant increase in pressure drop across the adsorption bed during about one hour of flow of water or saline at typical clinical flow rates. For instance, a suitable substrate rigidity is a <10-50% increase in pressure drop relative to the initial pressure drop (*e.g.*, measured within the first minute of flow) when measured at a similar flow rate, *e.g.*, of saline.

[0048] The adsorbent substrate beads may be made from a number of different biocompatible materials, such as natural or synthetic polymers or non-polymeric materials including glasses, ceramics and metals, that are essentially free of leachable impurities. Some exemplary polymers including polyurethane, polymethylmethacrylate, polyethylene or co-polymers of ethylene and other monomers, polyethylene imine, polypropylene, and polyisobutylene. Examples of useful substrates include nonporous Ultra High Molecular Weight PolyEthylene (UHMWPE). Other suitable beads are polystyrene, high density and low density polyethylene, silica, polyurethane, and chitosan.

[0049] Methods for making such beads are known in the art. For instance, suitable polyethylene beads and other polyolefin beads are produced directly during the synthesis process. In some instances, the beads are processed to the required size and shape. Other polymers may need to be ground or spray dried and classified, or otherwise processed to create beads of the desired size distribution and shape.

[0050] In some aspects, the adsorption media of the present invention provides a surface to attach a polysaccharide adsorbent that can bind the bacterial pathogen. In some embodiments, the adsorption media includes a solid substrate with a high surface area having at least one polysaccharide adsorbent on the surface thereof.

[0051] In other aspects, the adsorption media of the present invention provides a hydrophilic surface without a polysaccharide adsorbent ("a naked surface"). In some embodiments, the adsorption media includes a solid substrate with a high surface area and a hydrophilic cationic surface. In other embodiments, the adsorption media includes a solid substrate with a high surface area and a hydrophilic neutral surface.

[0052] The solid substrate is a material including, but not limited to, polyethylene, polystyrene, polypropylene, polysulfone, polyacrylonitrile, polycarbonate, polyurethane, silica, latex, glass, cellulose, crosslinked agarose, chitin, chitosan, crosslinked dextran, crosslinked alginate, silicone, fluoropolymer, and other synthetic polymers. The solid substrate with a high surface area can be a plurality of adsorbent monolayers, filters, membranes, solid fibers, hollow fibers, particles, or beads. Optionally, the solid substrate can be present in other forms or shapes providing a large surface area.

[0053] In certain instances, the solid substrate is a plurality of rigid polymer beads such as polyethylene, polystyrene, polypropylene, polysulfone, polyacrylonitrile, polycarbonate, polyurethane, silica, latex, glass, cellulose, crosslinked agarose, chitin, chitosan, crosslinked dextran, crosslinked alginate, silicone, fluoropolymer, and synthetic polymer beads. Preferably, the rigid polymer beads are polyethylene beads.

[0054] The size of the solid substrate can be selected according to the volume of the test sample used in the assay or other parameters. In some embodiments, the each bead of the plurality of rigid polymer beads has an average outer diameter of about 1 μm to about 1 mm, *e.g.*, 1 μm, 2 μm, 3 μm, 4 μm, 5 μm, 6 μm, 7 μm, 8 μm, 9 μm, 10 μm, 15 μm, 20 μm, 25 μm, 30 μm, 35 μm, 45 μm, 55 μm, 60 μm, 65 μm, 70 μm, 75 μm, 80 μm, 85 μm, 90 μm, 95 μm, 100 μm, 200 μm, 300 μm, 400 μm, 500 μm, 600 μm, 700 μm, 800 μm, 900 μm, or 1 mm. In

other embodiments, the each bead of the plurality of rigid polymer beads has an average diameter of about 10 μm to about 200 μm, *e.g.*, 10 μm, 15 μm, 20 μm, 25 μm, 30 μm, 35 μm, 45 μm, 55 μm, 60 μm, 65 μm, 70 μm, 75 μm, 80 μm, 85 μm, 90 μm, 95 μm, 100 μm, 105 μm,110 μm, 115 μm, 120 μm, 125 μm, 130 μm, 135 μm, 140 μm,145 μm, 150 μm,155 μm, 160 μm, 165 μm, 170 μm, 175 μm, 180 μm, 185 μm, 190 μm 195 μm, 200 μm or more.

[0055] In some embodiments, useful beads have a size ranging from about 100 microns (μm) to 500 μm, or more in diameter, *e.g.*, 100 μm, 150 μm, 200 μm, 250 μm, 300 μm, 350 μm, 400 μm, 450 μm, 500 μm, or more, in diameter. The average size of the beads can be from about 150 μm to about 450 μm in diameter, *e.g.*, 150 μm, 200 μm, 250 μm, 300 μm, 350 μm, 400 μm, or 450 μm in diameter. For example, polyethylene beads from DSM Biomedical (Berkeley, CA) having an average diameter of 300 μm are suitable for the present invention.

[0056] Beads can be sintered into a monolithic porous structure through either chemical or physical means. Polyethylene beads can be sintered by heating the beads above their melting temperature in a cartridge and applying pressure. The resulting interstitial pore size is slightly reduced from the interstitial pore size of a packed bed of non-sintered beads of equal size. This reduction can be determined empirically and used to produce the desired final interstitial pore size.

[0057] Reticulated foams have open cells and can be made from, for example, polyurethanes and polyethylenes. Control of pore size can be achieved by controlling the manufacturing method. In general, reticulated foams can have between 3 and 100 pores/inch and can exhibit a surface area of $\geq 66\ cm^2/cm^3$.

[0058] In some embodiments, the substrate is a barrier membrane, *e.g.*, a non-porous film. Alternatively, a microporous membrane may be rendered non-porous by filling the pores with essentially non-porous material, *e.g.*, a polymer. The membrane in the form of a sheet or a solid or hollow fiber may be arranged within a housing or a container.

[0059] The adsorption media can be in a vessel such as a column, cartridge, tube, centrifuge tube, and the like, or any vessel wherein the cells of the blood that are not captured onto polysaccharide bound adsorption media can be removed without disturbing the bacterial pathogen attached to the media.

[0060] The substrate is typically provided packed within a housing or container, such as a column, that is designed to hold the substrate within the container and permit the blood or serum to flow over the surface of the substrate. The substrate may be arranged within the container to maximize the binding of the adsorbates to the absorbent sides of the substrate. The housing or container may have a macroporous surface structure that provides a large surface area to the blood or serum.

[0061] A column or other housing shape can be packed with either woven or non-woven heparinized fabric or the heparin, heparan sulfate or optional non-heparin adsorption sites may be attached, *e.g.* by covalent, ionic or other chemical or physical bonds, after the housing has been filled with the substrate media. By controlling the fiber denier and density of the fabric during weaving or knitting or during the creation of a non-woven web, the interstitial pore size can be controlled. Useful non-woven fabrics may be in the form of felts, melt-blown, or electrostatically spun webs, having a random orientation held together by entanglement of the fibers and/or adhesion or cohesion of intersecting fibers. Useful woven fabrics have a more defined and non-random structure.

[0062] A column can be packed with fibers or yarns made from fibers. Polyethylene, and other fibers can be drawn into thin hollow or solid monofilament fibers or multifilament yarns, which can be packed into cartridges in the same way that hollow fiber membranes are installed within conventional hemodialysis cartridges or blood oxygenators. In the present invention originally porous hollow fibers are rendered dense or non-porous before, during or after binding heparin or other adsorbents to the outer and/or inner surfaces. Dyneema Purity® from Royal DSM is a high-strength solid fiber made of UHMWPE. Dyneema can be heparinized and packed into a cartridge to provide a high-surface area support for the removal of cytokines and pathogens.

[0063] A spiral wound cartridge contains a thin film or membrane that is tightly wound together with optional spacer materials to prevent contact of adjacent surfaces. The membrane can be made from polymers such as polyurethane, polyethylene polypropylene, polysulfone, polycarbonate, PET, PBT, and the like.

[0064] As noted above, for use in the method of the invention, the size of the channels or interstitial space between individual beads for extracorporeal blood filtration should be optimized to prevent a high-pressure drop between the inlet and outlet of the cartridge, to permit safe passage of the blood cells between the individual beads in a high flow

environment, and to provide appropriate interstitial surface area for binding of the polysaccharide adsorbent to the cytokines or pathogens in the blood. For example, in a close packed bed of 300-micron, roughly spherical beads, an appropriate interstitial pore size is approximately 68 microns in diameter.

[0065] Various methods of making adsorbents and the adsorbents per se are disclosed in U.S. Patent No. 8,663,148; U.S. Patent App. Publication Nos. US2009/0136586, US2010/0249689, US2011/0184377, and US2012/0305482, and U.S. Provisional Application Nos. 61/902,070, filed November 08, 2013 and 61/984,013, filed April 24, 2014, the disclosures of which are herein incorporated by reference in their entirety for all purposes.

[0066] In some embodiments, the blood-contacting surfaces of the device can be modified for improved or increased blood compatibility. For instances, the surfaces can be modified with optionally endpoint-attached heparin or other active, surface modifers

B. Methods of Use

[0067] The wearable devices and methods provided herein can be used to reduce the level of toxins and/or pathogens in an individual. The method can include obtaining blood from an individual, passing the blood through a cartridge containing an adsorption media, and re-infusing the pass-through blood into the individual. The devices and methods of using thereof can reduce the number of toxins and/or pathogens in the infected or contaminated blood of an individual.

[0068] In some embodiments, an anti-coagulation reagent has added to the blood after it enters the device. In other embodiments, a drug therapy, *e.g.*, antiviral therapy can also be administered to the pass-through blood before it re-enters the individual.

[0069] The devices can be used in the field, such as in a non-clinical setting. For instance, the device can be worn by an individual outside of a clinic or hospital. In some embodiments, the device is used in a clinical or hospital setting. It can be used as adjunct therapy and used in combination with a drug therapy, such as an antiviral drug.

[0070] The devices can be disposable or for single-use. In some instances, the device includes pre-attached blood lines, arterial and/or venous catheters, and a cartridge containing the adsortion media, and optionally a pump such as an integrated rotary pump. An external power source (e.g., battery) and electronics component can be attached to the device. In some embodiments, a kit used to perform the methods provided herein include a wearable,

extracorporeal device and an external battery and electronics which can be detached. An instruction manual can be included in the kit.

III. Examples

[0071] The following examples are offered to illustrate, but not to limit, the claimed invention.

[0072] Example 1 illustrates the use of a wearable, extracorporeal device that can remove a pathogen from blood of a patient infected or suspected of being infected with the blood-borne pathogen.

[0073] The device, as illustrated in FIG. 1, is connected to one of the patient's peripheral arteries via a dual lumen catheter or needle 140. The blood containing or suspected of containing a pathogen such as a virus flows into the device through an inlet port 150 and travels to the cartridge containing the adsorption media 110. A centrifugal or rotorary pump or pulsatile pump 120 that is integrated into the device housing facilitates the movement of the blood pass a first porous endplate 135 and into contact with the adsorption media. The pump is powered by battery 120 and controlled by electronics 120, both of which are housed in the device. The pathogen in the blood becomes immobilized on the surface of the adsorption media by binding to the media and/or one or more polysaccharides attached to the surface of the solid substrate of the media. The blood flow rate is set to optimize the immobilization of the pathogen onto the adsorption media. The constituents of the blood that are not bound to the adsorption media are passed through a second porous endplate 130 and exit the cartridge through an outlet port 160. A bloodline carries the blood containing a reduced level of pathogen back into the patient through the dual lumen catheter or needle 140.

[0074] Example 2 illustrates various embodiments of the present invention.

[0075] In certain instances, the portable and/or wearable device for extracorporeal affinity comprises an adsorbent media, which quickly and safely removes pathogens and toxins from whole blood in the treatment of a wide range of bloodstream infections. This includes drug-resistant bacteria, viruses and parasites as shown in Table 1. The media does not induce clotting or an inflammatory response in the blood that it contacts, a common problem with other dialysis-like devices that use different binding sites to capture a limited ranges of adsorbates.

[0076] The adsorbent media comprises small polyethylene beads with a permanent surface layer of chemically-bonded heparin. Its 'end-point-attached heparin' surface is extremely blood compatible. It mimics the properties of healthy blood vessels which bind 'Antithrombin III' to prevent the blood flowing through them from clotting. Heparin mimics the properties of heparan sulfate (HS) present on the endothelial cells that line veins and arteries, binding the same pathogens and toxins that target HS when invading the bloodstream. This diverts the disease-causing pathogens from the blood onto the surface of a disposable inventive cartridge. After a few hours of treatment, the device reduces the concentration of circulating pathogens to an undetectable level, without generating the toxic byproducts that are released when anti-infective drugs kill circulating pathogens.

Table 1

Drug-Resistant Bacteria	**Gram Positive Bacteria**	**Gram Negative Bacteria**	**Viruses, Fungi, and Toxins**
MRSA	*S. aureus*	*E. Coli*	HSV-1, HSV-2, CMV, Adenovirus, Ebola
CRE – *E. coli* and *K. pneumoniae*	*S. pneumoniae*	*K. pneumoniae*	*C. albicans*
ESBL - *K. pneumoniae*	*E. faecalis*	*Acinetobacter. baumannii*	LPS/Endotoxin*
VRE - *E. faecalis*	*E. faecium*	*P. aeruginosa**	S. a. α-hemolysin, Anthrax 'protective antigen'

[0077] Pathogens and toxins already confirmed to bind to the inventive adsorption media are listed in Table 1. The methods and devices herein are effective against Dengue and Malaria (including rosetted red blood cells) and a number of other pathogens and toxins.

[0078] In certain instances, the inventive cartridge is used in a dialysis-like therapy during which a dialysis machine continuously circulates blood from the patient through the cartridge and returns it to the patient. A typical treatment time is 4 hours, depending on flow rate and the starting concentration of pathogens in the blood. The current clinical unit is the size of a dialyzer cartridge and contains about 160 grams of the heparin-functional adsorbent 'media'. However, recent quantitative binding studies have shown that this much adsorbent provides up to 600 times more binding capacity than is needed to remove all the bacteria, fungus, or virus present during bloodstream infections.

[0079] In certain instances, the binding efficiency is 70 to 99% per pass through the inventive device. This makes it possible to quickly lower the concentration of pathogens in the blood. In MRSA bacteremia, for example, the bloodstream concentration is typically 10 to 1000 CFU/mL, and often less than 100 CFU/mL. One gram of heparin functional adsorption media has enough capacity to bind *all* the bacteria present in five liters of blood at 100 CFU/mL.

[0080] Furthermore, because the adsorption media prevents clotting and presents very low resistance to blood flow, it requires very little pressure differential to operate. In other instances, patients may be treated without dialysis machines.

[0081] Several low-cost alternatives to the use of dialysis machines exist and are part of the present invention. These include, for example:

A small reusable, battery-operated pump optionally integrated into the unit, requiring venous access with a dual-lumen needle;

Arterial to venous flow (with optional vasopressors) using blood pressure difference to generate flow through an inventive filter; and

Treatment via a single-needle venous line by using a standard blood bag with adsorbent 'filter' inserted into the blood tubing. (Vasopressors may be required with hypotension, although slow flow during collection is compensated by and more rapid reinfusion.)

[0082] Once the blood bag fills (≥ 10 min) it is raised above the patient, flowing back through the standard blood bag with adsorbent 'filter' for a second treatment. Since direction of flow does not affect performance, the single unit of blood gets two passes before returning to the patient, affecting a major reduction in pathogen and toxin levels. The process can be repeated several times as needed. Using a low-cost blood bag and needle set eliminates the need for any hardware or instrumentation (an IV pole or even two nails could suffice) and greatly reduces the need for monitoring by healthcare workers. See Figure 7A-B.

[0083] In summary, the cost to implement the present therapy in the treatment of diseases like dengue, malaria and hemorrhagic fevers can be kept very low by downsizing the current (over-sized) filter, and using gravity and/or blood pressure to create flow through the device.

[0084] With volume purchasing of heparin and other raw materials, and automated manufacturing of smaller filters, the present invention can be delivered at extremely low cost while benefiting millions of people infected with dengue and malaria.

[0085] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, one of skill in the art will appreciate that certain changes and modifications may be practiced within the scope of the appended claims. In addition, each reference provided herein is incorporated by reference in its entirety to the same extent as if each reference was individually incorporated by reference.

WHAT IS CLAIMED IS:

1. A portable and/or wearable device for extracorporeal removal of a toxin and/or pathogen from blood of an individual infected with the toxin and/or pathogen, the device comprising a cartridge, said cartridge comprising an adsorption media,

wherein the adsorption media is a solid substrate of high surface area having at least one polysaccharide adsorbent on the surface thereof with a binding affinity or binding site for the toxin and/or pathogen such that when the flowing blood is in contact with said adsorption media, the toxin and/or pathogen bind to binding sites on the at least one polysaccharide adsorbent and become separated from blood.

2. A portable and/or wearable extracorporeal hemoperfusion device, the device comprising:

a cartridge comprising adsorption media, the cartridge having a first endplate and a second endplate;

a blood influx port to allow blood to flow into the device; and

a blood efflux port to allow blood to flow out of the device, wherein the blood flows through the first endplate through the adsorption media and out the blood efflux port.

3. The portable and/or wearable device of claim **1** or **2**, further comprising a pump.

4. The portable and/or wearable device of claim **3**, wherein the pump is a rotary pump.

5. The portable and/or wearable device of claim **1** or **2**, further comprising a power source.

6. The portable and/or wearable device of claim **1** or **2**, further comprising an electronic control module.

7. The portable and/or wearable device of claims **5** or **6**, the power source or the electronic control module are detachable.

8. The portable and/or wearable device of claim **1**, wherein the least one polysaccharide adsorbent is selected from the group consisting of heparin, heparan sulfate,

hyaluronic acid, sialic acid, carbohydrates with mannose sequences, chitosan and a combination thereof.

9. The portable and/or wearable device of claim **1**, wherein the solid substrate comprises a plurality of rigid polymer beads.

10. The portable and/or wearable device of claim **9**, wherein the rigid polymer bead is selected from the group consisting of polyurethane, polymethylmethacrylate, polyethylene or co-polymers of ethylene and other monomers, polyethylene imine, polypropylene, and polyisobutylene.

11. The portable and/or wearable device of claim **1**, wherein the solid substrate comprises one or a plurality of hollow fibers.

12. The portable and/or wearable device of claim **1** or **2**, wherein the device is wearable.

13. The portable and/or wearable device of claim **1**, wherein the device is a blood bag.

14. The portable and/or wearable device of claim **2**, wherein the first endplate is porous.

15. The portable and/or wearable device of claim **2**, wherein the second endplate is porous.

16. The portable and/or wearable device of claim **2**, further comprising a dual lumen catheter adaptable to the blood influx port and the blood efflux port.

17. A *ex vivo* method of reducing a toxin and/or pathogen in the blood of an individual infected with the toxin and/or pathogen, the method comprising:

a) passing blood from the individual through a device comprising an adsorption media, wherein the adsorption media and toxins and/or pathogens in the blood form an adhering complex;

b) separating the resulting blood from the adhering complex to produce blood with a reduced level of the toxin and/or pathogen; and

c) infusing the blood with the reduced level of the toxin and/or pathogen into the individual.

18. The method of claim **17**, wherein the blood is selected from the group consisting of whole blood, serum and plasma.

19. The method of claim **18**, wherein the blood is whole blood.

20. The method of claim **17**, wherein the adsorption media is a solid substrate of high surface area having at least one polysaccharide adsorbent.

21. The method of claim **20**, wherein the least one polysaccharide adsorbent is selected from the group consisting of heparin, heparan sulfate, hyaluronic acid, sialic acid, carbohydrates with mannose sequences, chitosan, and a combination thereof.

22. The method of claim **20**, wherein the solid substrate comprises a plurality of rigid polymer bead.

23. The method of claim **22**, wherein the rigid polymer bead is selected from the group consisting of polyurethane, polymethylmethacrylate, polyethylene or co-polymers of ethylene and other monomers, polyethylene imine, polypropylene, and polyisobutylene.

24. The method of claim **20**, wherein the solid substrate comprises one or a plurality of hollow fibers.

25. The method of claim **20**, wherein the device further comprises a pump.

26. The method of claim **17**, wherein the toxin in the blood is reduced by about 10% to about 100%.

27. The method of claim **17**, wherein the pathogen in the blood is reduced by about 10% to about 100%.

28. The method of claim **17**, wherein the toxin is selected from the group consisting of *Clostridium botulinum* toxin, ricin toxin from *Ricinus communis*, epsilon toxin of *Clostridium perfringens*, Shiga toxin, and a combination thereof.

29. The method of claim **17**, wherein the pathogen is selected from the group consisting of Ebola virus, Marburg virus, Lassa virus, Junin virus, Machupo virus, Guanarito virus, Chapare virus, Lugo virus, Dengue virus, Garis virus, Ilesha virus, Rift Valley Fever virus, Kyasanur Forest disease virus, Yellow Fever virus, Seoul virus, Crimean-Congo hemorrhagic fever virus, Scandinavian nephropathia epidemica virus, hantavirus, smallpox virus, *Bacillus anthracis*, *Yersinia pestis*, *Francisella tularenis*, and a combination thereof.

30. A kit comprising the device of claim **1** and an instruction manual.

31. The kit of claim **30**, further comprising sterile saline.

Integrated Seraph®/pump device for portable field use – dual lumen catheter.

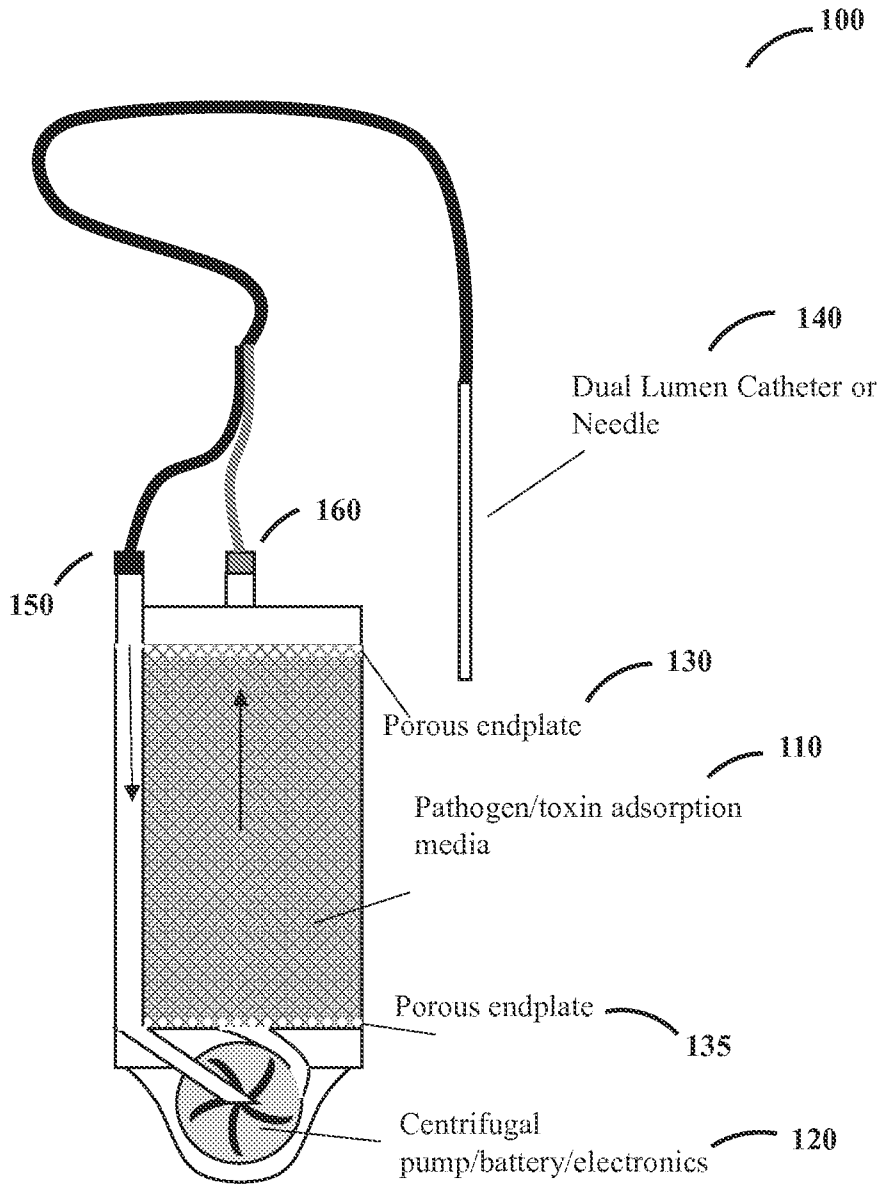


FIG. 1

Integrated Seraph®/pump device for portable field use – Arterial-venous blood access

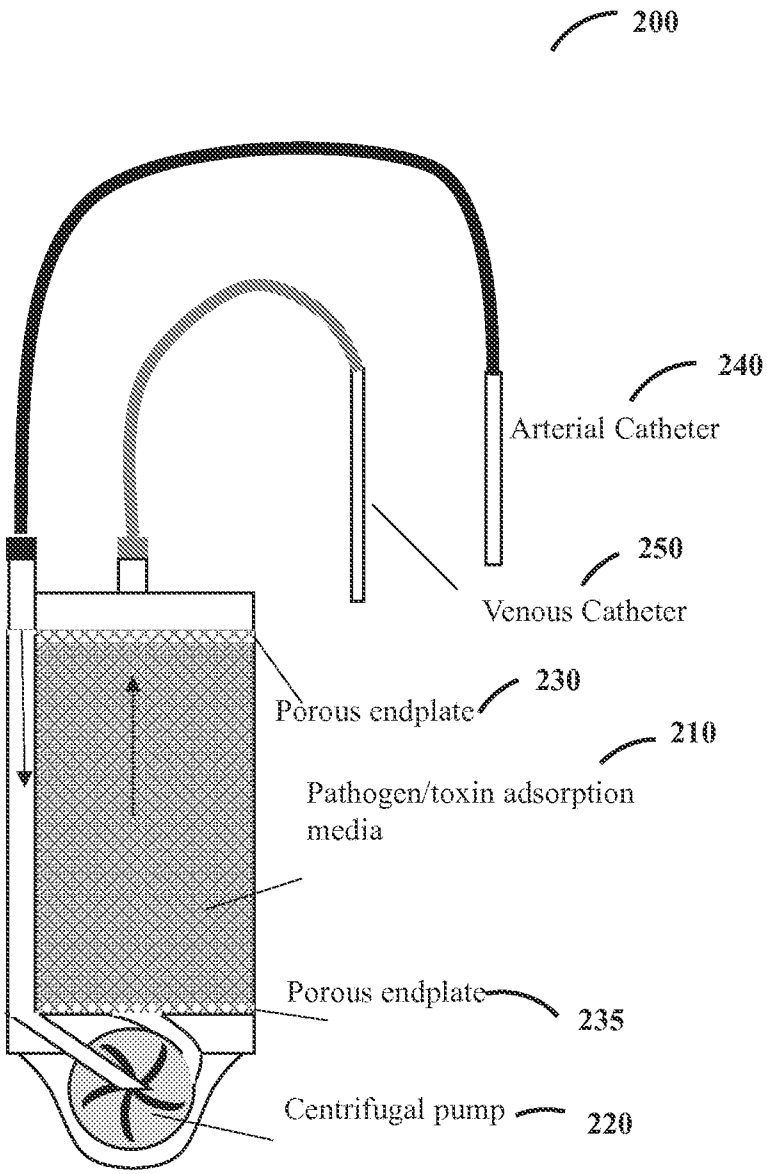


FIG. 2

Wearable Seraph® device for portable field use – Flow driven by differential pressure between aterial and venous pressure. No external pump is required.

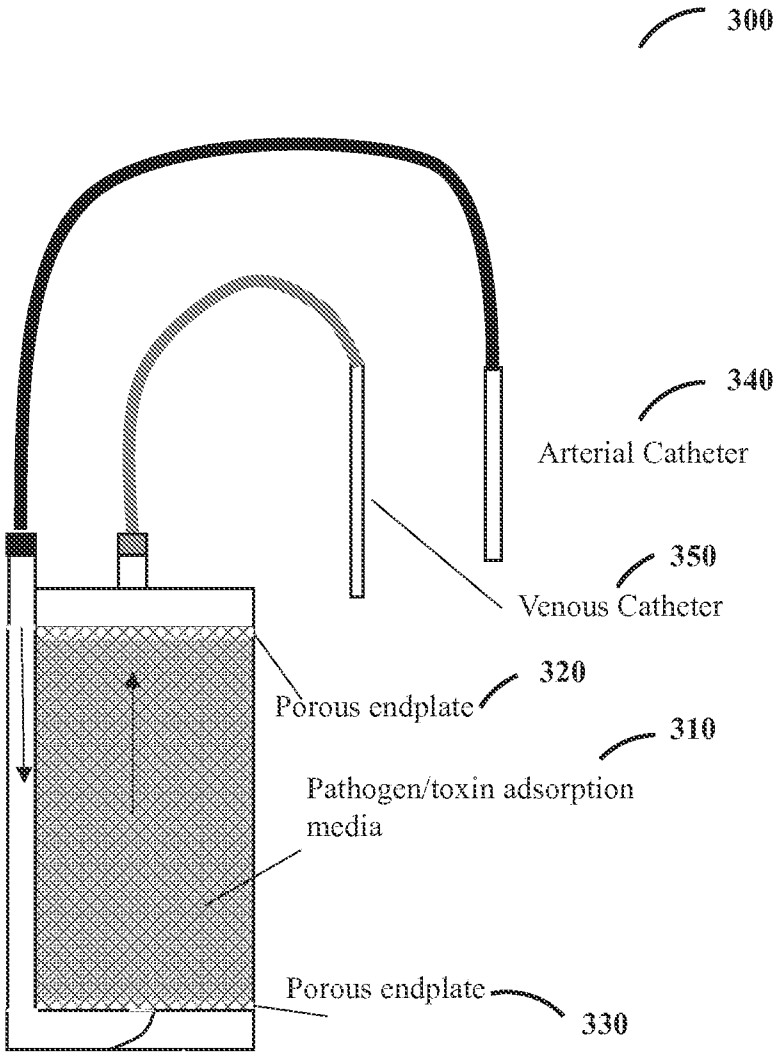


FIG. 3

Integrated Seraph®/pump device for portable field use – dual lumen catheter. Remote power and electronics.

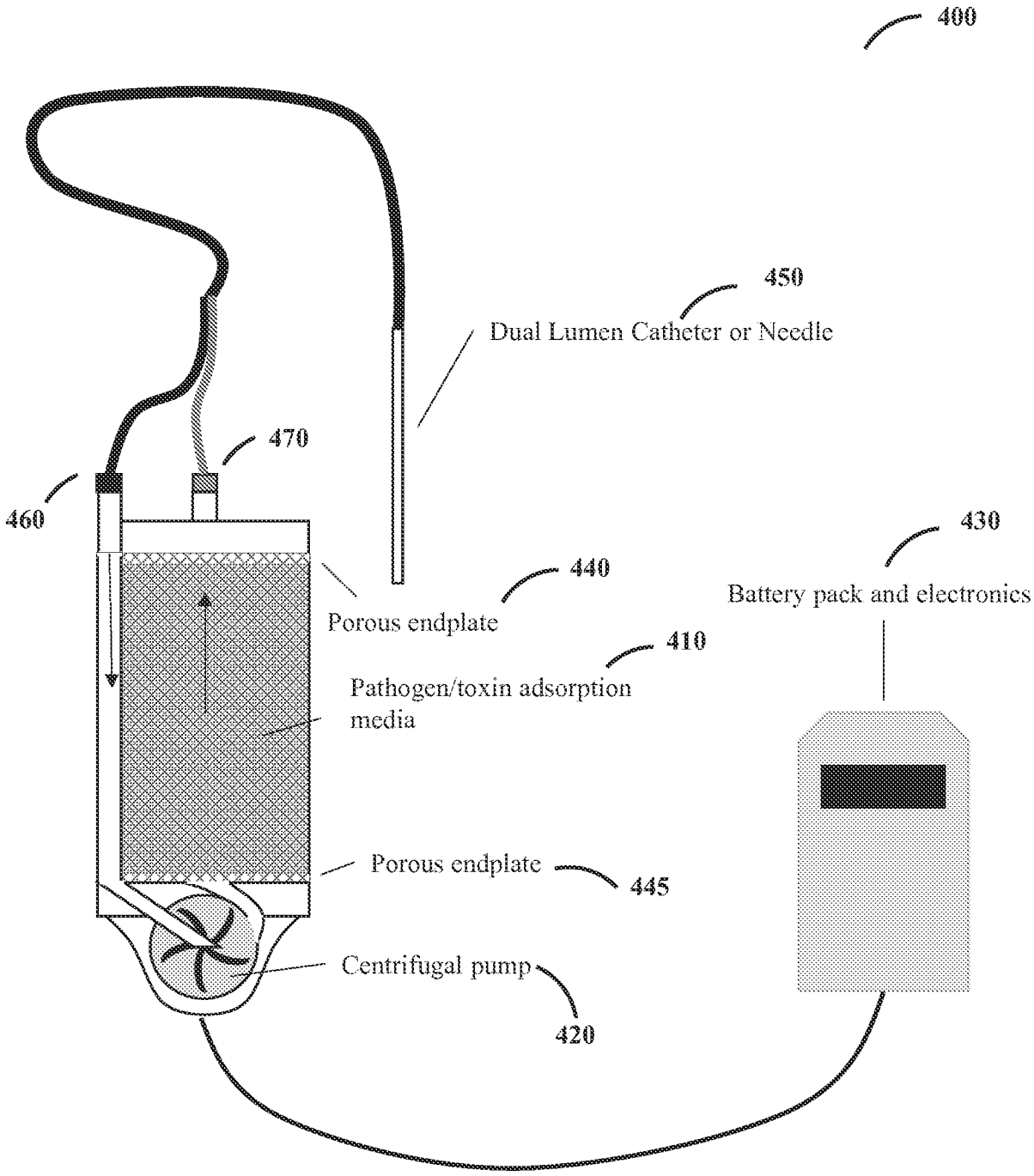


FIG. 4

Integrated Seraph®/pump device for portable field use – Arterial-venous blood access. Remote power and electronics

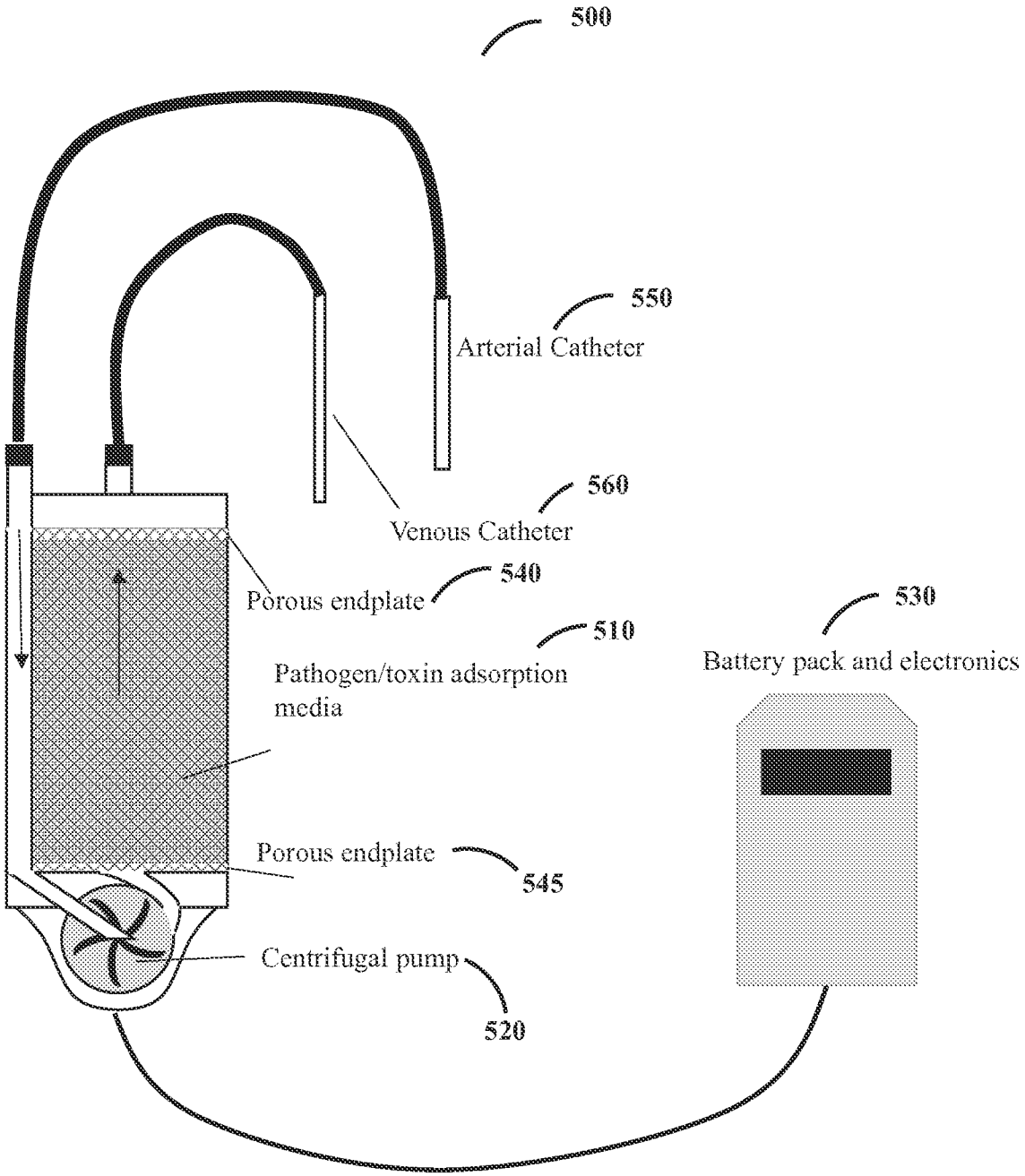
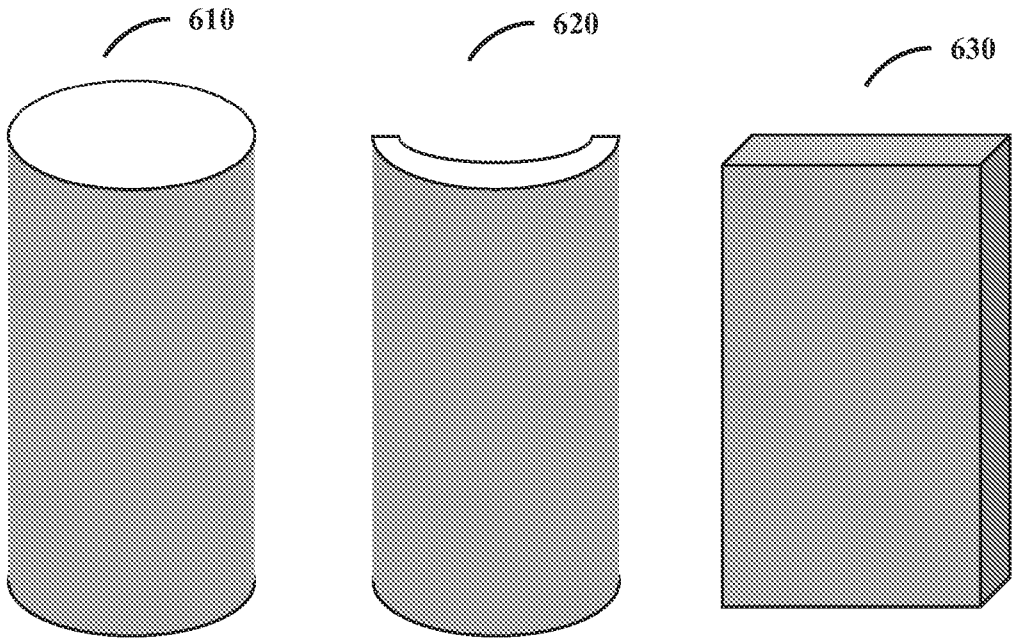


FIG. 5

Potential geometries for cartridge



"Cylindrical"

"Contoured" – Shape facilitates 'strapping' to leg or arm.

"Brick" – Optimizes storage volume

FIG. 6

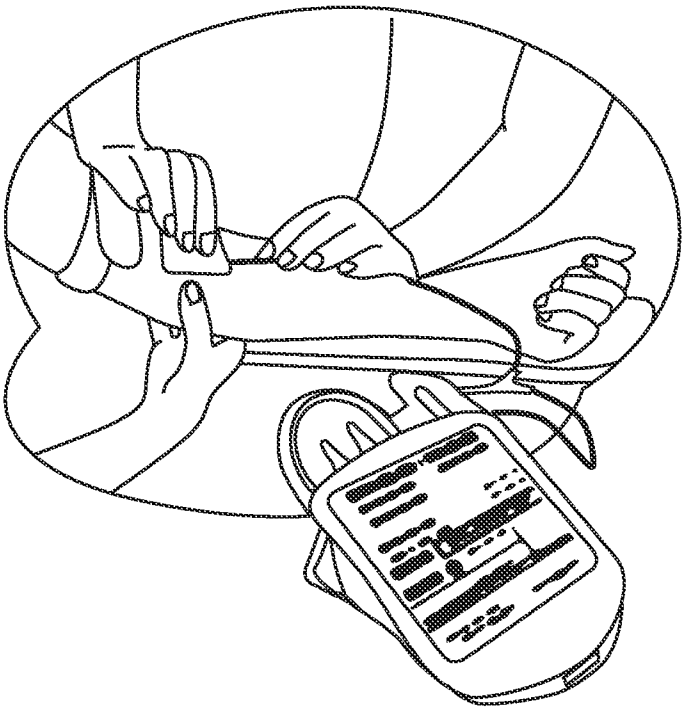


FIG. 7A

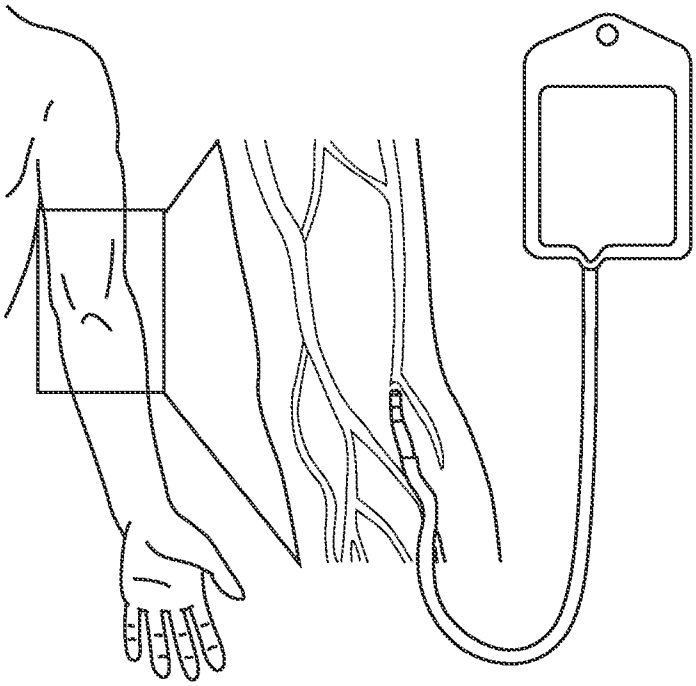


FIG. 7B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/051239

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61B 5/14 (2015.01)
CPC - A61B 5/145 (2015.11)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61B 5/00, 5/01, 5/02, 5/14; A61M 1/16 (2015.01)
CPC - A61B 5/00, 5/02, 5/02042, 5/026, 5/14, 5/145, 5/14525, 5/14546; A61M 1/16, 1/1625, 1/1627 (2015.11) (keyword delimited)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - (2015.10) (keyword delimited)
USPC - 435/287.1; 600/300, 301, 309, 326, 345, 363, 366, 369, 483

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Orbit, Google Patents, Google Scholar.
Search terms used: wearable blood filter, portable blood filtering device, pores, toxin, pathogen , influx, catheret, substrate cartridge

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2014/0012097 A1 (EXTHERA MEDICAL CORPORATION) 09 January 2014 (09.01.2014) entire document	1-5, 8-11, 14-27, 29 --- 6, 12, 13, 28, 30, 31
Y	EP 2 087 916 A1 (ICINNOVATION BV) 12 August 2009 (12.08.2009) entire document	6, 12, 13
Y	US 2013/0102948 A1 (REICH et al) 25 April 2013 (25.04.2013) entire document	28
Y	US 2004/0084358 A1 (O'MAHONY et al) 06 May 2004 (06.05.2004) entire document	30, 31

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 November 2015	17 DEC 2015
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/051239

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 7
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.