(54) Title: MEDICAL DEVICES HAVING A MICRO-FLUIDIC CHANNELED VASCULATURE

(57) Abstract: The present invention provides medical devices containing a micro-fluidic channeled vasculature capable of attaining fluid and gas flow there through, which are capable of augmenting or supplanting one or more physiological functions of an organ. The medical devices may be adapted to be exogenously seeded with at least organ specific cells. Methods of making and using the medical devices to supplant or augment one or more physiological functions of an organ are also provided.
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MEDICAL DEVICES HAVING A MICRO-FLUIDIC CHANNELED VASCULATURE

RELATED APPLICATIONS


FIELD OF THE INVENTION

The present invention is directed to medical devices. Specifically, the present invention is directed to medical devices containing a micro-fluidic channeled vasculature capable of attaining fluid flow there through, which are capable of augmenting or supplanting one or more physiological functions of an organ.

BACKGROUND OF THE INVENTION

Organ transplantation is often the only therapy for patients afflicted with diseases which destroy vital organs, including the heart, lungs, liver, kidneys and intestines. However, the shortage of donated organs for use in transplantation has severely limited the number of people able to receive organ transplantation. Due to the shortage of donated organs, many patients are placed on a waiting list before they can receive the needed organ. The period of time a patient may be on a waiting list before receiving a transplant depends on a number of factors including, how sick the person is, the person's blood type, and the availability of a suitably matched organ. Unfortunately, many people die before a compatible organ becomes available.

Liver failure specifically, affects thousands of people each year. Often, liver transplantation is the only option for people whose liver can no longer function. A complete liver can be obtained only from a person who has died, but a living donor can
provide a part of the liver. A donated liver can be stored for 8 to 24 hours. However, people often die while waiting for a compatible liver to become available.

Lung disease also affects thousands of people each year. More than 35 million Americans are living with chronic lung disease such as asthma, emphysema and chronic bronchitis. Chronic obstructive pulmonary disease (COPD) is a term referring to two lung diseases, chronic bronchitis and emphysema, that are characterized by obstruction to airflow that interferes with normal breathing. COPD leads to inadequate ventilation, chronic hypercapnea and often marginal oxygenation.

For most patients with end stage COPD, lung transplantation is often the only option. However, lung transplantation, like most organ transplantation, is limited by a long waiting list, with an average waiting time of two years. On average, 15% of patients die each year while waiting to receive a transplant. The five year survival rate of patients following lung transplantation is only 50%.

Recently, artificial organs such as artificial kidneys, artificial livers, and artificial lungs have found acceptance for use in those cases in which a donated organ is unavailable. Although these artificial organs overcome the shortage problem encountered by those waiting for a donated organ, there are still drawbacks associated with their use similar to other drawbacks associated with the use of a donated organ. Specifically, artificial organs and donated organs both require an extensive amount of coordination and effort between the supplier of the organ, and the team implanting the organ into the waiting patient. Additionally, there is a very short time frame during which a donated organ, or an artificial organ containing biological material, remains viable for use in vivo.

Additionally, there are other conventional artificial organs that are inert until in contact with a human or animal that are dependent on the use of methods and technologies of inducible migration of cells from the patient. However, such methods and technologies can require extended periods of time due to the dynamic, cyclical process of cell migration. Thus, such artificial organs are not well suited for use as organ transplants.
SUMMARY OF THE INVENTION

The present invention is directed to medical devices capable of supplanting or augmenting one or more functions of an organ. The medical devices of the present invention may be adapted to be exogenously seeded with at least organ specific cells. Thus, although there may be some migration of cells from the patient, the medical devices of the present invention do not rely on such migration in order to supplant or augment one or more functions of an organ. When used to supplant or augment one or more physiological functions of a liver, the medical devices of the present invention further provide a reduction in portal hypertension. In addition, the medical devices of the present invention may be adapted to be capable of attaining blood and oxygen flow there through. When used to supplant or augment one or more physiological functions of a lung, the medical devices of the present invention further provide a reduction in pulmonary hypertension.

In one aspect, the invention provides a medical device capable of performing a physiological function of an organ once surgically coupled to a patient and thereafter exogenously seeded with at least organ specific cells, said medical device comprising a first region defining a three dimensional micro-fluidic vasculature through which blood flows once coupled to a patient, said micro-fluidic vasculature comprising one or more channels having a radial bottom wall extending between a first sidewall and a second sidewall; a second region defining at least one chamber for holding a selected organ specific cell type; an ingress port to receive blood flow from the patient; an egress port to return blood flow to the patient; access ports through which at least one organ specific cell type is seeded; and a semi-permeable membrane positioned between the first and second regions, such that first region is separated from the second region by the semi-permeable membrane.

In one embodiment of this aspect, the first and second regions of the device comprise a material including at least one of polydimethyl siloxane, polylactic coglycolic acid, polyglycerol, polyurethane, polymethylmethacrylate, polystyrene and polycarbonate. In an exemplary embodiment, the regions comprise polydimethyl siloxane. In another embodiment of this aspect, the cells are autologous cells. In
another embodiment, the cells are modified autologous cells. In still another embodiment, the cells are allogeneic cells. In another embodiment, the cells are modified allogeneic cells. In another embodiment, the cells are parenchymal cells. In an exemplary embodiment, the parenchymal cells are derived from an organ selected from the group consisting of heart, liver, pancreas, intestine, brain, kidney, reproductive tissue, lung, muscle and bone marrow. In an exemplary embodiment, the organ is a liver.

In a further embodiment of this aspect, the semi-permeable membrane of the medical device is non-degradable. In one embodiment, the semi-permeable membrane comprises polyether sulfone.

In one embodiment of this aspect, the method by which the medical device is surgically coupled to the patient includes at least one of implantation into the patient’s body or attaching the device extracorporeally. In one embodiment, the device uses the patient’s body as a bioreactor, wherein the patient’s blood flow nourishes the organ specific cells seeded onto the scaffold. In another embodiment, the ingress port of the medical device receives blood from the patient’s venous blood flow. In one embodiment, the ingress port of the medical device receives blood flow from the patient’s portal vein. In another embodiment, the egress port of the medical device returns blood flow to the patient’s inferior vena cava.

In one embodiment, the medical device of the invention further comprises a first tubular member having a distal end, a proximal end, an inner wall, and an outer wall attached to the ingress port of the medical device, and a second tubular member having a distal end, a proximal end, an inner wall, and an outer wall, attached to the egress port of the medical device. In another embodiment, the first and second tubular members comprise silastic tubing. In one embodiment, the first and second tubular members are attached to the ingress and egress ports using an adhesive agent. In one embodiment, the adhesive agent is poly dimethylsiloxane. In one embodiment, the proximal end of the first tubular member is coupled to the patient’s portal vein.
In one embodiment, the first tubular member of the device further comprises a shunt extending outwardly from the outer wall at an angle offset from the longitudinal axis of the tubular member, such that the distal end of the shunt is substantially flush against the inner wall of the tubular member. In one embodiment, the proximal end of the second tubular member is coupled to the patient's inferior vena cava. In one embodiment, a pharmacological agent is introduced into the tubular member of the device through the shunt. In an exemplary embodiment, the pharmacological agent is an anti-coagulant. In another embodiment, a thrombolytic agent is introduced through the shunt.

In another aspect, the invention provides a medical device capable of performing a physiological function of an organ once surgically coupled to a patient and thereafter exogenously seeded with at least organ specific cells, said medical device comprising a first region defining a first three dimensional micro-fluidic vasculature through which blood flows once coupled to a patient; a second region defining at least one chamber for holding a selected organ specific cell type; a third region defining a second three dimensional micro-fluidic vasculature through which blood flows once coupled to a patient; a semi-permeable membrane positioned between the second and third region; an ingress port; and an egress port.

In one embodiment of this aspect, the first and/or the second three dimensional micro-fluidic networks comprise one or more channels having a radial bottom wall extending between a first side wall and a second side wall. In one embodiment, the first and second regions comprise a material including at least one of polydimethyl siloxane, polylactic coglycolic acid, polyglycerol, polyurethane, polymethylmethacrylate, polystyrene and polycarbonate. In an exemplary embodiment, the first and second regions comprise polydimethyl siloxane.

In another embodiment of this aspect, the cells are autologous cells. In one embodiment, the cells are modified autologous cells. In another embodiment, the cells are allogeneic cells. In one embodiment, the cells are modified allogeneic cells. In another embodiment, the cells are parenchymal cells. In one embodiment, the parenchymal cells are derived from an organ selected from the group consisting of heart,
liver, pancreas, intestine, brain, kidney, reproductive tissue, lung, muscle and bone marrow. In an exemplary embodiment, the organ is a liver.

In a further embodiment of this aspect, the semi-permeable membrane of the medical device is non-degradable. In one embodiment, the semi-permeable membrane comprises polyether sulfone.

In one embodiment of this aspect, the method by which the medical device is surgically coupled to the patient includes at least one of implantation into the patient’s body or attaching the device extracorporeally. In one embodiment, the device uses the patient’s body as a bioreactor, wherein the patient’s blood flow nourishes the organ specific cells seeded onto the scaffold. In another embodiment, the ingress port of the medical device receives blood from the patient’s venous blood flow. In one embodiment, the ingress port of the medical device receives blood flow from the patient’s portal vein. In another embodiment, the egress port of the medical device returns blood flow to the patient’s inferior vena cava.

In one embodiment, the medical device of the invention further comprises a first tubular member having a distal end, a proximal end, an inner wall, and an outer wall attached to the ingress port of the medical device, and a second tubular member having a distal end, a proximal end, an inner wall, and an outer wall, attached to the egress port of the medical device. In another embodiment, the first and second tubular members comprise silastic tubing. In one embodiment, the first and second tubular members are attached to the ingress and egress ports using an adhesive agent. In one embodiment, the adhesive agent is polydimethylsiloxane. In one embodiment, the proximal end of the first tubular member is coupled to the patient’s portal vein.

In one embodiment, the first tubular member of the device further comprises a shunt extending outwardly from the outer wall at an angle offset from the longitudinal axis of the tubular member, such that the distal end of the shunt is substantially flush against the inner wall of the tubular member. In one embodiment, the proximal end of the second tubular member is coupled to the patient’s inferior vena cava. In one embodiment, a pharmacological agent is introduced into the tubular member of the
device through the shunt. In an exemplary embodiment, the pharmacological agent is an anti-coagulant. In another embodiment, the pharmacological agent is a thrombolytic agent.

In another aspect, the invention provides a method for forming a structure for use in the aforementioned medical devices, said method comprising forming a first region defining a three dimensional vasculature comprising one or more channels having a radial bottom wall extending between a first side wall and a second side wall; forming a second region defining at least one chamber for holding at least one selected organ specific cell type; forming an ingress port and an egress port into the second region; selecting a semi-permeable membrane; attaching the semi-permeable membrane to the design surface of the first region; and attaching the second region to the first region/semi-permeable membrane structure, such that the semi-permeable membrane is positioned between the chamber of the second region and the design surface of the first region, forming an ingress port and an egress port into the first region/semi-permeable membrane structure such that the ingress and egress ports of both regions are aligned.

In one embodiment of this aspect, the step of creating the first region comprises selecting a substrate for use as a mold; transferring the pattern for the desired vasculature like structure onto the surface of the mold; casting a material onto the mold; curing the material; and removing the material from the mold. In one embodiment, the substrate selected for use as a mold includes at least one of glass, graphite, metals, and silicon. In an exemplary embodiment, the substrate is metal. In another embodiment, the substrate is aluminum. In one embodiment, the material cast onto the mold is a polymer. In one embodiment, the polymer includes at least one of polydimethylsiloxane, polylactic coglycolic acid, polyglycerol, polyurethane, polycarbonate, polystyrene and polymethylmethacrylate. In an exemplary embodiment, the polymer is polydimethylsiloxane.

In another embodiment of this aspect, the step of creating the second region comprises selecting a substrate for use as a mold; transferring the desired pattern for a chamber or chambers onto the surface of the mold; casting a material onto the mold; curing the material; and removing the material from the mold. In one embodiment, the
substrate selected for use as a mold includes at least one of glass, graphite, metals, and silicon. In one embodiment, the substrate is a metal. In an exemplary embodiment, the substrate is aluminum. In one embodiment, the material cast onto the mold is a polymer. In one embodiment, the polymer includes at least one of polydimethylsiloxane, polylactic coglycolic acid, polyglycerol, polyurethane, polycarbonate, polystyrene and polymethylmethacrylate. In an exemplary embodiment, the polymer material polydimethylsiloxane.

In another aspect, the invention provides a method for forming a medical device capable of performing a physiological function of an organ once surgically coupled to a patient and thereafter exogenously seeded with at least organ specific cells, said medical device comprising at least one stacked structure defining a three dimensional vasculature through which blood flows once coupled to a patient, the three dimensional vasculature comprising one or more channels having a radial bottom wall extending from a first side wall to a second side wall, and defining at least one chamber for holding a selected organ specific cell type; a semi-permeable membrane separating the chamber and the vasculature like structure; an ingress port to receive blood flow from the patient; and an egress port to return blood flow to the patient; wherein said method comprises placing at least two stacked structures one on top of the other such that the ingress and egress ports of each structure align; attaching each stacked structure to the structure above and/or below it; and sealing the edges of the stacked structures.

In a related aspect, the invention provides a method for forming a medical device capable of performing a physiological function of an organ once surgically coupled to a patient and thereafter exogenously seeded with at least organ specific cells, said medical device comprising at least two stacked structures, each structure comprising a first side defining a three dimensional micro-fluidic vasculature through which blood flows once coupled to a patient; a second side defining at least one chamber for holding a selected organ specific cell type; an ingress port to receive blood flow from the patient; an egress port to return blood flow to the patient; and access ports through which at least one organ specific cell type is seeded; wherein each stacked structure is placed one on top of the other with a semi-permeable membrane placed between each structure, such that the first side of one structure is separated from the second side of the next structure by the
semi-permeable membrane; wherein the method comprises placing at least two stacked structures one on top of the other such that the ingress and egress ports of each structure align; attaching each stacked structure to the structure above and/or below it; and sealing the edges of the stacked structures.

In another aspect, the invention provides a method for forming a medical device capable of performing a physiological function of an organ once surgically coupled to a patient and thereafter exogenously seeded with at least organ specific cells, said medical device comprising at least one stacked structure comprising a first region defining a first three dimensional micro-fluidic vasculature through which blood flows once coupled to a patient; a second region defining at least one chamber for holding a selected organ specific cell type; a third region defining a second three dimensional micro-fluidic vasculature through which blood flows once coupled to a patient; a semi-permeable membrane positioned between the second and third region; an ingress port; and an egress port, wherein said method comprises placing at least two stacked structures one on top of the other such that the ingress and egress ports of each structure align; attaching each stacked structure to the structure above and/or below it; and sealing the edges of the stacked structures.

In one embodiment of these aspects, the step of attaching each stacked structure comprises using an adhesive agent to bond the structures together. In one embodiment, the adhesive agent is poly dimethylsiloxane. In another embodiment of these aspects, the step of sealing the edges of the stacked structure comprises applying a sealant along each edge of the stack. In one embodiment, the sealant is a polymer. In another embodiment, the sealant is poly dimethylsiloxane. In another embodiment of these aspects, the ingress and egress ports of the structure that comprises the bottom of the medical device do not extend through the entire structure.

In one aspect, the invention provides an acellular medical device capable of performing a physiological function of an organ once surgically coupled to a patient and thereafter attaining blood and oxygen flow there through, said medical device comprising a first region defining a three dimensional micro-fluidic vasculature through
which blood flows once coupled to a patient, said micro-fluidic vasculature comprising one or more channels having a radial bottom wall extending between a first sidewall and a second sidewall; a second region defining at least one chamber through which oxygen flows; an ingress port to receive blood flow from the patient; an egress port to return blood flow to the patient; access ports through which oxygen is provided; and an oxygen and carbon dioxide permeable membrane positioned between the first and second regions, such that first region is separated from the second region by the oxygen and carbon dioxide permeable membrane.

In one embodiment of this aspect, the first and second regions comprise a material including at least one of polydimethyl siloxane, polylactic coglycolic acid, polyglycerol, polyurethane, polymethylmethacrylate, polystyrene and polycarbonate. In one embodiment, the regions comprise polydimethyl siloxane. In another embodiment, the oxygen and carbon dioxide permeable membrane is non-degradable. In one embodiment, the oxygen and carbon dioxide permeable membrane is a polymer. In one embodiment, the oxygen and carbon dioxide permeable membrane comprises a material selected from the group consisting of polyether sulfone, silicone, or a medical grade elastomer. In an exemplary embodiment, the oxygen and carbon dioxide permeable membrane comprises polyether sulfone. In another embodiment, the oxygen and carbon dioxide permeable membrane comprises silicone. In another embodiment, the oxygen and carbon dioxide permeable membrane comprises a medical grade elastomer.

In another embodiment of this aspect, the method by which the medical device is surgically coupled to the patient includes at least one of implantation into the patient’s body or attaching the device extracorporeally. In one embodiment, the ingress port of the medical device receives blood from the patient’s arterial blood flow. In another embodiment, the ingress port of the medical device receives blood flow from the patient’s pulmonary artery. In one embodiment, the egress port of the medical device returns blood flow to the patient’s left atrium.

In another embodiment, the device further comprises a first tubular member having a distal end, a proximal end, an inner wall, and an outer wall attached to the ingress port of the medical device, and a second tubular member having a distal end, a
proximal end, an inner wall, and an outer wall, attached to the egress port of the medical
device. In one embodiment, the first and second tubular members comprise silastic
tubing. In another embodiment, the first and second tubular members are attached to the
ingress and egress ports using an adhesive agent. In one embodiment, the adhesive
agent is polydimethylsiloxane.

In one embodiment, the proximal end of the first tubular member is coupled to
the patient’s pulmonary artery. In another embodiment, the first tubular member further
comprises a shunt extending outwardly from the outer wall at an angle offset from the
longitudinal axis of the tubular member, such that the distal end of the shunt is
substantially flush against the inner wall of the tubular member. In one embodiment, the
proximal end of the second tubular member is coupled to the patient’s left atrium. In
another embodiment, a pharmacological agent is introduced into the tubular member
through the shunt. In one embodiment, the pharmacological agent is an anti-coagulant.

In another embodiment, a thrombolytic agent is introduced through the shunt.

In another aspect, the invention provides an acellular medical device capable of
performing a physiological function of an organ once surgically coupled to a patient and
blood and oxygen flow there through are established, said medical device comprising a
first region defining a first chamber through which oxygen flows; a second region
defining a first three dimensional micro-fluidic vasculature through which blood flows
once coupled to a patient; a third region defining a second chamber through which
oxygen flows; an oxygen and carbon dioxide permeable membrane positioned between
the second and third region; an ingress port; an egress port; and access ports through
which oxygen is provided.

In one embodiment of this aspect, the first three dimensional micro-fluidic
networks comprise one or more channels having a radial bottom wall extending between
a first side wall and a second side wall. In another embodiment, the first, second, and
third regions comprise a material including at least one of polydimethyl siloxane,
polylactic coglycolic acid, polyglycerol, polyurethane, polymethylmethacrylate,
polystyrene and polycarbonate. In one embodiment, the first, second, and third regions
comprise polydimethyl siloxane. In another embodiment, the oxygen and carbon
dioxide permeable membrane is non-degradable. In one embodiment, the oxygen and
carbon dioxide permeable membrane is a polymer. In another embodiment, the oxygen
and carbon dioxide permeable membrane comprises a material selected from the group
consisting of polyether sulfone, silicone, or a medical grade elastomer. In one
embodiment, the oxygen and carbon dioxide permeable membrane comprises polyether
sulfone. In one embodiment, the oxygen and carbon dioxide permeable membrane
comprises silicone. In one embodiment, the oxygen and carbon dioxide permeable
membrane comprises a medical grade elastomer.

In another embodiment, the method by which the medical device is surgically
coupled to the patient includes at least one of implantation into the patient’s body or
attaching the device extracorporeally. In one embodiment, the ingress port of the
acellular medical device receives blood from the patient’s arterial blood flow. In
another embodiment, the ingress port of the acellular medical device receives blood flow
from the patient’s pulmonary artery. In one embodiment, the egress port of the acellular
medical device returns blood flow to the patient’s left atrium.

In another embodiment of this aspect, the device further comprises a first tubular
member having a distal end, a proximal end, an inner wall, and an outer wall attached to
the ingress port of the medical device, and a second tubular member having a distal end,
a proximal end, an inner wall, and an outer wall, attached to the egress port of the
acellular medical device. In one embodiment, the first and second tubular members
comprise silastic tubing. In another embodiment, the first and second tubular members
are attached to the ingress and egress ports using an adhesive agent. In one embodiment,
the adhesive agent is poly dimethylsiloxane.

In one embodiment, the proximal end of the first tubular member is coupled to
the patient’s pulmonary artery. In another embodiment, the first tubular member further
comprises a shunt extending outwardly from the outer wall at an angle offset from the
longitudinal axis of the tubular member, such that the distal end of the shunt is
substantially flush against the inner wall of the tubular member. In one embodiment, the
proximal end of the second tubular member is coupled to the patient’s left atrium.
In another embodiment, a pharmacological agent is introduced into the tubular member through the shunt. In one embodiment, the pharmacological agent is an anticoagulant. In an exemplary embodiment, the pharmacological agent is a thrombolytic agent.

In another aspect, the invention provides a method for forming a structure for use in the acellular medical device of the invention, comprising forming a first region defining a three dimensional vasculature comprising one or more channels having a radial bottom wall extending between a first side wall and a second side wall; forming a second region defining at least one chamber through which oxygen flows; forming an ingress port and an egress port into the second region; selecting an oxygen and carbon dioxide permeable membrane; attaching the oxygen and carbon dioxide permeable membrane to the design surface of the first region; and attaching the second region to the first region/ oxygen and carbon dioxide permeable membrane structure, such that the oxygen and carbon dioxide permeable membrane is positioned between the chamber of the second region and the design surface of the first region, forming an ingress port and an egress port into the first region/ oxygen and carbon dioxide permeable membrane structure such that and the ingress and egress ports of both regions are aligned.

In one embodiment of this aspect, the step of creating the first region comprises selecting a substrate for use as a mold; transferring the pattern for the desired vasculature like structure onto the surface of the mold; casting a material onto the mold; curing the material; and removing the material from the mold. In one embodiment, the substrate selected for use as a mold includes at least one of glass, graphite, metals, and silicon. In one embodiment, the substrate is a metal. In an exemplary embodiment, the substrate is aluminum. In one embodiment, the material cast onto the mold is a polymer. In one embodiment, the polymer includes at least one of polydimethylsiloxane, polylactic coglycolic acid, polyglycerol, polyurethane, polycarbonate, polystyrene and polymethylmethacrylate. In an exemplary embodiment, the polymer is polydimethylsiloxane.

In another embodiment of this aspect, the step of creating the second region comprises selecting a substrate for use as a mold; transferring the desired pattern for a
chamber or chambers onto the surface of the mold; casting a material onto the mold; curing the material; and removing the material from the mold. In one embodiment, the substrate selected for use as a mold includes at least one of glass, graphite, metals, and silicon. In another embodiment, the substrate is a metal. In an exemplary embodiment, the substrate is aluminum. In another embodiment, the material cast onto the mold is a polymer. In one embodiment, the polymer includes at least one of polydimethylsiloxane, polylactic coglycolic acid, polyglycerol, polyurethane, polycarbonate, polystyrene and polymethylmethacrylate. In an exemplary embodiment, the polymer material is polydimethylsiloxane.

In another aspect, the invention provides a method for forming an acellular medical device capable of performing a physiological function of an organ once surgically coupled to a patient and thereafter attaining blood and oxygen flow through, comprising at least one stacked structure defining a three dimensional vasculature through which blood flows once coupled to a patient, the three dimensional vasculature comprising one or more channels having a radial bottom wall extending from a first side wall to a second side wall, and defining at least one chamber through which oxygen flows; an oxygen and carbon dioxide permeable membrane separating the chamber and the vasculature like structure; an ingress port to receive blood flow from the patient; and an egress port to return blood flow to the patient; wherein said method comprises placing at least two stacked structures one on top of the other such that the ingress and egress ports of each structure align; attaching each stacked structure to the structure above and/or below it; and sealing the edges of the stacked structures.

In a related aspect, the invention provides a method for forming an acellular medical device capable of performing a physiological function of an organ once surgically coupled to a patient and thereafter attaining blood and oxygen flow through, comprising at least two stacked structures, each structure comprising a first side defining a three dimensional micro-fluidic vasculature through which blood flows once coupled to a patient; a second side defining at least one chamber through which oxygen flows; an ingress port to receive blood flow from the patient; an egress port to return blood flow to the patient; and access ports through which oxygen is provided; wherein each stacked structure is placed one on top of the other with an oxygen and carbon
dioxide permeable membrane placed between each structure, such that the first side of one structure is separated from the second side of the next structure by the oxygen and carbon dioxide permeable membrane; wherein said method comprises placing at least two stacked structures one on top of the other such that the ingress and egress ports of each structure align; attaching each stacked structure to the structure above and/or below it; and sealing the edges of the stacked structures.

In another aspect, the invention provides a method for forming an acellular medical device capable of performing a physiological function of an organ once surgically coupled to a patient and thereafter attaining blood and oxygen flow there through, said acellular medical device comprising at least one stacked structure comprising a first region defining a first chamber or chambers through which oxygen flows; a second region defining a three dimensional micro-fluidic vasculature through which blood flows once coupled to a patient; a third region defining a second chamber or chambers through which oxygen flows; an oxygen and carbon dioxide permeable membrane positioned between the second and third region; an ingress port; and an egress port, wherein said method comprises placing at least two stacked structures one on top of the other such that the ingress and egress ports of each structure align; attaching each stacked structure to the structure above and/or below it; and sealing the edges of the stacked structures.

In one embodiment of these aspects, the step of attaching each stacked structure comprises using an adhesive agent to bond the structures together. In one embodiment, the adhesive agent is poly dimethylsiloxane. In another embodiment, the step of sealing the edges of the stacked structure comprises applying a sealant along each edge of the stack. In one embodiment, the sealant is a polymer. In another embodiment, the sealant is poly dimethylsiloxane. In another embodiment, the sealant is a medical grade elastomer. In another embodiment of these aspects, the ingress and egress ports of the structure that comprises the bottom of the medical device do not extend through the entire structure.

In another aspect, the invention provides a catheter comprising a tubular member having a flared proximal end, a distal end, an inner wall, and an outer wall; a stiffening
member associated with a first portion of the outer wall of the tubular member, having a proximal end, and a distal end; and a shunt extending outwardly from the outer wall at an angle offset from a longitudinal axis of the tubular member, such that the distal end of the shunt is substantially flush against the inner wall of the tubular member of the catheter.

In one embodiment of this aspect, the flared proximal end of the tubular member comprises a flared base member associated with the proximal end of the tubular member. In another embodiment, the flared proximal end of the tubular member is capable of being attached to a selected fluid carrying organ of a subject. In one embodiment the fluid carrying organ is a vein. In an exemplary embodiment, the vein is the subject's portal vein. In one embodiment, the fluid carrying organ is an artery. In another exemplary embodiment, the artery is the pulmonary artery. In another embodiment, the flared proximal end of the tubular member has a suture region.

In another embodiment of this aspect a pharmacological agent is introduced into the tubular member of the catheter through the shunt. In one embodiment, the pharmacological agent comprises an anticoagulant. In another embodiment, a diagnostic agent is introduced into the tubular member of the catheter though the shunt.

In another embodiment, the catheter further comprises a leur lock at the distal end of the catheter. In one embodiment, the tubular member and the stiffening member comprise a monolithic structure. In another embodiment, an adhesive agent is used to attach the tubular member of the catheter to the stiffening member of the catheter. In another embodiment, the stiffening member comprises a tube associated with the tubular member of the catheter, wherein the tube has a proximal end, a distal end, an inner wall and outer wall. In one embodiment, the diameter of the inner wall of the stiffening member is substantially equivalent to the diameter of the outer wall of the tubular member.

In another aspect, the invention provides a method for manufacturing a catheter, the method comprising the steps of electing a desired length of a flexible tubular member; creating a flared proximal end of the tubular member; selecting a desired
stiffening member; associating the stiffening member with a first portion of the tubular member; and attaching a shunt.

In one embodiment of this aspect, the method further comprises boring an aperture into the stiffening member and/or tubular member at a dimension to receive the shunt, such that the shunt extends outwardly from the outer wall at an angle offset from a longitudinal axis of the tubular member, such that the distal end of the shunt is substantially flush against the inner wall of the tubular member of the catheter. In one embodiment, the step of creating a flared proximal end further comprises using a flare tool to flare the proximal end of the tubular member. In another embodiment, the step of creating a flared proximal end further comprises attaching a flared base member to the proximal end of the tubular member. In one embodiment, the flared base member is attached to the proximal end of the tubular member by at least one of adhesive bonding, chemical bonding, and thermal bonding. In one embodiment, the flared base member is attached to the proximal end of the tubular member by adhesive bonding. In another embodiment, the step of associating a stiffening member with a first portion of the tubular member further comprises attaching the stiffening member to the tubular member by at least one of adhesive bonding, chemical bonding, and thermal bonding. In one embodiment, the stiffening member is attached to the tubular member by adhesive bonding.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other aspects, embodiments, objects, features and advantages of the invention can be more fully understood from the following description in conjunction with the accompanying drawings. In the drawings like reference characters generally refer to like features and structural elements throughout the various figures. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating the principles of the invention.

Figure 1A is a schematic of an exemplary medical device in accordance with the teachings of the present invention.
Figure 1B is a schematic of an exemplary medical device in accordance with the teachings of the present invention.

Figure 1C is a schematic of the exchange of gas that occurs in an exemplary medical device of the present invention.

Figure 1D is a schematic of an exemplary medical device in accordance with the teachings of the present invention.

Figure 2A is a schematic of an embodiment of an exemplary medical device of the present invention in accordance with the teachings of the present invention.

Figure 2B is a schematic of an embodiment of an exemplary medical device of the present invention in accordance with the teachings of the present invention.

Figure 3A is a schematic of an embodiment of an exemplary medical device of the present invention in accordance with the teachings of the present invention.

Figure 3B is a schematic of an embodiment of an exemplary medical device of the present invention in accordance with the teachings of the present invention.

Figure 3C is a schematic of an embodiment of an exemplary medical device of the present invention in accordance with the teachings of the present invention.

Figure 3D is a schematic of an embodiment of an exemplary medical device of the present invention in accordance with the teachings of the present invention.

Figure 4A is a schematic of an embodiment of an exemplary medical device of the present invention in accordance with the teachings of the present invention.

Figure 4B is a schematic of an embodiment of an exemplary medical device of the present invention in accordance with the teachings of the present invention.
Figure 5A is a schematic of a perspective view of an exemplary embodiment of the micro-fluidic channeled vasculature of the medical device of the present invention.

Figure 5B is a schematic of an end view of one or more of the channels in one embodiment of the micro-fluidic channeled vasculature of the medical device of the present invention.

Figure 5C is a schematic of an end view of one or more of the channels in one embodiment of the micro-fluidic channeled vasculature of the medical device of the present invention.

Figure 5D is a schematic of an end view of one or more of the channels in one embodiment of the micro-fluidic channeled vasculature of the medical device of the present invention.

Figure 5E is a schematic of an end view of one or more of the channels in one embodiment of the micro-fluidic channeled vasculature of the medical device of the present invention.

Figure 6A is a schematic of a perspective view of one or more of the channels in one embodiment of the micro-fluidic channeled vasculature of the medical device of the present invention.

Figure 6B is a schematic of a side view of one or more of the channels in one embodiment of the micro-fluidic channeled vasculature of the medical device of the present invention.

Figure 6C is a schematic of a side view of one or more of the channels in one embodiment of the micro-fluidic channeled vasculature of the medical device of the present invention.
Figure 6D is a schematic of a top view of one or more of the channels in one embodiment of the micro-fluidic channeled vasculature of the medical device of the present invention.

Figure 6E is a schematic of a top view of one or more of the channels in one embodiment of the micro-fluidic channeled vasculature of the medical device of the present invention.

Figure 7A is a schematic of an embodiment for placement of an exemplary medical device of the present invention *in vivo* in a subject when used to augment or supplant the function of a liver.

Figure 7B is a schematic of an embodiment for placement of an exemplary medical device of the present invention *in vivo* in a subject when used to augment or supplant the function of a lung.

Figure 8A is a schematic diagram of another embodiment for placement of an exemplary medical device of the present invention *in vivo* in a subject when used to augment or supplant one or more functions of a liver.

Figure 8B is a schematic diagram of another embodiment for placement of an exemplary medical device of the present invention *in vivo* in a subject when used to augment or supplant one or more functions of a lung.

Figure 9A is a schematic diagram of another embodiment in which a plurality of the medical devices of the present invention can be coupled to a patient.

Figure 9B is a schematic diagram of another embodiment in which a plurality of the medical devices of the present invention can be coupled to a patient.

Figure 10A is a flow chart outlining the steps for forming an exemplary medical device of the present invention.
Figure 10B is a flow chart outlining the steps for forming an exemplary medical device of the present invention.

Figure 11A is a flow chart outlining the steps for forming the bottom layer of an exemplary medical device of the present invention.

Figure 11B is a flow chart outlining the steps for forming the bottom layer of an exemplary medical device of the present invention.

Figure 12 is a flow chart outlining the step of forming a region or regions of an exemplary medical device of the present invention.

Figure 13 illustrates steps taken to form a medical device of the present invention.

Figure 14 is a flow chart illustrating the steps taken for exogenously seeding cells into an exemplary medical device of the present invention.

Figure 15 is a flowchart outlining an exemplary method for coupling a patient to a medical device of the present invention.

Figure 16A is a side perspective of an exemplary catheter in accordance with the teachings of the present invention.

Figure 16B is a side perspective of an exemplary catheter coupled to a medical device in accordance with the teachings of the present invention.

Figure 16C is a cross sectional view of an exemplary catheter for use with the medical device of the present invention.

Figure 17 is a side perspective of a flared base member attached to the proximal end of the tubular member of an exemplary catheter, and the suture region of the flared
base member of an exemplary catheter in accordance with the teachings of the present invention.

Figure 18 is a cross-sectional view of the flared proximal end of the tubular member of an exemplary catheter for use with the medical device of the present invention after being attached to a selected fluid carrying organ of a subject in accordance with the teachings of the present invention.

Figure 19 is a schematic of a cross sectional view of an exemplary catheter attached to an exemplary medical device in accordance with the teachings of the present invention.

Figure 20 is a graphical depiction of the transfer of oxygen and carbon dioxide with an increase of blood flow in an exemplary medical device in accordance with the teachings of the present invention.

Figure 21 is a graphical depiction of the partial pressure of oxygen and carbon dioxide with an increase in blood flow in an exemplary medical device in accordance with the teachings of the present invention.

DETAILED DESCRIPTION

In one aspect, the present invention is directed to medical devices having a vasculature like structure that are capable of performing the physiological function of an organ once surgically coupled to a patient and exogenously seeded with cells after blood flow through the vasculature has been established. In another aspect, the present invention is directed to medical devices having a vasculature like structure that are capable of performing the physiological function of an organ once surgically coupled to a patient and exogenously seeded with cells after blood flow through the vasculature has been established. The present invention is also directed to methods of making and using medical devices having a vasculature like structure.
Before continuing with detailed description, it is helpful to first define a few terms as used herein.

As used herein, the terms "medical device having a vasculature like structure" or "vascularized medical device" or "medical device" refers to a medical device having a spatially varied structure defining a three dimensional vasculature like structure that includes a micro-fluidic network defining a plurality of channels that substantially mimics the physiologic flow of fluid through a circulatory structure, e.g., capillaries, and having a chamber, or a plurality of chambers. In one embodiment, the chambers are useful for holding or containing whole tissue, part of a tissue, or a group of cells (e.g., culture, population, or strain of cells). In exemplary embodiments, the cells have a desired natural origin, source or phenotype and are capable of performing a desired function or having a desired structure, e.g., tissue specific or organ specific cells. In other exemplary embodiments, precursor or progenitor cells are used which are capable of developing or differentiating into cells having the desired function or structure. The group of cells seeded onto the chamber or chambers can include intercellular substances. The desired function or structure of the group of cells seeded onto the device is dependent on the physiological function of the organ which the medical device is intended to supplant or augment. In another embodiment, the medical device is an acellular medical device. In this embodiment, the device contains a chamber or a plurality of chambers, through which oxygen flow and carbon dioxide removal can be attained.

As used herein, the term "vasculature like structure" or "vasculature" or "micro-fluidic channeled vasculature" or "micro-fluidic vasculature" refers to the micro-fluidic network, defined above, formed on at least one region of the medical device of the present invention. In one embodiment, the three dimensional vasculature of a medical device of the present invention allows the blood that flows there through to interact with the whole tissue, part of a tissue, or group of cells contained in the chamber or chambers of the medical device, once the device is coupled to a patient. In another embodiment, the three dimensional vasculature of a medical device of the present invention allows the blood that flows there through to interact with the oxygen
flowing through the chamber or chambers of the medical device, once the device is coupled to a patient.

As used herein, the phrase "exogenously seeding" refers to the process of seeding the cells into the medical devices of the present invention, i.e., the cells are placed into the device by a person and/or another entity; the exogenously seeded cells do not migrate naturally from the body once the device is surgically coupled to the patient. For example, once blood is flowing through the medical device of the present invention, organ specific cells are seeded into the device.

As used herein, the term "acellular" in the context of the medical device of the present invention refers to a device which is substantially free of intact cells, other than the cells contained in the fluid flowing through the micro-fluidic channeled vasculature of the device. That is, the acellular medical devices of the present invention do not contain or rely on a biologically relevant amount of cells in order to function as an organ replacement or assist device.

The term "fluid carrying organ" as used herein refers to an organ capable of carrying a fluid, e.g., blood, from one area to another area. Examples of fluid carrying organs include, but are not limited to, veins, arteries, and the heart.

As used herein, the term "polymer", includes polymers and monomers that can be polymerized or adhered to form an integral unit.

As used herein, the term "biodegradable" refers to materials that are bioreabsorbable and/or degrade and/or break down by mechanical, chemical, or biological degradation upon interaction with a physiological environment into components that are metabolizable or excretable, over a period of time.

Figure 1A illustrates one embodiment of the medical device 10A of the present invention. The medical device 10A is capable of attaining one or more physiological functions of an organ once coupled to a patient and attaining blood flow through the micro-fluidic vasculature and thereafter being exogenously seeded with organ specific
cells. Further, the medical device is capable of augmenting an organ function or providing complete or near complete organ functionality in place of an organ. In this manner, the medical device 10A can mitigate a wide variety of side effects from a diseased or impaired organ. Further, the medical device 10A can have a varying level of organ functionality in order to address additional disease etiologies and severities, as well as the issues of transplant complications and organ rejection. The medical device 10A is well suited for use as a liver assist device, a kidney assist device, a liver replacement device, a kidney replacement device or any other organ assist device or organ replacement device.

In one embodiment, the medical device 10A is configured to include one or more replaceable portions and/or the entire medical device may be replaceable. In this manner, as the medical device 10A ages, as the severity of the organ disease increases, or both, portions of the medical device 10A and/or the entire medical device 10A can be replaced or added to as needed.

As can be seen in Figure 1A, in one embodiment, the stacked structure 21A includes the first region 22A defining a three dimensional micro-fluidic channeled vasculature 24A formed therein, a second region 22A defining at least one chamber 34A formed therein, and a semi-permeable membrane 32A between the first and second regions 22A and 22B. The micro-fluidic vasculature like structure is interconnected with one or more channels 44A, allowing blood to flow through the three dimensional micro-fluidic channeled vasculature 24A of the first region. The medical device 10A further includes an ingress port 36A to receive blood flow from the patient and an egress port 38A to return blood flow to the patient. In one embodiment, the ingress port 36A receives blood flow from the patient’s portal vein. In one embodiment, the egress port 38A returns blood flow to the patient through the inferior vena cava.

The first region 22A and second region 22B of the medical device of the present invention can be defined in a variety of configurations. For example, in one embodiment, the first region 22A is defined in a first layer, and the second region 22B is defined in a second layer. In another embodiment, the first region 22A and the second region 22B are defined in a first layer. In yet another embodiment, the first region 22A
and second region 22B are defined in a plurality of layers. Any combination of regions and layers can be used with the medical device of the present invention.

In one embodiment, the chamber(s) 34A contains a plurality of posts 42A. The plurality of posts included in the chamber(s) 34A serve multiple purposes, including, but not limited to, providing support for the semi-permeable membrane 32A, and/or providing a surface for the organ specific cells to attach to in order to grow.

Additionally, the medical device 10A can include additional access ports 40A and 40B to provide access to the chamber(s) 34A. The access ports 40A and/or 40B can be used to exogenously seed the chamber(s) 34A using either positive pressure to push cells into the chamber(s) 34A or negative pressure to pull or vacuum cells into the chamber(s) 34A. In one embodiment, the chamber(s) 34A is exogenously seeded with organ specific cells, once blood flow is established through the micro-fluidic channeled vasculature 24A. The organ specific cells are selected depending on the organ the medical device 10A is targeted to augment or supplant.

In one embodiment, the access ports 40A and 40B can be left open after the chamber(s) 34A have been exogenously seeded with organ specific cells. In another embodiment, the access ports 40A and 40B can be tied off after the cells have been seeded into the chamber(s) 34A. In yet another embodiment, the access ports 40A and 40B can be joined into an additional drainage tube, and allowed to empty into the intestine after the chamber(s) 34A have been exogenously seeded. A filter can also be included in the additional drainage tube.

The medical device 10A is adapted to be exogenously seeded with at least organ specific cells. Referring again to Figure 1A, the semi-permeable membrane 32A separates the vasculature like structure 24A from the chamber(s) 34A containing the organ specific cells 30A. In one embodiment, the semi-permeable membrane 32A comprises a non-degradable material. In one embodiment, blood is flowing through the micro-fluidic channeled vasculature 24A. The semi-permeable membrane 32A of the present invention is selected to have a pore size smaller than the cell diameter of the red blood cells flowing through the micro-fluidic channeled vasculature 24A and the organ.
specific cells 30A. Thus, neither the red blood cells flowing through the channeled vasculature nor the organ specific cells 30A will be able to pass through the semi-permeable membrane 32A. However, the semi-permeable membrane does allow low molecular weight nutrients and oxygen to pass through, as well as proteins produced by the organ specific cells 30A. Cell sizes vary, but they are generally in the range of microns. For example, a red blood cell has a diameter of 8 \( \mu \)m. In one embodiment, the average membrane pore size is on a submicron-scale to ensure effective screening of the cells. In one example of the present invention, a polyethersulfone membrane with 0.22 \( \mu \)m pores separates the micro-fluidic channeled vasculature from the chamber(s) containing the organ specific cells, e.g., primary human hepatocytes.

In one embodiment, the micro-fluidic channeled vasculature 24A is not seeded with cells. In another embodiment, the micro-fluidic channeled vasculature 24A is seeded with cells 26A, e.g., endothelial cells.

Once surgically coupled to a patient and in operation, the medical device 10A having a vasculature like structure 24A efficiently supplies nutrients to sustain exogenously seeded cells, for example, the viability of exogenously seeded hepatocytes. Moreover, when the medical device 10A having a vasculature like structure 24A acts as a liver assist device or liver replacement device the semi-permeable membrane 32A, analogous to the fenestrae of the liver sinusoid, allows for selective transport of liver specific proteins secreted by the seeded hepatocytes to the effluent.

The medical device having a vasculature like structure of the present invention advantageously allows the patient’s body to act as a bioreactor once the device is exogenously seeded with organ specific cells. In this manner, the patient’s body nourishes the seeded cells. For example, when the medical device having a vasculature like structure is coupled to a patient, the ingress and egress ports provide for the immediate supply of blood to the medical device. Organ specific cells are then exogenously seeded into the device, and the blood flowing through the device provides the cells with the requisite oxygen and nutrient supply needed to grow and survive.
Semi-permeable membranes of the present invention comprise a wide array of different membrane types and morphologies, which can be classified as follows:

(1) Track-etch membranes consisting of cylindrical through-holes in a dense polymer matrix. These membranes are typically made by ion-etching; or

(2) Fibrous membranes made by various deposition techniques of polymeric fibers. While these membranes do not have a well-defined pore topology, production methods have been sufficiently refined so that fibrous membranes have specific molecular weight cut-offs.

In one embodiment, track-etch type membranes are used, as they limit the fluid motion in one direction. For example, fluid motion may be in the vertical direction. Fibrous membranes permit fluid motion both laterally and vertically.

Figure 1B illustrates an embodiment of the medical device 10B of the present invention. The medical device 10B is capable of attaining one or more physiological functions of an organ once coupled to a patient and blood flow through the micro-fluidic vasculature, and oxygen flow through the chamber or chambers is attained. Further, the medical device is capable of augmenting an organ function or providing complete or near complete organ functionality in place of an organ. In this manner, the medical device 10B can mitigate a wide variety of side effects from a diseased or impaired organ. Further, the medical device 10B can have a varying level of organ functionality in order to address additional disease etiologies and severities, as well as the issues of transplant complications and organ rejection. The medical device 10B is well suited for use as a lung assist or lung replacement device.

In one embodiment, the medical device 10B is configured to include one or more replaceable portions and/or the entire medical device may be replaceable. In this manner, as the medical device 10B ages, as the severity of the organ disease increases, or both, portions of the medical device 10B and/or the entire medical device 10B can be replaced or added to as needed.

As can be seen in Figures 1B and 1C, in one embodiment, the stacked structure 21B includes the first region 22C defining a three dimensional micro-fluidic channeled
vasculature 24B formed therein, a second region 22D defining at least one chamber 34B formed therein, and a membrane 32B permeable to oxygen and carbon dioxide and impermeable to fluids between the first and second regions 22C and 22D. The microfluidic vasculature like structure is interconnected with one or more channels 44B, allowing blood to flow through the three dimensional micro-fluidic channeled vasculature 24B of the first region. The medical device 10B further includes an ingress port 36B to receive blood flow from the patient and an egress port 38B to return blood flow to the patient. In one embodiment, the ingress port 36B receives blood flow from the patient’s pulmonary artery. In one embodiment, the egress port 38B returns blood flow to the patient through the left atrium.

The first region 22C and second region 22D of the medical device of the present invention can be defined in a variety of configurations. For example, in one embodiment, the first region 22C is defined in a first layer, and the second region 22D is defined in a second layer. In another embodiment, the first region 22C and the second region 22D are defined in a first layer. In yet another embodiment, the first region 22C and second region 22D are defined in a plurality of layers. Any combination of regions and layers can be used with the medical device of the present invention.

In one embodiment, the chamber(s) 34B contains a plurality of posts 42B. The plurality of posts included in the chamber(s) 34B serve multiple purposes, including, but not limited to, providing support for the membrane 32B.

Additionally, the medical device 10B can include additional access ports 40C and 40D to provide access to the chamber(s) 34B. The access ports 40C and/or 40D allow for oxygen to be supplied to the device such that the oxygen flows through the chamber or chambers. Oxygen can be supplied to the medical device 10B using any art known technique suitable for providing oxygen in vivo, including but not limited to, by an oxygen tank or pump.

Referring again to Figure 1B, the membrane 32B separates the vasculature like structure 24B from the chamber(s) 34B through which oxygen flows. In one embodiment, the oxygen and carbon dioxide permeable membrane 32B comprises a
non-degradable material. In one embodiment, blood is flowing through the micro-fluidic channeled vasculature 24B. The membrane 32B of the present invention is selected to have a pore size smaller than the cell diameter of the red blood cells flowing through the micro-fluidic channeled vasculature 24B. Thus, the red blood cells flowing through the channeled vasculature will not be able to pass through the membrane 32B. However, the permeable membrane does allow for the transfer of oxygen and carbon dioxide between the chamber(s) through which the oxygen is flowing and the blood flowing through the microfluidic channeled vasculature.

In one embodiment, the micro-fluidic channeled vasculature 24B is not seeded with cells. In another embodiment, the micro-fluidic channeled vasculature 24B is seeded with cells 26B, e.g., endothelial cells.

Once surgically coupled to a patient and in operation, the medical device 10B having a vasculature like structure 24B efficiently allows for the transport of oxygen and carbon dioxide between the chamber(s) and the blood flowing through the microfluidic network of the device.

Figure 1c is a schematic of the oxygen/carbon dioxide transfer that takes place when the medical device 10B of the present invention is used as a lung replacement/augmentation device. When the medical device having a vasculature like structure is coupled to a patient, the ingress and egress ports provide for the immediate supply of blood to the medical device. Oxygen flow through the device is then established. When the device is used as a lung replacement or augmentation device, the de-oxygenated blood flowing into the device becomes oxygenated as oxygen passes from the chamber through the permeable membrane into the blood flowing through the micro-fluidic vasculature. Carbon dioxide is also removed from the blood flowing through the micro-fluidic channeled vasculature.

In one embodiment, the material selected for use as an oxygen and carbon dioxide permeable membrane has a high gas permeability to allow for the passage of oxygen and carbon dioxide, but is also impermeable to fluids. In one embodiment, a solid polymer sheet is selected for use as an oxygen and carbon dioxide permeable
membrane. The thickness of the polymer sheet can range from about 1 micron to about 400 microns. In some embodiments, the permeable membrane comprises silicone. In other embodiments, the permeable membrane comprises a medical grade elastomer, for example Silastic® MDX4-4210 Medical Grade Elastomer.

The material selected for use as an oxygen and carbon dioxide permeable membrane can also be coated with an additional material, including, but not limited to a polymer or a mix of polymers. For example, in some embodiments, polycarbonate is selected for use as an oxygen and carbon dioxide permeable membrane, and is coated with a polymer, e.g., polyether sulfone or PDMS, or a medical grade elastomer, e.g., Silastic® MDX4-4210 Medical Grade Elastomer, or combinations thereof. The coating can be in the range of about 0.1 microns to about 100 microns.

In one embodiment, at least one region of the stacked structure 21 is formed from biodegradable polymer. In another embodiment, at least one region of the stacked structure 21 is formed from a non-biodegradable polymer. In yet another embodiment, at least one region of the structure is formed from a non-polymer material, e.g., a ceramic.

Examples of suitable polymers for forming one or more regions of the stacked structure 21 include poly dimethyl siloxane (PDMS), poly lactic co-glycolic acid (PLGA), and polyglycerol-sebacate (PGS), polystyrene and poly methylmethacrylate (PMMA). In one embodiment, the medical device of the present invention is coupled to the patient via implantation into the patient's body. Polymer material for implantation should be selected for biocompatibility. Any degradation products should also be biologically compatible. The material selected is relatively distensible in order to allow for flexibility during changes in pressure, as well as to aid in ease of implantation. Use of a relatively distensible material during implantation near an internal organ is advantageous due to the fragility of these organs. A biologically compatible degradable polymer and its degradation products are non-toxic toward the recipient.

Other examples of suitable polymers for forming one or more regions of the structure 21 include, but are not limited to, polylactic acid (PLA), poly-L-lactic acid
(PLLA), poly-D-lactic acid (PDLA), polyglycolide, polyglycolic acid (PGA),
polydioxanone, polygluconate, polylactic acid-polyethylene oxide copolymers, modified
cellulose, collagen, polyhydroxybutyrate, polyhydroxpropionic acid, polyphosphoester,
poly(alpha-hydroxy acid), polycaprolactone, polycarbonates, polyamides,
polyanhydrides, polyamino acids, polyorthoesters, polycetals, polyacyanoacrylates,
degradable urethanes, aliphatic polyesterspolyacrylates, polymethacrylate, acyl
substituted cellulose acetates, non-degradable polyurethanes, polystyrenes, polyvinyl
chloride, polyvinyl fluoride, polyvinyl imidazole, chlorosulphonated polyolifins,
polyethylene oxide, polyvinyl alcohol, teflon RTM, nylon silicon, and shape memory
materials, such as poly(styrene-block-butadiene), polynorbornene, hydrogels, metallic
alloys, and oligo(ε-caprolactone)diole as switching segment/oligo(p-dioxanone)diole as
physical crosslink. Those of skill in the art will recognize other suitable polymers for
use with the present invention, for example by reference to The Polymer Handbook, 3rd
edition (Wiley, N.Y., 1989). Combinations of these polymers may also be used.

Polylactide-co-glycolides (PLGA), as well as polylactides (PLA) and
polyglycolides (PGA) have been used to make biodegradable implants for drug delivery.
See U.S. Pat. No. 6,183,781 and references cited therein. Biodegradable materials have
been developed for use as implantable prostheses, as pastes, and as templates around
which the body can regenerate various types of tissue. Polymers that are both
biocompatible and resorbable in vivo are known in the art as alternatives to autogenic or
allogeneic substitutes.

Solvents for most of the thermoplastic polymers are known, for example,
methylene chloride or other organic solvents. Organic and aqueous solvents for protein
and polysaccharide polymers are also known. The binder can be the same material as is
used in conventional powder processing methods or can be designed to ultimately yield
the same binder through chemical or physical changes that occur as a result of heating,
photopolymerization, or catalysis.

Those skilled in the art will appreciate that Figures 1A and 1B are meant to
facilitate explanation of the present invention and is not meant to be limiting of the
present invention. That is, although a medical device comprising a stacked structure
with two regions and one micro porous membrane is illustrated, the medical device 10A can have a larger number of regions and membranes in fluid communication, for example, 1, 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1000, or more structures in fluid communication. In another embodiment, 50, 60, 70, 80, 90, or 100 or more structures are in fluid communication. Likewise, although a medical device comprising a stacked structure with two regions and one oxygen and carbon dioxide permeable membrane is illustrated, the medical device 10B can have a larger number of regions and membranes in fluid communication, for example, 1, 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1000, or more structures in fluid communication. In another embodiment, 50, 60, 70, 80, 90, or 100 or more structures are in fluid communication. It is to be understood that all values and ranges between these values and ranges are meant to be encompassed by the present invention.

Figure 1D illustrates another embodiment of the stacked structure 21 having more than two regions stacked one on top of the other. The stacked structure 21 can have any number of regions stacked one on top of another, spaced apart in a distributed manner and interconnected by a plurality of lumens or in some combination of stacked and spaced apart distributed manner. The ingress 36 and egress port 38 allow for blood to flow through the micro-fluidic channeled vasculature 24 of each region of the stacked structure. In one embodiment, the access ports 40A and/or 40B allow for organ specific cells to be seeded through the chamber(s) 34 of each region of the stacked structure. The semi-permeable membrane 32A may or may not be intersected by the ingress port 36 and the egress port 38, and/or the access ports 40A and/or 40B. In another embodiment, the access ports 40C and/or 40D allow for oxygen to flow through the chamber(s) 34 of each region of the stacked structure. The membrane 32B may or may not be intersected by the ingress port 36 and the egress port 38, and/or the access ports 40C and/or 40D.

Figure 2A is a schematic of another embodiment of the medical device of the present invention. In one embodiment, the medical device 10 comprises a doubled sided layer 50 having a first region in which a vasculature like structure 52 is formed on one side and a second region on the opposite side of the layer 50 in which is formed at least one chamber 54. The chamber(s) 54 contains a plurality of posts 56. The plurality of
posts 56 included in the chamber(s) 54 serve multiple purposes, including, but not limited to, providing support for the semi-permeable membrane, and/or providing a surface for the organ specific cells to attach to in order to grow.

In this embodiment, the first and second region of the medical device of the present invention can be defined in a variety of configurations. For example, in one embodiment, the first and second regions are defined in a single layer. In another embodiment, the first and second regions are defined in a plurality of layers. In another embodiment, the first and second regions are defined in a plurality of non-abutting layers. Any combination of regions and layers can be used with the medical device of the present invention.

Those skilled in the art will appreciate that Figure 2A is meant to facilitate explanation of the present invention and is not meant to be limiting of the present invention. That is, although a medical device comprising a single structure with a single layer having two regions is illustrated, the medical device 10 can have a larger number of double sided single layers defining at least two regions, for example, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 or more double sided single layers.

Figure 2B illustrates two double sided layers 50A and 50B stacked one on top of another and each defining two regions. In other embodiments, the double sided layers 50A and 50B are spaced apart in a distributed manner and interconnected by a plurality of lumens or in some combination of stacked and spaced apart distributed manner. The vasculature like structure 52 of the second layer 50B is separated from the chamber(s) 54 of the first layer 50A by a membrane 58. In one embodiment, the membrane is a semi-permeable membrane. In another embodiment, the membrane is an oxygen and carbon dioxide permeable membrane. The ingress 60 and egress port 62 allow for blood to flow through the vasculature like structure 52 of each of the double sided layers 50A and 50B. In one embodiment, the access ports 64A and/or 64B allow for organ specific cells to be seeded through the chamber(s) 54 of each of the double sided layers 50A and 50B. The semi-permeable membrane 58 may or may not be intersected by the ingress port 60 and the egress port 62, and/or the access ports 64A and/or 64B. In another
embodiment, the access ports 64A and/or 64B allow for oxygen to flow through the chamber(s) 54 of each of the double sided layers 50A and 50B. The oxygen and carbon dioxide permeable membrane 58 may or may not be intersected by the ingress port 60 and the egress port 62, and/or the access ports 64A and/or 64B.

Figure 3A is a schematic of another embodiment of the medical device 10A of the present invention. In one embodiment, the stacked structure 70A of the medical device 10A comprises a first region 72A defining a first micro-fluidic channeled vasculature 80A, a second region 74A defining a chamber or chambers 82A capable of being exogenously seeded with at least organ specific cells, and a third region 76A defining a second micro-fluidic channeled vasculature 80B. The second region 74A and the third region 76A are separated by a semi-permeable membrane 78A. Cells are seeded into the device exogenously after the medical device 10A is surgically coupled to the patient and blood flow though the micro-fluidic vasculature 80A and 80B is established. The organ specific cells are selected depending on the organ the medical device 10A is targeted to augment or supplant.

The first region 72A, the second region 74A, and the third region 76A of the medical device of the present invention can be defined in a variety of configurations. For example, in one embodiment, each region is defined in a separate layer, i.e., the first region 72A is defined in a first layer, the second region 74A is defined in a second layer, and the third region 76A is defined in a third layer. In another embodiment, the first region 72A and the second region 74A are defined in a first layer, and the third region 76A is defined in a second layer. In yet another embodiment, the first region 72A, the second region 74A, and the third region 76A are defined in a plurality of layers. Any combination of regions and layers can be used with the medical device of the present invention.

In one embodiment, the chamber(s) 82A contains a plurality of posts 84A. The plurality of posts included in the chamber(s) 82A serve multiple purposes, including, but not limited to, providing support for the semi-permeable membrane, and/or providing a surface for the organ specific cells to attach to in order to grow.
The second region 74A comprises a material which allows for the transport of oxygen and nutrients between the vasculature like structure 80A defined by the first region 72A and the chamber(s) 82A defined by the second region 74A. In one embodiment, the second region 74A comprises a polymer. Any polymer suitable for in vivo use can be used in the medical device of the present invention, including, but not limited to, poly dimethyl siloxane, poly lactic coglycolic acid, and polyglycerol-sebacate, polystyrene and poly methylmethacrylate. In one embodiment, the second region 74A comprises PDMS. The “tri-stack” configuration of this embodiment of the medical device 10A allows for the organ specific cells exogenously seeded onto the medical device 10A to receive oxygen and nutrients from both above and below.

The distance that oxygen can diffuse across a membrane is limited. The limits on the distance that oxygen diffuses in turn limits the depth at which the chamber(s) 82A can contain viable organ specific cells, i.e., if the chambers are too deep and oxygen cannot reach all of the exogenously seeded organ specific cells, those cells without an oxygen supply will not survive. Providing an oxygen supply to the organ specific cells from both above and below allows one of skill in the art to construct a deeper chamber(s) 82A. A deeper chamber allows for more organ specific cells to be seeded on to the medical device 10A of the present invention increasing the functionality of the medical device 10A. Additionally, a deeper chamber(s) 82A allows more space for the seeding of more than one cell type. The desired cell mass seeded onto the medical device 10A of the present invention is dependent on the level of organ assistance or replacement the device is designed to provide to the subject. For example, in one embodiment, the device of the present invention is designed to replace about 15% of the function of a normal liver, and contains about 500 grams of hepatocytes. The amount of organ specific cells necessary to achieve the desired level of functionality of a medical device of the present invention will increase as the desired level of functionality increases.

Those skilled in the art will appreciate that Figure 3A is meant to facilitate explanation of the present invention and is not meant to be limiting of the present invention. That is, although a medical device comprising a stacked structure having three regions and one micro porous membrane is illustrated, the medical device 10 can
have a larger number of regions, for example, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 or more regions in a stacked or non stacked structure.

Figure 3B illustrates a stacked structure 70 comprising six regions and two semi-permeable membranes stacked one on top of another, spaced apart in a distributed manner and interconnected by a plurality of lumens or in some combination of stacking and spaced apart distributed manner. The ingress 86 and egress port 88 allow for blood to flow through the vasculature like structure 80 of each region. The access ports 90A and/or 90B allow for organ specific cells to be seeded through the chamber(s) 82 of each region. The semi-permeable membrane 78 may or may not be intersected by the ingress port 86 and the egress port 88, and/or the access ports 90A and/or 90B.

Figure 3C is a schematic of another embodiment of the medical device 10B of the present invention. In one embodiment, the stacked structure 70B of the medical device 10B comprises a first region 72B defining a chamber or chambers 80C capable of having oxygen flow there through, a second region 74B defining a first micro-fluidic channeled vasculature 82B, and a third region 76B defining a second chamber or chambers 80D capable of having oxygen flow there through. The second region 74B and the third region 76B are separated by a semi-permeable membrane 78B. Oxygen flow through the chamber or chambers of the first and second regions is established after the medical device 10B is surgically coupled to the patient and blood flow though the micro-fluidic vasculature 82B is established.

The first region 72B, the second region 74B, and the third region 76B of the medical device of the present invention can be defined in a variety of configurations. For example, in one embodiment, each region is defined in a separate layer, i.e., the first region 72B is defined in a first layer, the second region 74B is defined in a second layer, and the third region 76B is defined in a third layer. In another embodiment, the first region 72B and the second region 74B are defined in a first layer, and the third region 76B is defined in a second layer. In yet another embodiment, the first region 72B, the second region 74B, and the third region 76B are defined in a plurality of layers. Any combination of regions and layers can be used with the medical device of the present invention.
In one embodiment, the chamber(s) 80C and 80D contains a plurality of posts 84B. The plurality of posts included in the chamber(s) 80C and 80D serve multiple purposes, including, but not limited to, providing support for the oxygen and carbon dioxide permeable membrane.

The second region 74B comprises a material which allows for the transport of oxygen and carbon dioxide between the vasculature like structure 82B defined by the second region 74B and the chamber(s) 80C and 80D defined by the first region 72B, and the third region 76B. In one embodiment, the second region 74B comprises a polymer. Any polymer suitable for in vivo use can be used in the medical device of the present invention, including, but not limited to, poly dimethyl siloxane, poly lactic coglycolic acid, and polyglycerol-sebacate, polystyrene and poly methylmethacrylate. In one embodiment, the second region 74B comprises PDMS. The “tri-stack” configuration of this embodiment of the medical device 10 allows for the blood flowing through the microfluidic channeled vasculature of the second region 74 to receive oxygen and discharge carbon dioxide from both above and below.

The distance that oxygen can diffuse across a membrane is limited. The limits on the distance that oxygen diffuses in turn limits the depth at which the microfluidic channeled vasculature can be created. If the channels are too deep, oxygen does not reach a portion of the blood flowing there through, thereby limiting the amount of oxygenation of the blood. Therefore, in order to reach a desired level of organ functionality, the size of the device needs to be increased.

Providing an oxygen supply to the blood flowing through the device from both above and below allows one of skill in the art to construct a deeper micro-fluidic channeled vasculature 82B. A deeper channel allows for more blood to flow through the device and become oxygenated, thereby increasing the functionality of the device without increasing the size of number of regions of the device.

Those skilled in the art will appreciate that Figure 3C is meant to facilitate explanation of the present invention and is not meant to be limiting of the present
invention. That is, although a medical device comprising a stacked structure having three regions and one porous membrane is illustrated, the medical device 10 can have a larger number of regions, for example, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 or more regions in a stacked or non stacked structure. It is to be understood that all values and ranges between these values and ranges are meant to be encompassed by the present invention.

Figure 3D illustrates a stacked structure 70B comprising six regions and two semi-permeable membranes stacked one on top of another, spaced apart in a distributed manner and interconnected by a plurality of lumens or in some combination of stacking and spaced apart distributed manner. The ingress 86B and egress port 88B allow for oxygen to flow through the chamber(s) 80B of each region. The access ports 90C and/or 90D allow for blood to flow through the micro-fluidic channeled vasculature 82B of each region. The oxygen and carbon dioxide permeable membrane 78B may or may not be intersected by the ingress port 86B and the egress port 88B, and/or the access ports 90C and/or 90D.

Figure 4A is a schematic of another embodiment of the medical device 10 of the present invention. In one embodiment, the medical device comprises a first region 102 defining a micro-fluidic channeled vasculature 110 and a second region 104 defining a chamber 34. The first and second regions 102 and 104 are separated longitudinally by membrane 120. In this embodiment, the membrane is a semi-permeable membrane. The first region 102 is capable of attaining blood flow there through once the medical device 10 is coupled to a subject. In this embodiment, the second region 104 is capable of being exogenously seeded with at least organ specific cells. The regions 102 and 104 can be defined in a variety of ways, including, but not limited to, in a single layer, or in a plurality of layers.

In another embodiment, Figure 4A is a schematic of the medical device 10 of the present invention. In one embodiment, the medical device comprises a first region 102 defining a micro-fluidic channeled vasculature 110 and a second region 104 defining a chamber 34. The first and second regions 102 and 104 are separated longitudinally by a membrane 120. In this embodiment, the membrane is an oxygen and
carbon dioxide permeable membrane. The first region 102 is capable of attaining blood flow there through once the medical device 10 is coupled to a subject. The second region 104 is capable of having oxygen flow there through. The regions 102 and 104 can be defined in a variety of ways, including, but not limited to, in a single layer, or in a plurality of layers.

Although the medical device of the present invention is shown in Figure 4A as a single layer having a first region 102 defining a micro-fluidic channeled vasculature 110 and a second region 104 defining a chamber 34 formed on one side, multiple layers can be stacked on top of another, for example, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 or more layers can be stacked on top of another.

Figure 4B illustrates two layers 100A and 100B stacked on top of another. Each of the layers 100A and 100B comprises two regions defining a micro-fluidic vasculature and a chamber. The two regions are separated longitudinally by a membrane. In certain embodiments, the membrane is a semi-permeable membrane. In other embodiments the membrane is an oxygen and carbon dioxide permeable membrane. In some embodiments, the layers are spaced apart in a distributed manner and interconnected by a plurality of lumens or are in some combination of stacked and spaced apart distributed manner.

The exemplary embodiment of the medical device of the present invention shown in Figures 4A and 4B allows for both the vasculature and the organ specific cells to be contained on one side of a single layer, which can then be integrated into a multi-layered device. In another embodiment, the medical device of the present invention shown in Figures 4A and 4B allows for both the vasculature and the chamber(s) through which oxygen flows to be contained on one side of a single layer, which can then be integrated into a multi-layered device. Thus, the overall Z-dimension of the exemplary medical device of the present invention is reduced, making intracorporeal placement in a patient easier.

The thickness of the layers and/or regions of the medical device 10 can vary. In some embodiments, the layers and/or regions have a thickness of about 200 to about
7000 microns. In other embodiments, the layers and/or regions have a thickness of about 700 to about 5500 microns. It is to be understood that all values and ranges between these expressed values and ranges are meant to be encompassed by the present invention.

Figure 5A is a perspective view of an exemplary embodiment of the micro-fluidic channeled vasculature 24 of the medical device 10 of the present invention. The micro-fluidic channeled vasculature 24 includes one or more channels 510 having bottom and side walls such that fluid is capable of flowing there through. The bottom wall of the channels 510 can be, for example, radial, flat, or any combination or variation thereof. Further, the side walls of the one or more channels 510 can abut the bottom wall at any angle, including, but not limited to angles of 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or 110 degrees, or any incremental value thereof. It is to be understood that all values and ranges between these expressed values and ranges are meant to be encompassed by the present invention.

Figure 5B illustrates an end view of one or more of the channels 510 in one embodiment of the micro-fluidic channeled vasculature 24. One or more of the channels 510 can have a substantially flat bottom wall 550 that abuts a first side wall 560 at a 90 degree angle and abuts a second side wall 570 at a 90 degree angle.

Figure 5C illustrates an end view of one or more of the channels 510 in one embodiment of the micro-fluidic channeled vasculature 24. One or more of the channels 510 can include a radial bottom wall 520 extending from a first side wall 530 to a second side wall 540. The first and second side walls 530, 540 can be substantially perpendicular to a top surface or a bottom surface of the micro-fluidic channeled vasculature 24.

Figure 5D illustrates an end view of one or more of the channels 510 in one embodiment of the micro-fluidic channel vasculature 24. As illustrated, one or more of the channels 510 can include a radial bottom wall 520 extending from a first sloping sidewall 530A to a second sloping sidewall 540A. The first and second side walls 530A,
540B are offset from a plane perpendicular to a horizontal top or bottom surface plane of
the micro-fluidic channeled vasculature 24.

Figure 5E illustrates an end view of one or more of the channels 510 in one
embodiment of the micro-fluidic channel vasculature 24. As illustrated, one or more of
the channels 510 can include a substantially flat bottom wall 550 extending from a first
sloping sidewall 530A to a second sloping sidewall 540A. The first and second side
walls 530A, 540B are offset from a plane perpendicular to a horizontal top or bottom
surface plane of the micro-fluidic channeled vasculature 24.

The radial bottom wall 520 and the sidewalls 530, 530A, 540 and 540A allow
one or more of the channels 510 of the micro-fluidic vasculature 24 to have a structure
that mimics or replicates the circular structure of the blood vessels that form the vascular
network of an organ. More specifically, the radial bottom wall 520, the radial sidewalls
530 and 540 and the sloping sidewalls 530 and 540A are configurable so that one or
more of the channels 510 has a substantially circular cross section that replicates or
mimics the cross section of a blood vessel.

Additionally, the radial bottom channel wall, or the sloping side channel walls, or
both, of one or more of the channels 510 facilitates the removal of the micro-fluidic
vasculature 24 from a mold. That is, the absence of sidewalls that abut a bottom wall at
90 degree angles reduces the amount of friction necessary to remove the micro-fluidic
vasculature 24 from the mold. In turn, the channels 510 of the micro-fluidic vasculature
24 are substantially smoother (e.g., free of tears and rips) as compared to channels
formed from a mold having sidewalls and a bottom wall that abut at 90 degree right
angles. Without wishing to be bound by any particular theory, it is thought that
substantially smoother channels reduce the amount of clotting found inside the
channeled vasculature of the medical devices of the present invention.

Figure 6A is a perspective view of one or more of the channels 510 of the micro-
fluidic vasculature 24. In one embodiment, one or more of the channels 510 have a
tapered channel height/depth, a tapered channel width or both. That is, one or more of
the channels 510 of the micro-fluidic vasculature 24 have a first portion with a width \( W_1 \),
and a height $H_1$ and a second portion with a width $W_2$ and a height $H_2$. The channel width $W_1$ is different from the channel width $W_2$. Likewise, the channel height $H_1$ is different from the channel height $H_2$. The varying channel height, the varying channel width or both facilitates blood flow through the channels 510 of the micro-fluidic vasculature 24 of the medical device 10. The ability to taper a channel width, a channel height or both of one or more of the channels 510 facilitates maintaining a laminar blood flow when transitioning between micro-fluidic channels having different fluid capacities. For example, from an ingress port of the medical device 10 to portions of the micro-fluidic vasculature 24 having channels mimicking the size, function and operation of capillaries and in turn, from the portions of the micro-fluidic vasculature 24 having channels mimicking the size, function and operation of capillaries to the channels leading to an egress port of the medical device 10 leading to a vein or artery.

Figure 6A illustrates that one or more channels 510 of the micro-fluidic channel vasculature 24 can have a taper or a gradual change in channel height, channel width or both. The slope or degree of change of the channel taper in channel height can be related to slope or degree of change of the channel taper in the channel width of the channel 510. In this manner, the widest portion of the channel can also be the deepest and the shallowest portion of the channel can also be the narrowest. Likewise, the widest portion of the channel can also be the shallowest and the narrowest portion of the channel can also be the deepest. Additionally, the slope or degree of change of the channel taper in channel height can be unrelated to slope or degree of change of the channel taper in the channel width of the channel 510. In this manner, the widest portion and the narrowest portion of the channel can have the same depth or the deepest portion and the shallowest portion of the channel can have the same width.

Figure 6B depicts a side view of one of the one or more channels 510 having a tapered channel height. In some embodiments, the slope or degree of change in channel height from a first height $H_1$ to a second height $H_2$ is substantially constant.

Figure 6C depicts a side view of one of the one or more channels 510 having a tapered channel height. In some embodiments, the slope or degree of change in channel height can vary. The slope or the degree of change in the channel height of the one or
more channels 510 can change several times along a length of a channel. For example, a first portion of a channel can have a height \( H_1 \), a second portion of the channel can have a height \( H_2 \) that is shallower than the first portion of the channel, and a third portion of the channel can have third height \( H_3 \) that has a height between the first height \( H_1 \) and the second height \( H_2 \). In this manner, the slope or degree of change of a channel height can both increase and decrease along a length of a channel.

Figure 6D depicts a top view of one of the one or more channels 510 having a tapered channel width. In some embodiments the degree of change in channel width from a first width \( W_1 \) to a second width \( W_2 \) is substantially constant.

Figure 6E depicts a top view of one of the one or more channels 510 having a tapered channel width. In some embodiments, the degree of change in channel width can vary. The degree of change in the channel width of the one or more channels 510 can change several times along a length of a channel. For example, a first portion of a channel can have a width \( W_1 \), a second portion of the channel can have a width \( W_2 \), and a third portion of the channel can have a third width \( W_3 \) that has a width different than the first width \( W_1 \) and the second width \( W_2 \). In this manner, the degree of a change of channel width can both increase and decrease along a length of a channel.

In one aspect of the present invention an aspect ratio of 1:1 for channel height and channel width of the one or more channels 510 is maintained. In other aspects of the present invention aspect ratios of about 50:2 to a ratio of about 0.5 for channel height and channel width of the one or more channels 510 is maintained. Without wishing to be bound by any particular theory, it is thought that varying the height of a channel, the width of a channel, or both, aids in facilitating laminar flow throughout the medical device 10 of the present invention. Moreover, the gradual transition of a tapered channel height, of a tapered channel width, or both, tends to maintain a laminar flow by avoiding abrupt transitions that tend to cause turbulent flow.

The channels of the channeled vasculature of the medical device 10 of the present invention can vary in height, width or both. In some embodiments, the channels are about 200 to about 5000 microns in width and about 200 to about 5000 microns in
depth. Although the channels can vary in height, width or both, the channeled vasculature of the medical device of the present invention is designed such that the cross sectional area of the channeled vasculature is substantially equivalent at any point throughout the vasculature, despite the varied channels. For example, the cross sectional area of the channeled vasculature at the ingress port is substantially equivalent to the cross sectional area of the channeled vasculature at any other point throughout the vasculature.

In some embodiments, one or more of the channels 510 have any combination of a radial bottom wall 520, a sloping side wall 530A, a sloping side wall 540A, a perpendicular side wall 530, a perpendicular side wall 540, a flat bottom wall 550, a tapered channel height or a tapered channel width.

In one embodiment, the medical device 10 of the present invention augments or supplants one or more physiological functions of a liver. Figure 7A is a schematic of an embodiment for placement of an exemplary medical device of the present invention in vivo in a subject when used to augment or supplant the function of a liver. As can be seen in Figure 7, in one embodiment, the medical device 10 is attached via tubular member 720A to the portal vein and attached via tubular member 720B to the inferior vena cava. Thus blood flows through the medical device 10 from the portal vein to the inferior vena cava at a suprahepatic location. Additionally, the medical device 10 can be placed extracorporeal to the subject and the first and second tubular members 720A and 720B are coupled to the portal vein and the inferior vena cava at a suprahepatic location, respectively, through a venous attachment technique. Once surgically coupled to a patient, the medical device 10 of the present invention can augment or supplant one or more physiological functions of a damaged organ. When used to supplant or augment one or more physiological functions of a damaged liver, the medical device 10 of the present invention provides the further benefit of relieving portal hypertension.

A shunt 730A can be attached to the tubular member 720A which is attached to the portal vein. In one embodiment, a pharmacological agent can be administered through the shunt 730A, for example, a diagnostic agent, or an anticoagulant. In one embodiment, heparin is introduced into the shunt 730A. In another embodiment, tPA is
introduced into the shunt 730A. Introduction of an anticoagulant into the medical device reduces the amount of clotting that occurs in the device once blood flow through is established.

The shunt 730A extends outwardly from the outer wall of the tubular member 720A at an angle offset from the longitudinal axis of the tubular member, such that the distal end of the shunt 730A is substantially flush against the inner wall of the tubular member. The shunt is well suited for use to introduce a pharmacological agent into the medical device 10.

The introduction of the pharmacological agent in close proximity to the medical device in combination with the design of the device of the present invention beneficially limits the amount of pharmacological agent found outside of the device and thereby minimizing systemic distribution of the pharmacological agent. This is particularly important when the medical device is used to augment or supplant one or more physiological functions of a liver, and the pharmacological agent introduced is an anticoagulant. Homeostasis is related to liver function, because most coagulation factors are synthesized by liver parenchymal cells and the liver's reticuloendothelial system serves an important role in the clearance of activation products. Patients with liver disease often have coagulation abnormalities. Therefore, there is a need to limit the amount of an anti-coagulant circulating systemically in a patient with liver disease.

Exemplary anti-coagulation drugs and anti-platelet drugs for use with the present invention are shown below in Table 1.

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic</th>
<th>Metabolism</th>
<th>Site(s) of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anti-Coagulation Drugs</td>
<td>Direct Thrombin Inhibitor</td>
<td></td>
</tr>
<tr>
<td>Acova</td>
<td>Argatroban</td>
<td>Hepatic</td>
<td></td>
</tr>
<tr>
<td>Coumadin</td>
<td>Warfarin</td>
<td>Hepatic</td>
<td>Inhibits K Dependent Factors 7,9,10&amp;2; Prot C&amp;S</td>
</tr>
<tr>
<td>Heparin</td>
<td>Heparin</td>
<td>Hepatic</td>
<td>Inactivates Factor 10 - Requires Anti-Thrombin III Inhibits Fibrin Stabilizing Factor, Large doses inhibits Thrombin</td>
</tr>
<tr>
<td>Jantoven</td>
<td>Warfarin</td>
<td>Hepatic</td>
<td>Inhibits K Dependent Factors 7,9,10&amp;2; Prot C&amp;S</td>
</tr>
<tr>
<td>Refludan</td>
<td>Lepirudin</td>
<td>Serum enzyme</td>
<td>Direct Thrombin Inhibitor</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Anti-platelet Drugs</th>
<th>Enoxaparin</th>
<th>Hepatic</th>
<th>Direct inhibitor of Thrombin Anti-Factor 10a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggrastat</td>
<td>Tirofiban</td>
<td>None</td>
<td>Inhibits GP IIb/IIIa (platelet surface aggregation receptor)</td>
</tr>
<tr>
<td>Aggrenox</td>
<td>Aspirin/dipyridamole</td>
<td>See drugs</td>
<td>See individual drugs</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Aspirin</td>
<td>Renal</td>
<td>Inhibits prostaglandin release</td>
</tr>
<tr>
<td>Integrilin</td>
<td>Eptifibatide</td>
<td>Serum enzyme</td>
<td>Inhibits GP IIb/IIIa (Platelet surface aggregation receptor)</td>
</tr>
<tr>
<td>Persantine</td>
<td>Dipyridamole</td>
<td>Hepatic</td>
<td>Inhibition of uptake of adenosine decrease platelet responsiveness promotes EDRF effects</td>
</tr>
<tr>
<td>Plavix</td>
<td>Clopidogrel Bisulfate</td>
<td>Serum enzyme</td>
<td>Permanent direct inhibition of ADP binding in platelets-subsequent inhibition of ADP-mediated activation of the glycoprotein GPIIb/IIIa complex</td>
</tr>
<tr>
<td>Pletal</td>
<td>Cilostazol</td>
<td>Hepatic</td>
<td>PDE III inhibitor -platelet and blood vessel cAMP degradation inhibitor -inhibition of platelet aggregation and vasodilation</td>
</tr>
<tr>
<td>ReoPro</td>
<td>Abciximab</td>
<td>Serum enzyme</td>
<td>Inhibits GP IIb/IIIa (Platelet surface aggregation receptor) Inhibits vitronectin &amp; MAC-1</td>
</tr>
<tr>
<td>Ticlid</td>
<td>Ticlopidine</td>
<td>Hepatic</td>
<td>Inhibits ADP-induced platelet fibronogen binding -subsequent inhibition of platelet to platelet interactions</td>
</tr>
</tbody>
</table>

In another embodiment, a thrombolytic agent, for example, tissue plasminogen activator (tPA) is introduced through the shunt. tPA has been shown to dissolve blood clots, which cause most heart attacks and strokes. Without wishing to be bound by any particular theory, it is thought that introduction of tPA into the medical device of the present invention reduces the chance of a blood clot or clots from forming once the medical device is coupled to a patient and blood flow has been established there through. Additionally, it is thought that introduction of tPA into the medical device of the present invention also alleviates the formation of intimal hyperplasia, and improves uniform blood flow through the device.

In one embodiment, the medical device 10 of the present invention augments or supplants one or more physiological functions of a lung. The device can be coupled to a subject either intracorporeally or extracorporeally. Figure 7B is a schematic of an embodiment for placement of an exemplary medical device of the present invention in...
vivo in a subject when used to augment or supplant the function of a lung. As can be seen in Figure 7, in one embodiment, the medical device 10 is attached via tubular member 720C to the pulmonary artery and attached via tubular member 720D to the left atrium. Additionally, the medical device 10 can be placed extracorporeal to the subject and the first and second tubular members 720C and 720D are coupled to the pulmonary artery and the left atrium. Once surgically coupled to a patient, the medical device 10 of the present invention can augment or supplant one or more physiological functions of a damaged organ. When used to supplant or augment one or more physiological functions of a damaged lung, the medical device 10 of the present invention provides the further benefit of relieving pulmonary hypertension.

A shunt 730B can be attached to the tubular member 720C which is attached to the pulmonary artery. The shunt 730B extends outwardly from the outer wall of the tubular member 720C at an angle offset from the longitudinal axis of the tubular member, such that the distal end of the shunt 730B is substantially flush against the inner wall of the tubular member. The shunt is well suited for use to introduce a pharmacological agent into the medical device 10.

In one embodiment, a pharmacological agent can be administered through the shunt 730B, for example, a diagnostic agent, or an anticoagulant. In one embodiment, heparin is introduced into the shunt 730B. In another embodiment, tPA is introduced into the shunt 730B. Introduction of an anticoagulant into the medical device reduces the amount of clotting that occurs in the device once blood flow through is established.

Exemplary anti-coagulation drugs and anti-platelet drugs for use with the present invention are shown above in Table 1.

Alternatively, a thrombolytic agent, for example, tissue plasminogen activator (tPA) is introduced through the shunt. tPA has been shown to dissolve blood clots, which cause most heart attacks and strokes. Without wishing to be bound by any particular theory, it is thought that introduction of tPA into the medical device of the present invention reduces the chance of a blood clot or clots from forming once the medical device is coupled to a patient and blood flow has been established there through. Additionally, it is thought that introduction of tPA into the medical device of the present
invention also alleviates the formation of intimal hyperplasia, and improves uniform blood flow through the device.

Figure 8A is a schematic diagram of another embodiment for placement of an exemplary medical device of the present invention in vivo in a subject when used to augment or supplant one or more functions of a liver. In one embodiment, the medical device 10 is connected at one end to the portal vein of the subject, and at the other end to the inferior vena cava of the subject by a first tubular member 820A and a second tubular member 820B, respectively. A shunt 830A can optionally be attached between the first and second tubular members 820A, 820B. The tubular members 820A, 820B and shunt 830A can comprise numerous shapes and configurations. For example, in one embodiment, the tubular members 820A, 820B and the shunt 830A are a monolithic structure. In other embodiments, the tubular members 820A, 820B and the shunt 830A are separate and distinct tubing sections joined or coupled in any suitable manner, for example, in a variety of ways, including, but not limited to, by bonding, e.g., adhesive bonding, or by sutures.

The distal end of the first tubular member 820A is bifurcated into two branches prior to the point of attachment to the medical device 10. A first branch is attached to an ingress port of the medical device 10 and a second branch is positioned in a direction of the fluid flowing through the medical device 10. The distal end of the second tubular member 820B is bifurcated. A first branch of the second tubular member 820B is connected to the egress port of the medical device 10. The shunt 830A is connected between the second branch of the first tubular member 820A and the second branch of the second tubular member 820B.

A flow restrictor 850A may be attached to the shunt 830 to change the degree of portal hypertension in the portal vein, i.e., if the flow is restricted there is an increase in portal hypertension, and if the flow is increased there is a decrease in portal hyper tension. Further, a flow restrictor 860A can be placed around the portal vein. The flow restrictor 860A is adjustable to control blood flow into the liver.
Figure 8B is a schematic diagram of another embodiment for placement of an exemplary medical device of the present invention in vivo in a subject when used to augment or supplant one or more functions of a lung. In one embodiment, the medical device 10 is connected at one end to the pulmonary artery of the subject, and at the other end to the left atrium of the subject by a first tubular member 820C and a second tubular member 820D, respectively. A shunt 830B can optionally be attached between the first and second tubular members 820C, 820D. The tubular members 820C, 820D and shunt 830B can comprise numerous shapes and configurations. For example, in one embodiment, the tubular members 820C, 820D and the shunt 830B are a monolithic structure. In other embodiments, the tubular members 820C, 820D and the shunt 830B are separate and distinct tubing sections joined or coupled in any suitable manner, for example, in a variety of ways, including, but not limited to, by bonding, e.g., adhesive bonding, or by sutures.

The distal end of the first tubular member 820C is bifurcated into two branches prior to the point of attachment to the medical device 10. A first branch is attached to an ingress port of the medical device 10 and a second branch is positioned in a direction of the fluid flowing through the medical device 10. The distal end of the second tubular member 820D is bifurcated. A first branch of the second tubular member 820D is connected to the egress port of the medical device 10. The shunt 830B is connected between the second branch of the first tubular member 820C and the second branch of the second tubular member 820D.

A flow restrictor 850B may be attached to the shunt 830B to change the degree of pulmonary hypertension in the pulmonary artery, i.e., if the flow is restricted there is an increase in pulmonary hypertension, and if the flow is increased there is a decrease in pulmonary hypertension.

Figure 9A illustrates another embodiment in which a plurality of the medical devices 10 can be coupled to a patient. For example, 1, 2, 3, 4, or 5 medical devices can be coupled to a patient in serial fashion or in parallel fashion. Numerous configurations of multiple the medical devices 10 and the tubular members 720A, 720B, 820A, 820B, 830A, 920A and 920B may be used to couple the medical devices 10 to the patient. In
one embodiment, a first tubular member is attached at its distal end to the portal vein of a subject. The proximal end of the first tubular member is branched such that each branch of the tubular member connects to an ingress port of one of the medical devices 10. The proximal end of the second tubular member is similarly branched such that each branch of the second tubular member connects to an egress port of one of the medical devices 10. Like the first tubular member, the plurality of branches of the proximal end of the second tubular member merge at one or more junctions into a single lumen or branch associated with the distal end of the second tubular member.

In one embodiment, the tubular members 920A, 920B and the shunts 930A are a monolithic structure. In other embodiments, the tubular members 920A, 920B and the shunts 930A comprise a plurality of separate and distinct tubing sections joined or coupled in any suitable manner, for example, in a variety of ways, including, but not limited to, by bonding, e.g., adhesive bonding, or by sutures.

In another embodiment, each medical device 10 is coupled to the patient separately. For example, in one embodiment, the proximal ends of multiple first tubular members 920A can be connected to the portal vein of the subject, and the distal ends of multiple first tubular members 920A can be connected to respective ingress ports of the medical devices 10. In like fashion, the proximal ends of multiple second tubular members 920B can be connected to respective egress ports of the medical devices 10 of the present invention and have their distal ends connected to the inferior vena cava of the subject.

In another embodiment, a shunt 930A can be placed internally within the medical device of the present invention. The internal shunt 930A can run parallel to the direction of fluid, e.g., blood, flowing through the channeled vasculature of the medical device of the present invention. An internally placed shunt allows for the control of the amount of fluid flowing through the device.

Figure 9B illustrates another embodiment in which a plurality of the medical devices 10 can be coupled to a patient. For example, 1, 2, 3, 4, or 5 medical devices can be coupled to a patient in serial fashion or in parallel fashion. Numerous configurations
of multiple the medical devices 10 and the tubular members 720C, 720D, 820C, 820D, 830B, 920C and 920D may be used to couple the medical devices 10 to the patient. In one embodiment, a first tubular member is attached at its distal end to the pulmonary artery of a subject. The proximal end of the first tubular member is branched such that each branch of the tubular member connects to an ingress port of one of the medical devices 10. The proximal end of the second tubular member is similarly branched such that each branch of the second tubular member connects to an egress port of one of the medical devices 10. Like the first tubular member, the plurality of branches of the proximal end of the second tubular member merge at one or more junctions into a single lumen or branch associated with the distal end of the second tubular member.

In one embodiment, the tubular members 920C, 920D and the shunts 930B are a monolithic structure. In other embodiments, the tubular members 920C, 920D and the shunts 930B comprise a plurality of separate and distinct tubing sections joined or coupled in any suitable manner, for example, in a variety of ways, including, but not limited to, by bonding, e.g., adhesive bonding, or by sutures.

In another embodiment, each medical device 10 is coupled to the patient separately. For example, in one embodiment, the proximal ends of multiple first tubular members 920C can be connected to the pulmonary artery of the subject, and the distal ends of multiple first tubular members 920D can be connected to respective ingress ports of the medical devices 10. In like fashion, the proximal ends of multiple second tubular members 920D can be connected to respective egress ports of the medical devices 10 of the present invention and have their distal ends connected to the left atrium of the subject.

In another embodiment, a shunt 930B can be placed internally within the medical device of the present invention. The internal shunt 930B can run parallel to the direction of fluid, e.g., blood, flowing through the channeled vasculature of the medical device of the present invention. An internally placed shunt allows for the control of the amount of fluid flowing through the device.
The tubular members discussed herein can be comprised of any material suitable for biological use in vivo. For example, in one embodiment the tubular member comprises silastic tubing. In one embodiment, some or all of the tubular members are attached to the medical device prior to the medical device 10 being coupled to the patient. In one embodiment, some or all of the tubular members are attached to the patient and then attached to the medical device.

A variety of techniques can be used to make the medical devices of the present invention. Figure 10A is a flow chart outlining the steps for forming an exemplary medical device of the present invention. In step 1000A, a first region defining a three dimensional vasculature like structure is formed. The first region can be formed using a variety of techniques. In step 1010A, a second region defining at least one chamber for holding a selected organ specific cell type is formed. In step 1020A, ingress and egress ports are then formed in the second region. In one embodiment, the ingress and egress ports are bored into the second regions. The ingress and egress ports may be bored into the second region using any art known technique suitable for creating a hole in the region without compromising the strength of the region.

In step 1030A, a semi-permeable membrane is selected. The semi-permeable membrane can be made of a variety of materials including, but not limited to, biologically compatible, nondegradable materials such as PDMS, PMMA, PES, or degradable materials such as PLGA, PCL or biorubber. In one embodiment, the semi-permeable membrane is PES. The semi-permeable membrane is selected such that oxygen and nutrients can pass through the membrane from the blood flowing through the vasculature of the device, to the cells exogenously seeded onto the device.

In step 1040A, the semi-permeable membrane is attached to the design surface of the first region, i.e., to the surface of the first region on which the channeled vascular pattern has been transferred or etched. In step 1050A, the first region/semi-permeable membrane structure is then attached to the second region. The two regions are attached such that the semi-permeable membrane is positioned between the design surface of the first region, and the chamber or chambers of the second region. In step 1060A, the structure is cured. In step 1070A, ingress and egress ports are then formed on the first
region/semi-permeable membrane structure such that the ingress and egress ports of the first region/semi-permeable membrane structure are aligned with the ingress and egress ports of the second region.

Figure 10B is a flow chart outlining the steps for forming another exemplary medical device of the present invention. In step 1000B, a first region defining a three dimensional vasculature like structure is formed. The first region can be formed using a variety of techniques. In step 1010B, a second region defining at least one chamber through which oxygen can flow is formed. In step 1020B, ingress and egress ports are then formed in the second region. In one embodiment, the ingress and egress ports are bored into the second regions. The ingress and egress ports may be bored into the second region using any art known technique suitable for creating a hole in the region without compromising the strength of the region.

In step 1030B, an oxygen and carbon dioxide permeable membrane is selected. The oxygen and carbon dioxide permeable membrane can be made of a variety of materials including, but not limited to, biologically compatible, nondegradable materials such as PDMS, PMMA, PES, or degradable materials such as PLGA, PCL or biorubber. In one embodiment, the oxygen and carbon dioxide permeable membrane is PES. In one embodiment, the oxygen and carbon dioxide permeable membrane is silicone. In yet another embodiment, the oxygen and carbon dioxide permeable membrane is made of a medical grade elastomer, e.g., Silastic® MDX4-4210 Medical Grade Elastomer.

The oxygen and carbon dioxide permeable membrane can also comprise polycarbonate coated with a polymer, e.g., polyether sulfone or PDMS, or a medical grade elastomer, e.g., Silastic® MDX4-4210 Medical Grade Elastomer. The oxygen and carbon dioxide permeable membrane is selected such that highly permeable for gas exchange, e.g., oxygen and carbon dioxide, but impermeable to fluids.

In step 1040B, the oxygen and carbon dioxide permeable membrane is attached to the design surface of the first region, i.e., to the surface of the first region on which the channeled vascular pattern has been transferred or etched. In some embodiments, the permeable is coated with a material prior to attachment to the first region. For example, the selected permeable membrane is coated with a material. The coating
material can comprise a polymer or mixture of polymers, e.g., polyether sulfone, or PDMS, or a medical grade elastomer, or any combination thereof. The coated permeable membrane can then be attached to the first region, and secured in place, e.g., covered with a weight, or clamped into place. The coated permeable membrane/first region structure is then cured. Once cured, the coated permeable membrane/first region is then attached to the second region.

In step 1050B, the first region/oxygen and carbon dioxide permeable membrane structure is then attached to the second region. The two regions are attached such that the oxygen and carbon dioxide permeable membrane is positioned between the design surface of the first region, and the chamber or chambers of the second region. In step 1060B, the structure is cured. In step 1070B, ingress and egress ports are then formed on the first region/oxygen and carbon dioxide permeable membrane structure such that the ingress and egress ports of the first region/oxygen and carbon dioxide permeable membrane structure are aligned with the ingress and egress ports of the second region.

Figure 11A is a flow chart outlining the steps for forming the bottom most layer of a medical device of the present invention. In step 1100A, a first region defining a three dimensional channeled vasculature is formed. In step 1110A, a second region defining at least one chamber for holding a selected organ specific cell type is formed. In step 1120A, ingress and egress ports are formed in the first region. In step 1130A, a semi-permeable membrane is selected. In step 1140A, the selected semi-permeable membrane is attached to the design surface of the first region. In step 1150A, ingress ports which allow for access to the chambers of the second region once the second region is attached, are formed in the semi-permeable membrane. In step 1160A, the selected second region defining at least one chamber for holding a selected organ specific cell type is attached to the first region/semi-permeable membrane structure. The two regions are attached such that the semi-permeable membrane is positioned between the design surface of the first region and the chamber or chambers of the second region.

Figure 11B is a flow chart outlining the steps for forming another embodiment of the bottom most layer of a medical device of the present invention. In step 1100B, a first region defining a three dimensional channeled vasculature is formed. In step
1110B, a second region defining at least one chamber through which oxygen can flow is formed. In step 1120B, ingress and egress ports are formed in the first region. In step 1130B, an oxygen and carbon dioxide permeable membrane is selected. In step 1140B, the selected oxygen and carbon dioxide permeable membrane is attached to the design surface of the first region. In step 1150B, ingress ports which allow for access to the chambers of the second region once the second region is attached, are formed in the oxygen and carbon dioxide permeable membrane. In step 1160B, the selected second region defining at least one chamber through which oxygen can flow is attached to the first region/oxygen and carbon dioxide permeable membrane structure. The two regions are attached such that the oxygen and carbon dioxide permeable membrane is positioned between the design surface of the first region and the chamber or chambers of the second region.

Figure 12 is a flow chart outlining the step of forming a region or regions (steps 1000 and 1010 as shown in Figure 10) in more detail. In step 1200, a substrate for use as a mold is selected. As used herein, the term “mold” refers to a substrate or workpiece on which the shape or pattern of the vasculature, or the chamber(s) of the medical device, is formed, i.e., the mold provides the form for the region(s) comprising the vasculature and chambers of the medical device. In one embodiment, the region(s) comprising the vasculature or chamber(s) is removed from the mold after being formed thereon.

Fabrication of the mold begins by selection of an appropriate substrate. Any of a variety of materials can be used as a mold. In one embodiment, the material includes, but is not limited to, materials such as silicon, glass, graphite. In another embodiment, polymers such as polyethylene vinyl acetate, polycarbonate, and polypropylene, and materials such as hydroxyapatite can be used. In yet another embodiment, the mold can be constructed from materials, including but not limited to, metals, ceramics, semiconductors, organics, and composites. Exemplary metals and semiconductors include pharmaceutical grade stainless steel, gold, titanium, nickel, iron, gold, tin, chromium, copper, aluminum, alloys of these or other metals, silicon, and/or silicon dioxide. In one embodiment, the mold is made of a non-biodegradable material, so that the mold may be reused.
In one embodiment, the material selected for the mold is a metal. Metal molds allow for substantially even heat transfer between the mold and the structure formed thereon. Additionally, metal molds retain their structural strength after use, and can therefore be used multiple times.

In step 1210, the desired pattern, e.g., a three dimensional micro-fluidic vasculature or a chamber or chambers for holding selected organ specific cell types, or whole tissue or part of a tissue, is transferred onto the surface of the mold. The desired pattern can be transferred onto the mold using a variety of art known techniques. In one embodiment, the information is translated onto a transparency mask or a glass quartz mask. This step can be accomplished using any one of several masking techniques known to those of skill in the art, depending on the desired image resolution. In this manner the known Micro Electro Mechanical Systems (MEMS) fabrication methodologies and technologies are used to fabricate the mold. In another embodiment, a mold is formed based on the information defining the vasculature like structure of the medical device using an ultrasonic machining process. In another embodiment, a mold is formed based on the information defining the vasculature like structure of the medical device using three-dimensional printing (3DP).

In one embodiment, a mold for use in forming the region defining the micro-fluidic channeled vasculature of the medical device of the present invention is formed using an ultrasonic machining process. Ultrasonic machining provides numerous advantageous over conventional techniques. For example, when using ultrasonic machining techniques to form the pattern of a channeled vasculature into a mold, the channels formed can have sloping side walls that are offset from a vertical plane perpendicular to a top surface of the mold, as opposed to forming a channel having walls that abut at 90 degree angles. Ultrasonic machining also allows for deviation in the width and depth of the channels formed in the channeled vasculature. Thus, the bottom wall and the side walls of a channel in the channeled vasculature can abut at any angle between about 0 and about 45 degrees.
In another embodiment, three dimensional printing can be used to form the pattern of the three dimensional micro-fluidic network into a mold, or directly onto the design surface of the structure(s) of the medical device of the present invention. Three dimensional printing (3DP) is described by Sachs, et al., Manufacturing Review 5, 117-126 (1992) and U.S. Patent No. 5,204,055 to Sachs, et al. 3DP is used to create a solid object by ink-jet printing a binder into selected areas of sequentially deposited regions of powder. Each region is created by spreading a thin region of powder over the surface of a powder bed. The powder bed is supported by a piston, which descends upon powder spreading and printing of each region (or, conversely, the ink jets and spreader are raised after printing of each region and the bed remains stationary). Instructions for each region are derived directly from a computer-aided design (CAD) representation of the component. The area to be printed is obtained by computing the area of intersection between the desired plane and the CAD representation of the object. The individual sliced segments or regions are joined to form the three-dimensional structure. The unbound powder supports temporarily unconnected portions of the component as the structure is built but is removed after completion of printing.

In step 1220, a material is cast onto the mold. The material can be any material suitable for biological use. In one embodiment, the material is a polymer. Suitable polymers include, but are not limited to, PDMS, PLGA, PGS, polystyrene and PMMA. In one embodiment, PDMS is selected for use in forming a structure for use in the medical device of the present invention. In step 1230, the material is cured. Any technique known in the art for curing the selected material can be used. For example, the material can be cast onto the mold, and then the mold with the material on it can be placed on a hot plate or in an oven. For this method of curing, the mold selected should allow for sufficient heat transfer such that the material will cure. In step 1240, the material is removed from the mold.

In one embodiment, the pattern of the microfluidic channeled vasculature is transferred onto the surface of the mold.

Figure 13 illustrates steps taken to form a medical device of the present invention. In step 1300, at least two structures are stacked one on top of the other. The
structures are stacked in such a way that the ingress and egress ports of each structure are aligned. The structures will be stacked in a certain order depending on the configuration of the three dimensional vasculature like structure and the chamber(s) for holding selected organ specific cell types within each structure. For example, if the structure comprises a first region defining a vasculature like structure and a second region comprising at least one chamber seeded with organ specific cells, and a semi-permeable membrane positioned in between the first and second regions, and the structure stacked on top of the first structure is the same, then they can be stacked such that the regions alternate in order, i.e., a first region comprising a vasculature like structure, a semi-permeable membrane, a second region comprising a chamber or chambers for holding organ specific cells, another first region comprising a vasculature like structure, another semi-permeable membrane, another second region comprising a chamber or chambers for holding organ specific cells, etc.

In another embodiment, the structures will be stacked in a certain order depending on the configuration of the three dimensional vasculature like structure and the chamber(s) through which oxygen can flow within each structure. For example, if the structure comprises a first region defining a vasculature like structure and a second region comprising at least one chamber through which oxygen can flow, and an oxygen and carbon dioxide permeable membrane positioned in between the first and second regions, and the structure stacked on top of the first structure is the same, then they can be stacked such that the regions alternate in order, i.e., a first region comprising a vasculature like structure, an oxygen and carbon dioxide permeable membrane, a second region comprising a chamber or chambers through which oxygen can flow, another first region comprising a vasculature like structure, another oxygen and carbon dioxide permeable membrane, another second region comprising a chamber or chambers through which oxygen can flow, etc.

In step 1310, each structure is attached to the structure(s) stacked on top and/or below it. The structures can be attached through any art known technique, including, but not limited to, chemical bonding, thermal bonding, adhesive bonding, or any combination thereof. In one embodiment, the structures are attached to each other through the use of an adhesive agent, for example, PDMS. The structures can also be
attached to each other through mechanical means, e.g., screws, or clamps. In step 1320, the outer edges of the stacked structures are sealed. In one embodiment, PDMS is used as a sealant. In another embodiment, an elastomer is used as a sealant, for example, Silastic® MDX4-4210 Medical Grade Elastomer.

In one embodiment, after the structures are attached to each other, e.g., adhesively bonded together, a stiffening outer member is placed on the top side of the stacked structures, and on the bottom side of the stacked structures, and the two stiffening outer members are attached through mechanical means, e.g., screws or clamps. The stiffening outer member can be comprised of any material suitable for biological use, for example, acrylic.

In one embodiment, the ingress and egress ports of the medical device 10 of the present invention do not extend to the chamber through which oxygen flows of the structure located at the bottom of the stack. In one embodiment, the top structure of the medical device 10 of the present invention comprises a first region defining a three dimensional micro-fluidic channeled vasculature, a second region defining at least one chamber capable of attaining oxygen flow there through, and an oxygen and carbon dioxide permeable membrane positioned in between the first and second regions. The top structure may further comprise a blank region of polymer material, i.e., a region that does not have a vasculature or chamber defined therein. The blank region can be plasma bonded to the first region containing the three dimensional vasculature like structure. The plasma bonding of a blank region to the first region of the top structure aids in attaching the tubular members to the ingress and egress ports of the medical device of the present invention.

In one embodiment, the ingress and egress ports of the medical device 10 of the present invention do not extend to the chamber containing the organ specific cells of the structure located at the bottom of the stack. In one embodiment, the top structure of the medical device 10 of the present invention comprises a first region defining a three dimensional micro-fluidic channeled vasculature, a second region defining at least one chamber capable of holding organ specific cells, and a semi-permeable membrane positioned in between the first and second regions. The top structure may further
comprise a blank region of polymer material, i.e., a region that does not have a
vasculature or chamber defined therein. The blank region can be plasma bonded to the
first region containing the three dimensional vasculature like structure. The plasma
bonding of a blank region to the first region of the top structure aids in attaching the
tubular members to the ingress and egress ports of the medical device of the present
invention.

In one embodiment the organ specific cells seeded into the medical device 10 are
parenchymal cells, i.e., cells that include the functional elements of an organ, as
distinguished from the framework or stroma. In one embodiment, the parenchymal cells
for use in the present invention include, but are not limited to those cells derived from an
organ selected from the group consisting of heart, liver, pancreas, intestine, brain,
kidney, reproductive tissue, lung, muscle and bone marrow. In one embodiment, the
organ is a liver. In another embodiment, the organ is a kidney.

In one embodiment, the cells exogenously seeded into the device comprise
autologous cells. In another embodiment, the cells exogenously seeded into the device
comprise allogeneic cells. Cells for use in the present invention may be obtained by
methods known to those of skill in the art including, but not limited to, by biopsy or
harvest from a living donor, cell culture, or autopsy. Cells to be implanted can be
dissociated using standard techniques such as digestion with a collagenase, trypsin or
other protease solution and are then seeded into chamber(s) immediately or after being
maintained in culture.

Cells may be normal or modified, i.e., genetically engineered to provide
additional function, e.g., to increase proliferation. In one embodiment, the cells seeded
into the medical device comprise modified autologous cells. In another embodiment, the
cells exogenously seeded into the device comprise modified allogeneic cells. Cells that
are genetically engineered to avoid the need for immunosuppression can also be used.
Methods and drugs for immunosuppression are known to those skilled in the art of
transplantation.
Undifferentiated or partially differentiated precursor cells, such as embryonic germ cells (Gearhart, et al., U.S. Patent No. 6,245,566), embryonic stem cells (Thomson, U.S. Patent Nos. 5,843,780 and 6,200,802), mesenchymal stem cells (Caplan, et al. U.S. Patent No. 5,486,359), neural stem cells (Anderson, et al., U.S. Patent No. 5,849,553), hematopoietic stem cells (Tsukamoto, U.S. Patent No. 5,061,620), multipotent adult stem cells (Furcht, et al., WO 01/11011) may be used in this invention. Cells can be kept in an undifferentiated state by co-culture with a fibroblast feeder region (Thomson, U.S. Patent Nos. 5,843,780 and 6,200,802), or by feeder-free culture with fibroblast conditioned media (Xu, et al. Nat. Biotechnol., 19, 971 (2001)). Undifferentiated or partially differentiated precursor cells can be induced down a particular developmental pathway by culture in medium containing growth factors or other cell-type specific induction factors or agents known in the art.

A stem cell for use in the present invention can include, but is not limited to, embryonic stem cells, adult stem cells, neural stem cells, muscle stem cells, hematopoietic stem cells, mesenchymal stem cells, peripheral blood stem cells and cardiac stem cells. In one embodiment, the stem cell is a human stem cell. A “stem cell” is a pluripotent, multipotent or totipotent cell that can undergo self-renewing cell division to give rise to phenotypically and genotypically identical daughter cells for an indefinite time and can ultimately differentiate into at least one final cell type.

An exemplary stem cell is the embryonal stem cell (ES), as it has unlimited self-renewal and multipotent and/or pluripotent differentiation potential, thus possessing the capability of developing into any organ, tissue type or cell type. These cells can be derived from the inner cell mass of the blastocystoe, or can be derived from the primordial germ cells from a post-implantation embryo (embryonal germ cells or EG cells). ES and EG cells have been derived from mice, and more recently also from non-human primates and humans. Evans et al. (1981) Nature 292:154-156; Matsui et al. (1991) Nature 353:750-2; Thomson et al. (1995) Proc. Natl. Acad. Sci. USA. 92:7844-8; Thomson et al. (1998) Science 282:1145-1147; and Shamblott et al. (1998) Proc. Natl. Acad. Sci. USA 95:13726-31.

In one embodiment, hepatocytes may be seeded into one or more chambers or one or more channels or both of the medical device of the present invention. The hepatocytes seeded into the medical device of the present invention can be highly
proliferative hepatocytes, known as small hepatocytes (SHCs), which have the ability to proliferate in vitro for long periods of time (Mitaka, et al., Biochem Biophys Res Commun 214, 310 (1995); Taneto, et al, Am J Pathol 148, 383 (1996)). Small hepatocytes express hepatocyte specific functions such as albumin production (Mitaka, et al., Hepatology 29, 111 (1999)). In one aspect, the present invention provides methods for exogenously seeding cells into a medical device of the present invention.

Molecules such as growth factors or hormones can be attached to the surface of the structures and/or semi-permeable membrane to effect growth, division, differentiation or maturation of cells cultured thereon.

Figure 14 is a flow chart illustrating the steps taken for exogenously seeding cells into a medical device 10 having a vasculature like structure 24 of the present invention. In step 1410, the medical device 10 is coupled to a patient. In step 1420, blood flow through the micro-fluidic channeled vasculature 24 is established. In step 1430, pressure is applied to a port of the medical device using a source of pressure in order to seed the selected cells into the medical device 10. The pressure may be applied at any time during the seeding including, but not limited to, while the selected cells are being injected into the medical device, or after the selected cells have been injected into the medical device. In one embodiment, the pressure is applied continuously to the medical device while the seeding is occurring. In another embodiment, the pressure is applied at different times during the seeding process.

In one embodiment, the pressure from the source of pressure is negative pressure used to pull or vacuum cells into the medical device. In another embodiment, the pressure from the source of pressure is positive pressure used to push cells into the medical device. The source of negative pressure may include, but is not limited to, a syringe and/or a vacuum pump. The source of positive pressure may include, but is not limited to, a syringe and/or a pump.

In one embodiment, the selected organ specific cells are injected into the medical device 10 using a cell injection device. A "cell injection device" as used herein refers to an instrument capable of injecting the desired cells into a medical device 10 of the
present invention. Examples of cell injection devices for use with the medical devices of
the present invention include, but are not limited to, syringes, trocars and/or pumps.
One of skill in the art will recognize other devices suitable for such use. In one
embodiment, the selected organ specific cells may be autologous. In another
embodiment, the selected organ specific cells may be allogeneic.

The present invention also provides methods for coupling a medical device of the
present invention to a patient. Figure 15 is a flowchart outlining an exemplary method
for coupling a patient to a medical device 10 of the present invention. In step 1500, a
first tubular member is selected. The first tubular member can be any material suitable
for in vivo use, which is capable of allowing fluid to flow through it. In one
embodiment, the tubular member comprises a plastic tube, e.g., silastic tubing. In
another embodiment, the first tubular member comprises a graft. Material suitable for
use as a graft can include, but is not limited to, expanded polytetrafluoroethylene.

In step 1510, the distal end of the first tubular member is attached to a fluid
carrying organ of the patient. In one embodiment, the fluid carrying organ is a vein,
e.g., the portal vein. In another embodiment, the fluid carrying organ is an artery, e.g.,
the pulmonary artery. The first tubular member can be attached to the selected fluid
carrying organ by any means suitable for in vivo use, e.g., sutures, or adhesive. In one
embodiment, the first tubular member is sutured into place.

In step 1520, the proximal end of the first tubular member is attached to the
ingress port of the medical device. The first tubular member can be attached to the
ingress port of the medical device at any time, e.g., before being attached at the distal
distal end to a fluid carrying organ, after being attached at the distal end to a fluid carrying
organ. In one embodiment, the first tubular member is attached directly to the ingress
port of the medical device. The first tubular member can be attached to the ingress port
using conventional art known methods, e.g., adhesive bonding. In one embodiment, the
first tubular member has an inside diameter that substantially matches the inside
diameter of the ingress port of the medical device 10.
In step 1530, a second tubular member is selected. The second tubular member can comprise the same material of which the first tubular member was selected from or a different material. In one embodiment, the second tubular member comprises a plastic tube, e.g., silastic tubing. In another embodiment, the second tubular member comprises a graft. In step 1540, the distal end of the second tubular member is attached to a fluid carrying organ. In one embodiment, the fluid carrying organ is a vein, e.g., the inferior vena cava. In one embodiment, the first and second tubular members are connected to the same fluid carrying organ. In one embodiment, the first and second tubular members are connected to different fluid carrying organs. In another embodiment, the fluid carrying organ is the left atrium. The second tubular member can be attached to the selected fluid carrying organ by any means suitable for in vivo use, e.g., sutures, or adhesive. In one embodiment, the second tubular member is sutured into place.

In step 1550, the proximal end of the second tubular member is attached to the egress port of the medical device 10. The second tubular member can be attached to the egress port of the medical device at any time, e.g., before being attached at the distal end to a fluid carrying organ, after being attached at the distal end to a fluid carrying organ. In one embodiment, the second tubular member is attached directly to the egress port of the medical device 10. In one embodiment, the second tubular member is attached to the egress port of the medical device 10 using conventional art know methods, e.g., adhesive bonding. In one embodiment, the second tubular member has an inside diameter that is substantially the same as the inside diameter of the egress port of the medical device 10.

In one embodiment, the first tubular member is attached to the ingress port of the device, and the second the tubular member is attached at the egress port of the device prior to the device being coupled to the patient. The first and second tubular members can be of any length prior to attachment, and can then be sized to meet the needs of the patient to whom the medical device of the present invention is being coupled to. The tubular member selected for use with the medical device of the present invention can further comprise a stiffening member that abuts the tubular member. The stiffening member can increase the stiffness of the tubular member, preventing the tubular member from kinking or bending once fluid flow through has been established.
In another embodiment, the medical device of the present invention is coupled to a patient using a catheter. An exemplary catheter for use in the present invention is shown in Figure 16A. The catheter 1600 comprises a flared proximal end 1620, a distal end 1630, an inner wall 1640, and an outer wall 1650. The tubular member 1610 of the present invention may be comprised of any material suitable for biological use which allows for the flow of fluid from a subject into the tubular member 1610. For example, the tubular member can be comprised of polymers, or plastics, or combinations thereof. In one embodiment, the tubular member can be comprised of silicone.

The proximal end 1620 of the tubular member of an exemplary catheter for use with the medical device of the present invention is flared such that the diameter of the proximal end 1620 of the tubular member is larger than the diameter of the distal end 1630 of the tubular member. In one embodiment, the tubular member 1610 is flared at the proximal end 1620. For example, the desired tubular member 1610 is selected, and a flaring tool is then used to flare the proximal end 1620 of the tubular member 1610 to the desired diameter.

In another embodiment, shown in Figure 17, a separate flared base member 1700 is attached to the proximal end of the tubular member 1710 creating a flared proximal end on the tubular member. The flared base member 1700 may be comprised of any material suitable for biological use, including but not limited to, polymers. In one embodiment, the flared base member 1700 is a commercially available flange suitable for use in biological systems. The tubular member 1710 of the catheter is attached to the flared base member 1700 such that the proximal end of the tubular member is substantially flush against the proximal opening 1720 of the flange.

The tubular member 1710 may be attached to the flared base member 1700 by any method known to those of skill in the art, including, but not limited to, chemical bonding, thermal bonding, adhesive bonding, or any combination thereof. For example, in one embodiment, polydimethylsiloxane is used to attach the flared base member 1700 to the tubular member 1710. The flared base member 1700 can be attached to the tubular member 1710 at any time. For example, in one embodiment, the flared base member 1700 can be attached to the tubular member 1710 prior to the flared base
member 1700 being attached to a selected fluid carrying organ of a subject. In another embodiment, the tubular member 1710 can be attached to the flared base member 1700 after the flared base member 1700 has been attached to a selected fluid carrying organ of the subject.

In one embodiment, the flared proximal end of the tubular member, formed either from flaring the proximal end of the tubular member, or by attaching a separate flared base member, provides a surface through which the flared proximal end can be attached to a subject. For example, as can be seen in Figure 17, in one embodiment, the flared proximal end 1700 of the tubular member 1710 contains a suture region 1730. As used herein, the term “suture region” refers to a portion of the flared proximal end of the tubular member of a catheter for use with the medical device the present invention that is capable of being sutured to another object, e.g., a fluid carrying organ, bodily tissue, and/or internal organ.

In one embodiment, the flared proximal end 1700 of the tubular member 1710 is inserted into a selected fluid carrying organ of the subject. Sutures are then placed through the suture region of the flared proximal end 1700 of the tubular member 1710 and the wall of the fluid carrying organ, thereby attaching the catheter to the selected fluid carrying organ. Materials suitable for use in attaching the flared proximal end of a catheter for use with the medical device 10 of the present invention to a subject include, for example, nylon stitches.

The ability to attach an exemplary catheter for use with the medical device of the present invention to a wall of a fluid carrying organ by attachment through the suture region of the flared proximal end of the tubular member aids in maintaining the desired position of the catheter. Without wishing to be bound by any particular theory, it is also thought that the flow of fluid from the subject through the fluid carrying organ to which the catheter is attached further aids in maintaining the catheter in a desired position. For example, as shown in Figure 18, as the fluid from the subject flows through the selected fluid carrying organ 1810, the pressure exerted on the flared proximal end of the tubular member 1820 of the catheter will press the flared ends up against the inner wall of the selected fluid carrying organ (e.g., a vein, an artery), thus maintaining the position of the
catheter. It is also thought that having the flared proximal ends of the tubular member flush against the inner wall of the selected fluid carrying organ reduces pressure build up and/or fluid resistance, as well as clotting, at the point of contact between the catheter and the fluid carrying organ.

In one embodiment, the flared proximal end of the catheter is attached to a selected fluid carrying organ of a subject. In one embodiment, the selected fluid carrying organ is a vein. The selected vein may be any vein which is capable of providing blood flow through the tubular member of the catheter of the present invention. The selected vein may include, but is not limited to, the portal vein of a subject. The selected vein will depend on the intended use of the catheter. For example, if the catheter is selected for use in providing blood flow from a subject to a medical device of the present invention designed to augment or replace the function of an organ, the selected vein will correspond to the vein that normally provides blood flow to the organ that the medical device is intended to augment or replace.

In another embodiment, the selected fluid carrying organ is an artery. The selected fluid carrying organ may be any fluid carrying organ which is capable of providing blood flow through the tubular member of the catheter of the present invention. The selected fluid carrying organ may include, but is not limited to, the pulmonary artery of a subject. The selected fluid carrying organ will depend on the intended use of the catheter. For example, if the catheter is selected for use in providing blood flow from a subject to a medical device of the present invention designed to augment or replace the function of an organ, the selected fluid carrying organ will correspond to the fluid carrying organ that normally provides blood flow to the organ that the medical device is intended to augment or replace.

In another embodiment, the tubular member 1610 of an exemplary catheter for use with the present invention is designed to aid in the flow of fluid from a selected fluid carrying organ of a subject into a medical device. The length and diameter of the tubular member 1610 may vary depending on the desired characteristics and intended use of the catheter. Figure 16C is a cross sectional view of an embodiment of the tubular member of the catheter of the present invention. In some embodiments, the tubular member 1610
can have an inner diameter (d) of about 1 mm to about 10 mm. In some embodiments, the tubular member 1610 can have an outer diameter (D) of about 2 mm to about 15 mm. These dimensions are example embodiments only, and the size of the inner and outer diameter of the tubular member can vary greatly from the dimensions given, depending on the desired characteristics and function of the catheter.

Additionally, although shown in Figure 16A as having a generally round cross sectional shape, the tubular member 1610 of an exemplary catheter for use with the medical device of the present invention can include other shapes as well. For example, the tubular member 1610 may have a cross sectional shape of an oval, rectangle, square, or triangle.

As can be seen in Figure 16A, in one aspect, a catheter 1600 for use with the medical device of the present invention further comprises a stiffening member 1670 which is associated with a first portion (A) of the tubular member 1610. As used herein, the term “stiffening member” refers to a material associated with the external wall of the tubular member of a catheter for use with the medical device of the present invention that imparts a lower coefficient of flexibility on the portion of the tubular member to which it is associated. The term “coefficient of flexibility” as used herein, refers to the flexibility of a given substance, wherein a large coefficient of flexibility indicates a high degree of flexibility, and a small coefficient of flexibility indicates a low degree of flexibility. Materials suitable for use as a stiffening member 1670 of the present invention include, but are not limited to, metals, metal alloys, polymers, or combinations or mixtures thereof. In one embodiment, the stiffening member 1670 is comprised of a polymeric material.

In one embodiment, the stiffening member 1670 is associated with a first portion (A) of the tubular member along the length of the tubular member between the proximal end 1620 and the distal end 1630. Due to the lower coefficient of flexibility of the stiffening member 1670 as compared to the tubular member 1610, the portion of the tubular member 1610 associated with the stiffening member 1670 will have a lower coefficient of flexibility, i.e., will be less flexible, than the portion of the tubular member 1610 not associated with the stiffening member 1670 (B). Thus the application of a
stiffening member 1670 to only a portion of the tubular member 1610 creates a varying coefficient of flexibility along the length of the catheter 1600.

The stiffening member 1670 can be associated with a first portion (A) of the tubular member 1610 along the length of the tubular member 1610. The portion of the stiffening member 1670 associated with the tubular member can vary depending on the desired flexibility of the catheter of the present invention. For example, in one embodiment, the stiffening member is associated with a majority of the length of the tubular member 1610. In another embodiment, the stiffening member 1670 is associated with only a small portion of the tubular member 1610.

The stiffening member 1670 of an exemplary catheter for use with the medical device of the present invention is configured to have a desired level of flexibility. The dimensions, structure and material of the stiffening member 1670 will be dictated by the desired characteristics and use of the catheter 1600 with a medical device of the present invention. For example, in one embodiment, the stiffening member 1670 can be a tubular structure which associates with a first portion (A) of the outer wall 1650 of the tubular member 1610. In one embodiment, the inner diameter of the stiffening member 1670 is substantially equivalent to the outer diameter of the tubular member 1610. Thus the entire portion of the tubular member 1610 associated with the stiffening member 1670 will have a lower coefficient of flexibility than the portion of the tubular member 1610 that is not associated with the stiffening member (B).

In another embodiment, the stiffening member 1670 can be a tubular structure, with one or a plurality of apertures, e.g., slits, grooves, cuts, which associates with a first portion (A) of the outer wall 1650 of the tubular member 1610. In this configuration, the stiffening member imparts a lower coefficient of flexibility on the portion of the tubular member 1610 to which it is associated, while also allowing for a degree of flexibility for the area of the tubular member 1610 exposed through the one or more apertures. The number and position of the plurality of apertures can vary depending on the desired coefficient of flexibility of an exemplary catheter 1600 for use with the medical device of the present invention. In yet another embodiment, the stiffening
member 1670 can comprise a plurality of structures, e.g., strips or pieces of a selected material, which each associate with a portion of the tubular member 1610.

The stiffening member 1670 can be associated with the tubular member 1610 of a catheter for use with the medical device of the present invention through a variety of means, for example, by placing the tubular member within the stiffening member, or by attaching the stiffening member to the exterior wall of the tubular member. In one embodiment, the stiffening member 1670 is attached to the tubular member 1610 of a catheter of the present invention. The stiffening member 1670 may be attached to the tubular member 1610 by any suitable art recognized method. For example, chemical bonding, thermal bonding, adhesive bonding, or combinations thereof may be used to attach the stiffening member 1670 to the tubular member 1610 of the catheter 1600.

In another embodiment, the stiffening member 1670 and the tubular member 1610 comprise a monolithic structure. Suitable techniques for forming a monolithic structure include, but are not limited to, extrusion, co-extrusion, casting and/or molding.

As can be seen in Figure 16A, an exemplary catheter for use with the medical device of the present invention can further comprise a shunt 1680 extending outwardly from the outer wall 1650 at an angle offset from a longitudinal axis of the tubular member 1610, such that the distal end of the shunt is substantially flush against the inner wall 1640 of the tubular member 1610 of the catheter 1600. The shunt 1680 can be comprised of any material suitable for biological use. For example, the shunt 1680 can be comprised of silicone.

The shunt 1680 can be used to introduce an additional agent into the fluid passing through the tubular member 1610. For example, the agent introduced through the shunt may include, but is not limited to, a pharmacological agent, a diagnostic agent, or any other agent so desired. In one embodiment, the pharmacological agent may comprise anticoagulants, e.g., heparin. In another embodiment, a diagnostic agent is administered through the shunt, for example, iodinated compounds used in radiography and CT; and paramagnetic metallic ions, such as ions of gadolinium, iron, and manganese, linked to a variety of molecules and microparticles, such as
superparamagnetic iron oxide, used in MRI. The shunt 1680 allows for introduction of an additional agent into the catheter 1600 in a manner that substantially reduces the amount of agent found in the area surrounding the catheter.

A catheter 1600 for use with the medical device of the present invention can further comprise a luer lock 1690. In one embodiment, the luer lock 1690 is located towards the distal end 1630 of the catheter. The luer lock 1690 can be used to control the flow of blood through the tubular member 1610 from the selected fluid carrying organ of the subject. In another embodiment, the luer lock 1690 can be used to attach a catheter of the present invention to another structure, for example, a medical device.

The rate of fluid, e.g., blood, flowing through the tubular member of a catheter coupled to a medical device of the present invention varies due to a number of factors, for example, which fluid carrying organ the catheter is attached to, and the inner diameter of the tubular member. In one embodiment, the rate of fluid flowing through the tubular member of a catheter coupled to a medical device of the present invention is in the range from about 0.5 cc/min to about 2.0 cc/min. In another embodiment, the rate of fluid flowing through the tubular member of a catheter coupled to a medical device of the present invention is in the range from about 0.8 cc/min to about 1.5 cc/min. In one embodiment, the rate of fluid flowing through the tubular member of a catheter coupled to a medical device of the present invention is in the range from about 0.5 ml/min to about 2.5 ml/min. In another embodiment, the rate of fluid flowing through the tubular member of a catheter coupled to a medical device of the present invention is in the range from about 0.6 ml/min to about 2.0 ml/min. It is to be understood that all values and ranges between these values and ranges are meant to be encompassed by the present invention.

As can be seen in Figure 16B, in various embodiments, the distal end 1630 of the tubular member of an exemplary catheter is connected to a medical device 10 of the present invention. In one embodiment, as shown in Figure 19, the internal diameter 1920 of the tubular member 1910 of the catheter is equivalent to the diameter of the ingress port 1930 of the medical device to which the distal end of the tubular member of the catheter is connected to. Once connected, fluid, e.g., blood, flowing through the
tubular member 1910 of the catheter from the subject's fluid carrying organ, e.g., a vein or an artery, will flow into the medical device through the ingress port 1930. Without wishing to be bound by any particular theory, it is thought that the equivalence in diameter of the ingress port 1930 and the internal diameter of the tubular member 1920 of the catheter allows for fluid to flow through the tubular member into the medical device, without adverse effects, i.e., clotting or pressure build up in the fluid carrying organ, catheter, or attached medical device.

EXEMPLIFICATION

Example 1: In-vitro Evaluation of Lung Assist Device

In-vitro testing of a single layer medical device as described herein was performed to evaluate the device for use as a lung assist device. Microfabrication technology was used to manufacture a medical device comprising a first region containing a micro-fluidic channeled vasculature, a second region containing a chamber through which oxygen flows, and an oxygen and carbon dioxide permeable membrane comprised of silicone positioned between the first and second regions. The first and second regions were created in poly-dimethyl siloxane (PDMS).

The micro-fluidic channeled vasculature had an array of channels 200μm by 200 μm in cross section. The gas transfer surface area of a single layer of the device was 25cm² and the oxygen flow rate was 100 ml/min. Anti-coagulated porcine blood was pumped through the micro-fluidic channeled vasculature while the oxygen flowed through the adjacent chamber. The blood flow was varied to evaluate the potential gas exchange capacity of the device. The oxygenation and removal of carbon dioxide from the blood was assessed using blood gas analysis.

The transfer of oxygen into the blood and the transfer of carbon dioxide out of the blood increased with increasing blood flow through the device, as can be seen in Figure 20. With this level of functionality of a single layer of the device, the lung assist device would need 515 layers to support 20% of the baseline lung function of an adult.
The partial pressure of oxygen in the blood post-device decreased towards the baseline with increasing blood flow through the device. Similarly the partial pressure of carbon dioxide increased towards the baseline with increasing blood flow. This is due to the channels having a larger diameter than a normal capillary. At higher flow rates there is a portion of the blood flow which is too distant from the chamber through which oxygen is flowing through to become oxygenated. However, there was still adequate oxygen absorption by the hemoglobin and removal of carbon dioxide to achieve increasing mass transfer with increasing blood flow (see Figure 21). Thus the medical device tested oxygenated and removed carbon dioxide from venous blood.

EQUIVALENTS

Numerous modifications and alternative embodiments of the present invention will be apparent to those skilled in the art in view of the foregoing description. Accordingly, this description is to be construed as illustrative only and is for the purpose of teaching those skilled in the art the best mode for carrying out the present invention. Details of the structure may vary substantially without departing from the spirit of the invention, and exclusive use of all modifications that come within the scope of the appended claims is reserved. It is intended that the present invention be limited only to the extent required by the appended claims and the applicable rules of law.

All literature and similar material cited in this application, including, patents, patent applications, articles, books, treatises, dissertations and web pages, regardless of the format of such literature and similar materials, are expressly incorporated by reference in their entirety. In the event that one or more of the incorporated literature and similar materials differs from or contradicts this application, including defined terms, term usage, described techniques, or the like, this application controls.

The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described in any way.

While the present inventions have been described in conjunction with various embodiments and examples, it is not intended that the present teachings be limited to such embodiments or examples. On the contrary, the present inventions encompass
various alternatives, modifications, and equivalents, as will be appreciated by those of skill in the art.

The claims should not be read as limited to the described order or elements unless stated to that effect. It should be understood that various changes in form and detail may be made without departing from the scope of the appended claims. Therefore, all embodiments that come within the scope and spirit of the following claims and equivalents thereto are claimed.
What is claimed:

1. A medical device capable of performing a physiological function of an organ once surgically coupled to a patient and thereafter exogenously seeded with at least organ specific cells, said medical device comprising:
   a first region defining a three dimensional micro-fluidic vasculature through which blood flows once coupled to a patient, said micro-fluidic vasculature comprising one or more channels having a radial bottom wall extending between a first sidewall and a second sidewall;
   a second region defining at least one chamber for holding a selected organ specific cell type;
   an ingress port to receive blood flow from the patient;
   an egress port to return blood flow to the patient;
   access ports through which at least one organ specific cell type is seeded;
   and a semi-permeable membrane positioned between the first and second regions, such that first region is separated from the second region by the semi-permeable membrane.

2. The device of claim 1, wherein the first and second regions comprise a material including at least one of polydimethyl siloxane, polylactic coglycolic acid, polyglycerol, polyurethane, polymethylmethacrylate, polystyrene and polycarbonate.

3. The device of claim 1, wherein the regions comprise polydimethyl siloxane.

4. The device of claim 1, wherein the cells are autologous cells.

5. The device of claim 1, wherein the cells are modified autologous cells.

6. The device of claim 1, wherein the cells are allogeneic cells.

7. The device of claim 1, wherein the cells are modified allogeneic cells.
8. The device of claim 1, wherein the cells are parenchymal cells.

9. The device of claim 8, wherein the parenchymal cells are derived from an organ selected from the group consisting of heart, liver, pancreas, intestine, brain, kidney, reproductive tissue, lung, muscle and bone marrow.

10. The device of claim 9, wherein the organ is a liver.

11. The device of claim 1, wherein the semi-permeable membrane is non-degradable.

12. The device of claim 1, wherein the semi-permeable membrane comprises polyether sulfone.

13. The device of claim 1, wherein the method by which the medical device is surgically coupled to the patient includes at least one of implantation into the patient’s body or attaching the device extracorporeally.

14. The device of claim 1, wherein the device uses the patient’s body as a bioreactor, wherein the patient’s blood flow nourishes the organ specific cells seeded onto the scaffold.

15. The device of claim 1, wherein the ingress port of the medical device receives blood from the patient’s venous blood flow.

16. The device of claim 1, wherein the ingress port of the medical device receives blood flow from the patient’s portal vein.

17. The device of claim 1, wherein the egress port of the medical device returns blood flow to the patient’s inferior vena cava.

18. The device of claim 1, further comprising a first tubular member having a distal end, a proximal end, an inner wall, and an outer wall attached to the ingress port of the
medical device, and a second tubular member having a distal end, a proximal end, an inner wall, and an outer wall, attached to the egress port of the medical device.

19. A medical device capable of performing a physiological function of an organ once surgically coupled to a patient and thereafter exogenously seeded with at least organ specific cells, said medical device comprising:

a first region defining a first three dimensional micro-fluidic vasculature through which blood flows once coupled to a patient;

a second region defining at least one chamber for holding a selected organ specific cell type;

a third region defining a second three dimensional micro-fluidic vasculature through which blood flows once coupled to a patient;

a semi-permeable membrane positioned between the second and third region;

an ingress port; and

an egress port.

20. A method for forming a structure for use in the medical device of any of the preceding claims, said method comprising:

forming a first region defining a three dimensional vasculature comprising one or more channels having a radial bottom wall extending between a first side wall and a second side wall;

forming a second region defining at least one chamber for holding at least one selected organ specific cell type;

forming an ingress port and an egress port into the second region;

selecting a semi-permeable membrane;

attaching the semi-permeable membrane to the design surface of the first region;

attaching the second region to the first region/semi-permeable membrane structure, such that the semi-permeable membrane is positioned between the chamber of the second region and the design surface of the first region,

forming an ingress port and an egress port into the first region/semi-permeable membrane structure such that and the ingress and egress ports of both regions are aligned.
Figure 1c.
Figure 78
Figure 8A
Figure 9A
Figure 9B
First region defining a three-dimensional channeled vasculature formed

Second region defining at least one chamber for holding a selected organ specific cell type formed

Ingress and egress ports formed on the second region

Semi-permeable membrane selected

Semi-permeable membrane attached to design surface of the first region

First region/semi-permeable membrane structure attached to second region

Structure is cured

Ingress and Egress ports are formed on the first region/semi-permeable membrane structure

Figure 10A
First region defining a three dimensional channeled vasculature formed

Second region defining at least one chamber through which oxygen flows formed

Ingress and egress ports formed on the second region

Oxygen and carbon dioxide permeable membrane selected

Oxygen and carbon dioxide permeable membrane attached to design surface of the first region

First region/oxygen and carbon dioxide permeable membrane structure attached to second region

Structure is cured

Ingress and Egress ports are formed on the first region/oxygen and carbon dioxide permeable membrane structure

Figure 10B
First region defining a three dimensional channeled vasculature formed

Second region defining at least one chamber for holding a selected organ specific cell type formed

Ingress and egress ports formed on the first region

Semi-permeable membrane selected

Semi-permeable membrane attached to design surface of the first region

Ingress ports to chamber(s) of second region formed on the semi-permeable membrane

First region/semi-permeable membrane structure attached to second region

Figure 11A
1100 - First region defining a three dimensional channeled vasculature formed

1110 - Second region defining at least one chamber through which oxygen flows formed

1120 - Ingress and egress ports formed on the first region

1130 - Oxygen and carbon dioxide permeable membrane selected

1140 - Oxygen and carbon dioxide permeable membrane attached to design surface of the first region

1150 - Ingress ports to chamber(s) of second region formed on the oxygen and carbon dioxide permeable membrane

1160 - First region/oxygen and carbon dioxide permeable membrane structure attached to second region

Figure 18
1200 — Substrate for use as mold selected

1210 — Desired pattern transferred onto surface of mold

1220 — Material for use as structure cast onto mold

1230 — Material for use as structure cured

1240 — Material for use as structure removed from the mold

Figure 12
1300 — At least two structures placed one on top of the other

1310 — Each structure attached to the structure above and/or below it

1320 — Edges of the stacked structure sealed

Figure 13
1410 - Couple medical device to patient

1420 - Establish blood flow through medical device

1430 - Apply pressure to a port of the medical device to seed cells onto medical device

Figure 14
Select first tubular member

Distal end of first tubular member attached to fluid carrying organ

Proximal end of first tubular member attached to ingress port of the medical device

Second tubular member selected

Distal end of second tubular member attached to fluid carrying organ

Proximal end of second tubular member attached to egress port of medical device

Figure 15
Fig. 16A
Figure 30

Oxygen Transfer (ml/min)

Carbon Dioxide Transfer (ml/min)
Figure 21