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(54) Title: DEVICES AND METHODS FOR ENDOTHELIALIZATION OF MAGNETIC VASCULAR GRAFTS

FIG. 1

	Graft A		Graft B		Graft C	
	lumen (µm)	cross section (µm)	lumen (µm)	cross section (µm)	lumen (µm)	cross section (µm)
	40.2	87.5	44.1	66.4	44.9	59.6
	73	30.6	20.1	61.6	46.1	48.8
	107	40	102	29.3	53.1	29.3
	56.4	41.6	28.3	35.2	58.2	48.9
	39.4	37.3	49.6	26.4	70.5	49.4
	46.9	49.6	49	31.5	77.2	51.5
	19.9	45.4	43.3	72.5	77.7	42.2
Average	54.7	47.4	48.1	46.1	61.1	47.1
Max	107	87.5	102	72.5	77.7	59.6
Min	19.9	30.6	20.1	26.4	44.9	29.3

(57) Abstract: Magnetic vascular grafts and methods for their use are provided herein. This document is based at least in part on the development of vascular grafts, and methods for making vascular grafts, that have magnetic and porous properties to attract and culture cells, thus promoting endothelialization of the grafts. Coating the inside of a graft with cells can reduce the risk of clotting and scar tissue formation.



DEVICES AND METHODS FOR ENDOTHELIALIZATION OF MAGNETIC VASCULAR GRAFTS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims benefit of priority from U.S. Provisional Application Serial No. 61/991,253, filed on May 9, 2014.

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TECHNICAL FIELD

This document relates to magnetic vascular grafts, and methods for their use.

BACKGROUND

10

Coronary bypass surgery requires the use of vascular grafts, which can be taken from autologous vessels or can be synthetic. Synthetic vascular grafts cannot be used to bypass or replace small-diameter vessels, however, due to the risk of blood clot and/or scar tissue formation.

15

SUMMARY

This document is based at least in part on the development of vascular grafts, and methods for making vascular grafts, that have magnetic and porous properties to attract and culture cells, thus promoting endothelialization of the grafts. Coating the inside of a graft with cells can reduce the risk of clotting and scar tissue formation.

20

In one aspect, this document features a method for making a porous, magnetic device. The method can include providing a solvent containing an uncured polymer, a poragen, and a magnetic substance, providing an elongate mandrel having a length of at least about 3 cm and a diameter of about 100 μm to about 3 mm, dipping at least a portion of the mandrel into the solvent containing the polymer, poragen, and magnetic

25

substance, curing the polymer, and removing the poragen. The polymer can be, for example, polyurethane. The poragen can be sodium chloride, and the magnetic substance can be cobalt-chrome. The solvent can be dimethylacetamide. The method can further

include repeating the dipping and curing steps one or more times. The method can further include winding a thread around the device after a curing step, and subsequently repeating the dipping and curing steps. The thread can include, for example, polypropylene (e.g., the thread can be a polypropylene suture thread).

5 In another aspect, this document features a method for making a porous, magnetic device. The method can include providing a nanofiber mesh, using electrospinning to deposit the mesh onto a rotating elongate mandrel, where the mandrel has a length of at least about 3 cm and a diameter of about 10 μm to about 100 μm , and incorporating a magnetic substance into the deposited mesh. The nanofiber mesh can be a polyurethane
10 mesh. The magnetic substance can be cobalt-chrome. The method can further include incorporating a poragen (e.g., sodium chloride) into the nanofiber mesh.

 In another aspect, this document features a method for making a magnetic stent-graft, where the method includes depositing one or more layers of material inside and/or outside of a magnetic stent. The depositing can include electrospinning. The one or
15 more layers of material can include polyurethane. The magnetic stent can include stainless steel.

 Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. Although methods and materials similar or equivalent to those
20 described herein can be used to practice the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

25 The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

DESCRIPTION OF DRAWINGS

FIG. 1 is a table providing cross sectional measurements and lumen diameter measurements along the length of three exemplary grafts (Graft A, Graft B, and Graft C) as provided herein.

FIGS. 2A-2D are pictures of the walls of grafts having varying degrees of porosity due to their composition.

DETAILED DESCRIPTION

Implanted medical devices that include surfaces in contact with a patient's bloodstream can present risks that include, for example, acute thrombosis and chronic instability (e.g., calcification) of the implant surface. One approach that has been used to reduce these problems is "endothelial seeding," which places viable endothelial cells onto the blood contacting surface of a device (e.g., the lumen surface of a vascular graft, to mimic the surface of natural blood vessels). This surface modification can produce a confluent, biologically active surface of viable endothelial cells which, by definition, is anti-thrombogenic.

This document provides grafts for vascular use, as well as methods for making the grafts. The grafts can have any or all of the following characteristics and abilities:

- porous
- magnetic
- suitable wall thickness
- suturable
- resistance to kinking
- compliant; and
- strong.

The grafts provided herein can be used to maintain patency of the vessels into which they are placed, and can have improved blood compatibility and overall graft performance as compared to other grafts (e.g., non-porous and/or non-magnetic grafts).

In addition, the grafts can promote endothelialization at their site of placement, thus reducing the risks of blood clot and/or scar tissue formation. In particular, the grafts can have surfaces to which viable biological cells are magnetically attracted and retained. Thus, in some embodiments, methods for using the grafts provided herein can include attraction and retention of magnetically labelled cells to the magnetic grafts. In some
5 embodiments, the magnetic vascular grafts can attract and capture magnetically-labeled therapeutic compounds, which also may be used to improve blood compatibility and overall graft performance.

The grafts provided herein can be made from any suitable material, including
10 polymers such as polyurethane (PU), poly(lactic acid), poly(L-lactic acid), poly(glycolic acid), poly(lactic-co-glycolic acid), poly(glycerol sebacate), and polycaprolactone, as well as polyethylene terephthalate (DACRON[®]) and expanded polytetrafluoroethylene (GORE-TEX[®]). The grafts can be rendered magnetic by incorporating a compound such as cobalt-chrome (CoCr; also referred to as cobalt-chromium), a metal alloy of cobalt and
15 chromium. In some embodiments, the grafts can be rendered magnetic by incorporating one or more of permalloy, 420 stainless steel, and 2205 stainless steel. The porosity of the grafts provided herein can result from the use of a poragen such as sodium chloride (NaCl) during the manufacturing process. In some embodiments, however, a poragen is not necessary to generate a porous graft. *See, e.g.,* US2013/0018220, US2013/0122248,
20 which are incorporated herein by reference in their entirety.

The vascular grafts provided herein are generally tubular, having a cylindrical body with a first end and a second end, and a lumen extending between the first and second ends to permit blood flow after placement in a patient. A graft can have any suitable dimensions. For example, a graft can have a length of about 0.5 cm to about 10
25 cm (e.g., about 0.5 to 1 cm, about 1 to 1.5 cm, about 1.5 to 2 cm, about 2 to 2.5 cm, about 2.5 to 3 cm, about 3 to 3.5 cm, about 3.5 to 4 cm, about 4 to 4.5 cm, about 4.5 to 5 cm, about 5 to 6 cm, about 6 to 7 cm, about 7 to 8 cm, about 8 to 9 cm, about 9 to 10 cm, or about 10 cm). The diameter of the lumen can vary along the length of the graft, but in general the diameter of the lumen can be about 100 μ m to about 6 mm (e.g., about 100 to

250 μm , about 250 to 500 μm , about 500 to 750 μm , about 750 μm to 1 mm, about 1 to 1.5 mm, about 1.5 to 2 mm, about 2 to 2.5 mm, about 2.5 to 3 mm, or about 3 mm).

Further, the grafts can have a wall thickness of about 5 μm to about 1 mm (e.g., about 5 to 10 μm , about 10 to 15 μm , about 15 to 20 μm , about 20 to 25 μm , about 25 to 100 μm ,
5 about 100 to 500 μm , about 500 to 750 μm , or about 750 μm to 1 mm). FIG. 1 provides cross section and lumen diameter measurements at various points along the length of three different graft preparations (A, B, and C).

The porosity of a graft can be controlled or modified by varying the amount of PU, NaCl, and solvent in the slurry from which the graft is formed. For example, a
10 solvent mixture can contain about 5% to about 25% PU (e.g., about 5 to 10%, about 10 to 15%, about 15 to 20%, about 20 to 25%, or about 25% PU), and about 50% to about 80% NaCl (e.g., about 50 to 55%, about 55 to 60%, about 60 to 65%, about 65 to 70%, about 70 to 75%, about 75 to 80%, or about 80% NaCl). Controlling the porosity can be vital for graft optimization. NaCl can be ground, sieved into a certain diameter range (e.g.,
15 about 10 μm to about 100 μm), and mixed into a slurry of PU, CoCr, and solvent. After curing of the PU polymer and leaching of the NaCl poragen, a porous graft is formed.

The porosity of a graft can be measured using, for example, a computer program that converts photos into binary images, and then calculates porosity. Exemplary photos of porous grafts made by the methods provided herein are shown in FIGS. 2A-2D. The
20 grafts were made with 10% PU and 60% NaCl (FIG. 2A), 10% PU and 70% NaCl (FIG. 2B), 15% PU and 60% NaCl (FIG. 2C), or 15% PU and 70% NaCl (FIG. 2D).

Any suitable method can be used to fabricate the grafts provided herein. In some embodiments, for example, grafts can be produced by dipping at least a portion of an elongate mandrel into a viscous solution of PU, NaCl, and CoCr in a solvent (e.g.,
25 dimethylacetamide (DMA); $\text{CH}_3\text{C}(\text{O})\text{N}(\text{CH}_3)_2$). The graft can be cured as the DMA evaporates, leaving behind a solid mixture of PU, NaCl, and CoCr. Multiple layers can be dipped and cured to achieve a desired wall thickness. Once the desired all thickness is achieved, the NaCl can be leached out, leaving behind a porous solid mixture of PU and CoCr.

The elongate mandrel can be essentially cylindrical, with any suitable dimensions. For example, a mandrel can have a length of at least about 3 cm (e.g., at least 3 cm, at least 4 cm, at least 5 cm, at least 6 cm, at least 7 cm, or at least 8 cm). The diameter of the mandrel will determine the diameter of the lumen of the grafts that will be formed thereon. Thus, the mandrel can have a diameter of about 100 μm to about 3 mm (e.g.,
5 about 100 to 250 μm , about 250 to 500 μm , about 500 to 750 μm , about 750 μm to 1 mm, about 1 to 1.5 mm, about 1.5 to 2 mm, about 2 to 2.5 mm, about 2.5 to 3 mm, or about 3 mm).

In some embodiments, the grafts provided herein can be fabricated to be resistant to kinking. Grafts with low kink resistance can develop sharp bends, causing the grafts to
10 fail at a specific radius. In some embodiments, the kink resistance of the grafts provided herein can be increased by incorporating a thread, such as a polypropylene (e.g., prolene) suture winding between at least two of the dipped layers. A magnetic wire coil also can be used to provide kink resistance, as well as to provide additional magnetic properties. The degree of kink resistance can be modulated based on the coil/cm; a specific coil/cm
15 value can be used to allow for smaller bend radii before a sharp bend or kink develops.

In some embodiments, the grafts provided herein can be produced using electrospinning. *See*, e.g., WO2012/103501, US2013/0238086, US2013/0245748, US2013/0018220, and US2013/0122248, which are incorporated herein by reference in
20 their entirety. Electrospinning can be used to generate a mesh of nanofibers (e.g., PU nanofibers), which can impart desirable mechanical and cell adhesion properties. The parameters of the electrospinning can be varied to achieve a desired degree of porosity. In some cases, a poragen such as NaCl can be used to provide porosity to an electrospun graft. Electrospun grafts can be rendered magnetic by incorporation of CoCr (e.g., CoCr
25 powder). Further, an electrospinning graft preparation process can include the step of incorporating a thread (e.g., a polypropylene suture) into the graft to increase its kink resistance.

Electrospinning also can be used to fabricate magnetic stent-grafts. For example, a magnetic stent-graft can be generated by electrospinning one or more layers of a

polymer (e.g., PU) inside and/or outside of a magnetic stent (e.g., a magnetic stent comprising a material such as stainless steel). Such a device can be crimped to a diameter suitable for percutaneous delivery into the vascular system. Any suitable magnetic material can be used to fabricate the stent (e.g., 2205 stainless steel, 420 stainless steel, cobalt chromium, or permalloy), and any suitable material can be layered on the inner and/or outer surface of the stent. Useful layering materials include, without limitation, polymers such as polyurethane, polyethylene terephthalate, expanded polytetrafluoroethylene, polycaprolactone, poly(lactic acid), poly(l-lactic acid), poly(glycolic acid), poly(lactic-co-glycolic acid), and poly(glycerol sebacate), as well as collagen. As alternatives or in addition to electrospinning, methods for making such magnetic stent grafts can include solvent casting, electrospraying, and/or weaving, for example.

Once placed, a stent-graft can act as an intraluminal graft with cell capture and cell adhesion properties. Such devices can be used to, for example, cover small tears in blood vessels to stop hemorrhaging, to act as a flow diverter for treating aneurysms by keeping the flow confined to the blood vessel, thus diverting it away from the aneurysm bleb/injury, or to act as a normal stent with enhanced biocompatibility and bio-integration, promoted by the electrospun nanofiber scaffold around the stent structure.

In use, the magnetic, porous grafts as provided herein can attract and retain biological cells having a magnetic label. In some embodiments, for example, a pharmacologically acceptable carrier containing a population of magnetically labelled cells can be delivered to the vicinity of a magnetic graft placed in a vessel, such that the cells become associated with the graft surface(s). In other embodiments, biological cells can be magnetically attached to an implantable medical device *in vitro*, by placing a magnetic graft as provided herein in a carrier liquid containing a plurality of magnetically-labeled cells, where a plurality of the plurality of magnetically labelled cells are magnetically attracted to and retained on the implantable medical device. The graft and the cells then can be implanted in a vessel. See, e.g., U.S. Patent Nos. 8,465,453 and 8,544,474, which are incorporated herein by reference in their entirety.

OTHER EMBODIMENTS

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended
5 claims. Other aspects, advantages, and modifications are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A method for making a porous, magnetic device, comprising:
 - providing a solvent containing an uncured polymer, a poragen, and a magnetic substance;
 - providing an elongate mandrel having a length of at least about 3 cm and a diameter of about 100 μm to about 6 mm;
 - dipping at least a portion of the mandrel into the solvent containing the polymer, poragen, and magnetic substance;
 - curing the polymer; and
 - removing the poragen.
2. The method of claim 1, wherein the polymer is polyurethane.
3. The method of claim 1, wherein the poragen is sodium chloride.
4. The method of claim 1, wherein the magnetic substance is cobalt-chrome.
5. The method of claim 1, wherein the solvent is dimethylacetamide.
6. The method of claim 1, further comprising repeating the dipping and curing steps one or more times.
7. The method of claim 1, further comprising winding a thread around the device after a curing step, and subsequently repeating the dipping and curing steps.
8. The method of claim 7, wherein the thread comprises polypropylene.
9. The method of claim 8, wherein the thread is a polypropylene suture thread.
10. A method for making a porous, magnetic device, comprising:
 - providing a nanofiber mesh;

using electrospinning to deposit the mesh onto a rotating elongate mandrel, wherein the mandrel has a length of at least about 3 cm and a diameter of about 10 μm to about 100 μm ; and

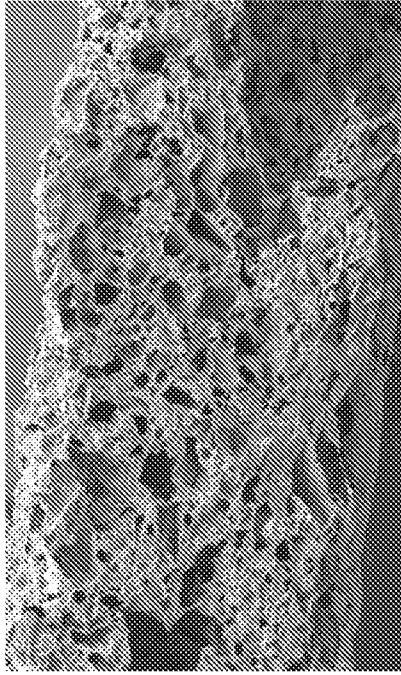
incorporating a magnetic substance into the deposited mesh.

11. The method of claim 10, wherein the nanofiber mesh is a polyurethane mesh.
12. The method of claim 10, wherein the magnetic substance is cobalt-chrome.
13. The method of claim 10, further comprising incorporating a poragen into the nanofiber mesh.
14. The method of claim 13, wherein the poragen is sodium chloride.
15. A method for making a magnetic stent-graft, comprising depositing one or more layers of material inside and/or outside of a magnetic stent.
16. The method of claim 15, wherein the depositing comprises electrospinning.
17. The method of claim 15, wherein the one or more layers of material comprise polyurethane.
18. The method of claim 15, wherein the magnetic stent comprises stainless steel.

FIG. 1

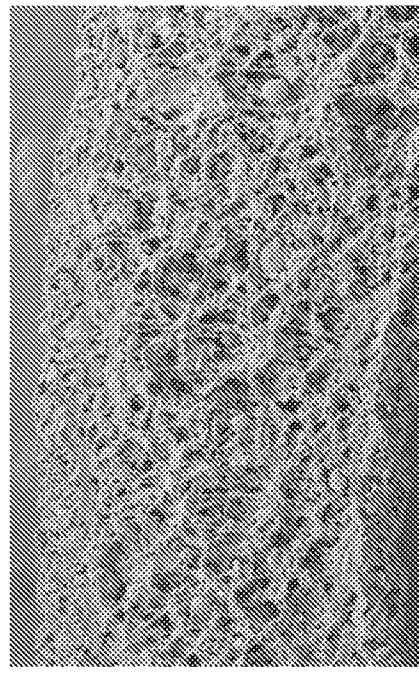
	Graft A		Graft B		Graft C	
	lumen (μm)	cross section (μm)	lumen (μm)	cross section (μm)	lumen (μm)	cross section (μm)
	40.2	87.5	44.1	66.4	44.9	59.6
	73	30.6	20.1	61.6	46.1	48.8
	107	40	102	29.3	53.1	29.3
	56.4	41.6	28.3	35.2	58.2	48.9
	39.4	37.3	49.6	26.4	70.5	49.4
	46.9	49.6	49	31.5	77.2	51.5
	19.9	45.4	43.3	72.5	77.7	42.2
Average	54.7	47.4	48.1	46.1	61.1	47.1
Max	107	87.5	102	72.5	77.7	59.6
Min	19.9	30.6	20.1	26.4	44.9	29.3

FIG. 2B



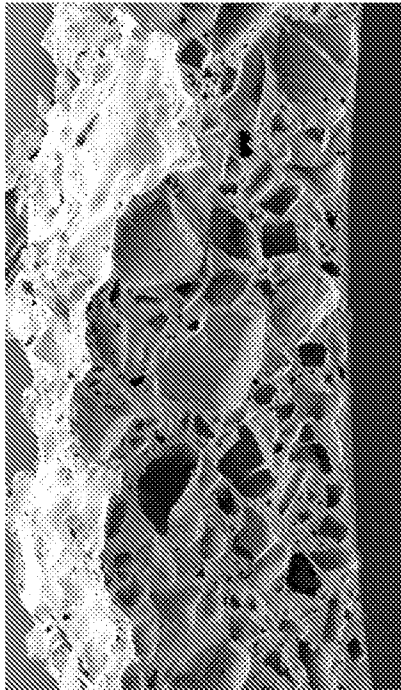
10%PU, 70% NaCl

FIG. 2D



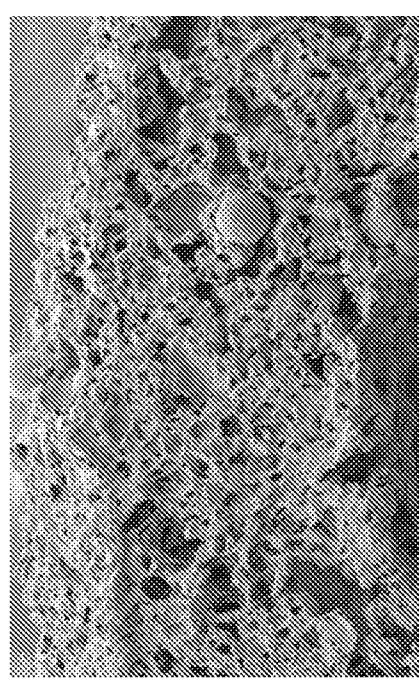
15%PU, 70% NaCl

FIG. 2A



10%PU, 60% NaCl

FIG. 2C



15%PU, 60% NaCl

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2015/029695

<p>A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61F 2/07 (2015.01) CPC - A61F 2/07 (2015.07) According to International Patent Classification (IPC) or to both national classification and IPC</p>																										
<p>B. FIELDS SEARCHED</p> <p>Minimum documentation searched (classification system followed by classification symbols) IPC(8) - A61F 2/02, 2/06, 2/07; A61L 27/28, 27/30, 31/14, 31/16 (2015.01) CPC - A61F 2/06, 2/07, 2002/072; A61L 27/28, 27/30 (2015.07) (keyword delimited)</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC - 623/1, 1.32, 1.39, 1.42, 1.44, 1.49</p> <p>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Orbit, Google Patents, Google Scholar. Search terms used: stent, graft, stainless steel, cobalt, porous, magnetic, coat, cast, mandrel, dip, helical, thread</p>																										
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X</td> <td>US 2008/0147177 A1 (SCHEUERMANN et al) 19 June 2008 (19.06.2008) entire document</td> <td>15, 17, 18</td> </tr> <tr> <td>X</td> <td>US 2009/0030504 A1 (WEBER et al) 29 January 2009 (29.01.2009) entire document</td> <td>10, 12, 13, 15, 16</td> </tr> <tr> <td>---</td> <td></td> <td>-----</td> </tr> <tr> <td>Y</td> <td></td> <td>11, 14</td> </tr> <tr> <td>Y</td> <td>US 2006/0167540 A1 (MASTERS et al) 27 July 2006 (27.07.2006) entire document</td> <td>1-9</td> </tr> <tr> <td>Y</td> <td>US 2008/0033233 A1 (JENSEN) 07 February 2008 (07.02.2008) entire document</td> <td>1-9, 11, 14</td> </tr> <tr> <td>Y</td> <td>US 5,873,906 A (LAU et al) 23 February 1999 (23.02.1999) entire document</td> <td>7-9</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	US 2008/0147177 A1 (SCHEUERMANN et al) 19 June 2008 (19.06.2008) entire document	15, 17, 18	X	US 2009/0030504 A1 (WEBER et al) 29 January 2009 (29.01.2009) entire document	10, 12, 13, 15, 16	---		-----	Y		11, 14	Y	US 2006/0167540 A1 (MASTERS et al) 27 July 2006 (27.07.2006) entire document	1-9	Y	US 2008/0033233 A1 (JENSEN) 07 February 2008 (07.02.2008) entire document	1-9, 11, 14	Y	US 5,873,906 A (LAU et al) 23 February 1999 (23.02.1999) entire document	7-9
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<p><input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.</p>																										
<p>* Special categories of cited documents:</p> <table border="0"> <tr> <td>“A” document defining the general state of the art which is not considered to be of particular relevance</td> <td>“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td> </tr> <tr> <td>“E” earlier application or patent but published on or after the international filing date</td> <td>“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td> </tr> <tr> <td>“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td> <td>“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td> </tr> <tr> <td>“O” document referring to an oral disclosure, use, exhibition or other means</td> <td>“&” document member of the same patent family</td> </tr> <tr> <td>“P” document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </table>			“A” document defining the general state of the art which is not considered to be of particular relevance	“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	“E” earlier application or patent but published on or after the international filing date	“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	“O” document referring to an oral disclosure, use, exhibition or other means	“&” document member of the same patent family	“P” document published prior to the international filing date but later than the priority date claimed															
“A” document defining the general state of the art which is not considered to be of particular relevance	“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention																									
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“O” document referring to an oral disclosure, use, exhibition or other means	“&” document member of the same patent family																									
“P” document published prior to the international filing date but later than the priority date claimed																										
<p>Date of the actual completion of the international search 20 July 2015</p>		<p>Date of mailing of the international search report 07 AUG 2015</p>																								
<p>Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300</p>		<p>Authorized officer Blaine Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774</p>																								

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2015/029695

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

Magnetic vascular grafts and methods for their use are provided herein. This document is based at least in part on the development of vascular grafts, and methods for making vascular grafts, that have magnetic and porous properties to attract and culture cells, thus promoting endothelialization of the grafts. Coating the inside of a graft with cells can reduce the risk of clotting and scar tissue formation.