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(54) Title: BIOLOGICAL PACEMAKER SCAFFOLD

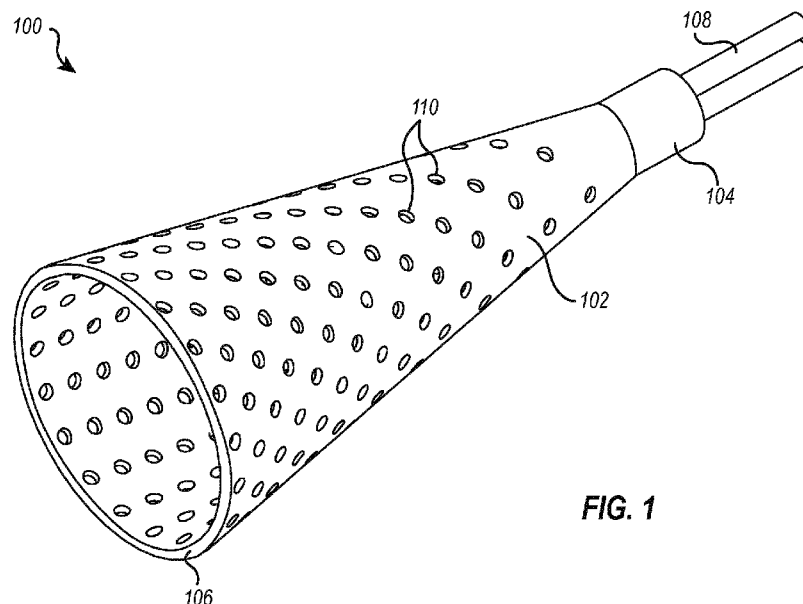


FIG. 1

(57) Abstract: A biological pacemaker device functions as a scaffold for constraining and concentrating pacemaker cells in proximity to cardiomyocytes to allow the propagation of action potentials from the pacemaker cells to the cardiomyocytes. The scaffold is an elongate member with a cone shape or cylindrical shape and an interior lumen. A barrier separates a proximal section of the interior, which houses pacemaker cells, from a distal section. A plurality of perforations are provided in the outer wall of the elongate member and in the barrier to allow the communication of action potentials and the transfer of gases and/or nutrients.



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BIOLOGICAL PACEMAKER SCAFFOLD**CROSS-REFERENCE TO RELATED APPLICATIONS**

- 5 **[0001]** This application claims the benefit of and priority to United States Provisional Patent Application No. 62/714,329, filed on August 3, 2018 and titled “Biological Pacemaker Scaffold,” the entirety of which is incorporated herein by this reference.

BACKGROUND

- 10 **[0002]** There are several heart conditions that can lead to an irregular heartbeat. Cardiac fibrosis, micro infarcts, remodeling, and aging are some of the threats that render more than 1 million hearts per year with no functional autonomous pace-makers. Sick Sinus Syndrome is a collection of disorders marked by the heart’s inability to perform pace-making functions. Its origin is not well known, although many factors can be involved including degenerative fibrosis, ion channel dysfunction, and heart remodeling.
- 15 **[0003]** Such conditions create the intense need of xenopacers that require a reliable electrical output to guide atrial and/or ventricular stimulation and further contraction. Conventional electrical pacing aids have been improved somewhat in recent years. For example, many are wireless, avoiding the risks of broken leads. However, despite these advances, there has been little improvement in secondary events related to the implant or
- 20 underlying condition. Issues often arise when the heart musculature is too thin at atrial regions, or in the hearts of small children where a smaller pacemaker device is necessary.
- 25 **[0004]** Conventional electrical-powered pacemaker devices have other limitations as well. These devices must typically be replaced every 7-10 years. Issues may also arise related to battery power levels, rate adjustments (e.g., to exercise or emotions),
- 30 infections, and lead replacements. Those with such conventional pacemakers must also avoid exposure to powerful magnets, meaning they must avoid MRI procedures. This limits the use of this important cardiac imaging technique and compromises diagnostic ability for patients with pacemakers. Problems may also be exacerbated when children are involved, as it is difficult to adapt implanted devices to a growing patient, due in part
- 30 to the increased frequency for invasive procedures.
- 30 **[0005]** Initial attempts to create a biological pacemaker involved the injection of enzymatically isolated pacemaker cells directly into the myocardium. This approach has not been very successful, however, as the injected cells find themselves within a different extracellular matrix environment and tend to undergo cellular dispersion and/or de-

differentiation. The injected pacemaker cells are also often immune-incompatible with the subject. As a result of mechanical damage, injected pacemaker cells grow immersed in fibrotic repair, reducing the ability to propagate action potentials. The production of pacemaker cells using embryonic stem cells may provide some pace-making, but also
5 raises the risk of neoplasia formation.

[0006] There is therefore a long felt and ongoing need for improved pacemaker devices and approaches to heart pacing interventions. In particular, there is a need for an effective biological replacement to the conventional electrical pacemaker capable of recreating the normal function of the heart using biological materials.

10

BRIEF SUMMARY

[0007] The present disclosure describes biological pacemaker devices and related methods enabling the functional integration of pacemaker cells with surrounding cardiac tissue at an implant site. Embodiments described herein can beneficially provide reliable and longer-lasting pacemakers that function without power supplies or further invasive
15 procedures utilizing biological components, including in some embodiments a patient's own biological components. Biological pacemaker cells described herein may also beneficially respond to adrenergic and cholinergic stimuli to permit proper responses to stress and exercise. In at least some circumstances, biological pacemaker devices implanted during youth do not need further modification over time.

[0008] In one embodiment, a biological pacemaker device includes a scaffold formed as an elongate member. The elongate member extends between a proximal end and a distal end along a longitudinal axis and has an outer wall that defines an inner lumen. The distal end is open. In some embodiments, the distal end has a larger diameter than the proximal end. For example, the elongated member may be substantially cone-shaped.
25 The pacemaker device also includes a barrier disposed within the lumen of the elongate member. The barrier separates and defines a proximal section within the lumen from a distal section within the lumen.

[0009] The proximal section encloses a plurality of pacemaker cells. The pacemaker cells may be autologous pacemaker cells obtained from a patient in which the device is
30 expected to be implanted or may additionally or alternatively include pacemaker cells derived from pluripotent stem cells.

[0010] The outer wall includes a plurality of perforations covered by an ECM layer to allow for the diffusion of gases (e.g., oxygen and carbon dioxide) into and out of the

device and to allow for the transfer of nutrients and/or waste products from one side to the other (e.g., the transfer of nutrients into the device and transfer of waste products out of the device). The barrier also includes a plurality of perforations covered by an ECM layer to allow for the diffusion of gases/nutrients and to allow electrical communication
5 between pacemaker cells within the proximal section and cardiomyocytes within the distal section. The perforations of the barrier may be larger than the perforations of the outer wall, and the ECM layer of the barrier may be thinner than the ECM layer of the outer wall.

[0011] When the device is implanted, cardiomyocytes enter the distal section and are
10 brought into contact with the pacemaker cells of the proximal section. The barrier is configured to allow the propagation of action potentials from the pacemaker cells of the proximal section to the cardiomyocytes of the distal section. The amplified signal may then propagate beyond the device to other cardiomyocytes.

[0012] Additional features and advantages will be set forth in part in the description
15 that follows, and in part will be obvious from the description, or may be learned by practice of the embodiments disclosed herein. The objects and advantages of the embodiments disclosed herein will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing brief summary and the following detailed description are exemplary
20 and explanatory only and are not restrictive of the embodiments disclosed herein or as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] A more particular description will be rendered by the embodiments illustrated in the appended drawings. It is appreciated that these drawings depict only exemplary
25 embodiments of the disclosure and are therefore not to be considered limiting of its scope. In the accompanying drawings:

[0014] Figures 1 through 3 illustrate various views of an exemplary biological pacemaker device;

[0015] Figures 4A through 4C illustrate a cannula assembly of the biological
30 pacemaker device of Figures 1 through 3 showing various media and/or cell transfer functions provided by the cannula assembly;

[0016] Figures 5A through 5C illustrate an exemplary implantation procedure for implanting the biological pacemaker device at an implantation site within a subject's heart; and

[0017] Figures 6A through 6C illustrate an alternative embodiment of a biological pacemaker device and an associated implantation procedure for implanting the device at an implantation site within a subject's heart.

DETAILED DESCRIPTION

[0018] This disclosure describes biological pacemaker devices that may be implanted into cardiac tissue of a subject (e.g., human or animal) to provide pacemaker functionality, to repair pacemaker functionality, and/or to improve cardiac pacing in the subject. Embodiments described herein include an implantable scaffold configured to house (i.e., constrain and concentrate) pacemaker cells and to enable the functional integration of the pacemaker cells with other cardiac cells (e.g., paranodal cells and cardiac myocytes) at an implantation site.

[0019] Figures 1 through 3 illustrate an exemplary embodiment of a biological pacemaker scaffold 100, with Figure 1 illustrating the scaffold 100 in isometric view of the device, Figure 2 providing a cross-sectional view along the longitudinal axis of the device, and Figure 3 providing an additional view to better show a distal end 106 and associated distal opening of the device.

[0020] The scaffold 100 may be made from one or more biocompatible polymer materials, such as polystyrene. It may be coated with one or more compatibility-enhancing polymers known in the art, such as Parylene. In some embodiments, the scaffold structure may be formulated to be biodegradable. For example, the scaffold 100 may be formed from a material designed to degrade over a time period sufficiently long to allow the pacemaker cells implanted with the device to successfully integrate with the surrounding tissue and provide functional pacemaking.

[0021] As shown, the exemplary scaffold 100 includes an elongated member 102 extending between a proximal end 104 and a distal end 106. In this embodiment, the circumference of the elongated member 102 at the distal end 106 is larger than the circumference at the proximal end 104. The elongated member 102 is preferably cone-shaped, with the wider base of the cone being disposed at the distal end 106 and the narrower apex of the cone being disposed at the proximal end 104 of the cone. Other embodiments may include elongated members having other shapes. For example, some

elongated members may have a cylindrical shape where the circumference is substantially uniform along the length of the device. The cross-sectional shape of the elongated member will typically be circular. However, other embodiments may include an elongated member having other cross-sectional shapes, such as a polygonal or ovoid shapes.

[0022] As explained in more detail below, structural features of the pacemaker device are configured to correspond to the anatomical features of a regular sinoatrial node (SA node) and function to beneficially amplify pacemaker signals generated within the scaffold 100 as they propagate distally and outwardly to other cardiac tissues. The cone shape of the device as illustrated here includes a substantially continuous taper. Other embodiments may have a taper that varies between the proximal and distal end. For example, one embodiment includes an increasing taper toward the distal end to form a flatter and wider shape at the distal end as opposed to the linear taper illustrated in the Figures. A tapered profile can beneficially aid in amplifying action potential signals as they propagate from the proximal section to the distal section. The tapered profile may also beneficially facilitate implantation of the device during an implantation procedure (which is described in more detail below in relation to Figures 5A through 5C).

[0023] As best shown in the cross-sectional view of Figure 2, the elongated member 102 of the scaffold 100 is divided into a proximal section 112 and a distal section 114. A barrier 116, oriented transverse to the longitudinal axis of the elongate member 102, separates the proximal section 112 from the distal section 114. The distal section 114 terminates to a distal opening at the distal end 106. The proximal section 112 includes a coupler 107 that allows a cannula assembly 108 to couple to the elongated member 102 at the proximal end 104. The cannula assembly 108, when attached, may be fluidly connected to the interior of the proximal section 112 as shown.

[0024] As described in more detail below, the cannula assembly 108 enables the transfer of materials (e.g., concentrated pacing cells, carrier media, nutritional supplements, stabilizers, soft scaffolding materials, and/or hydrogels) into and/or out of the interior of the proximal section 112. The cannula assembly 108 may include one or more cannula members, though in preferred embodiments the cannula assembly 108 includes at least two cannula members. When multiple cannula members are included, for example, the interior of the proximal section 112 may be flushed by directing fluid and/or other materials through one cannula or a subset of cannulas and allowing and/or materials to exit through another cannula or subset of cannulas.

[0025] The illustrated embodiment is designed such that when implanted, the distal end 106 is delivered into cardiac tissue at an implant site. A portion of the subject's cardiac tissue will enter the interior of the distal section 114 as the device is implanted. The proximal section 112 houses pacemaker cells. The pacemaker cells are beneficially restricted within a defined space to limit dispersion losses and maintain a critical mass and concentration of pacemaker cells to provide effective pacemaking. As used herein, the term "effective pacemaking" may refer to pacemaking that meets or exceeds a threshold actional potential capable of actuating the surrounding heart muscles in order to pace actual beating of the heart.

[0026] The barrier 116 is configured to restrict dispersion of the pacemaker cells housed (i.e., constrained and concentrated) within the proximal section 112 while also allowing sufficient communication of propagating action potentials between the pacemaker cells and the cardiac myocytes within the distal section 114. Similarly, the wall of the elongated member 102 is configured to restrict dispersion of the cell populations within the proximal and distal sections 112, 114 while also allowing sufficient transfer of nutrients and gases (e.g., oxygen) to the cells.

[0027] Housing the pacemaker cells within the proximal section 112 beneficially reduces migration losses and may additionally help in maintaining the pacemaker cells within a sufficiently concentrated environment to limit de-differentiation losses. In conventional approaches where pacemaker cells are injected into the myocardium, typically only about 10% of the cells remain in the injected region. Users must counteract these heavy losses by over-injecting an excess of cells. Suitable pacemaker cells, however, are difficult/expensive to prepare and the over-injecting approach increases costs and inefficiencies. In contrast, it is believed that the biological pacemaker devices described herein are able to provide effective pacemaking in a human with a starting pacemaker cell population of about 2,000 to 5,000 cells. In time, such a population may progress to a about 4,000 to 10,000 beating cells, possibly followed by even more proliferation.

[0028] As shown, the outer wall of the scaffold 100 includes multiple outer perforations 110. The perforations 110 may be covered by an extracellular matrix (ECM) layer to prevent cell dispersion while allowing oxygen diffusion to minimize ischemia. The ECM layer provides structural support to the device, and additionally beneficially provides biochemical and mechanical cues to the cells to promote better maintenance of cell phenotypes and better pacemaking activity. The ECM layer may include ECM

derived from suitable tissues (e.g., from cardiac tissues), and may additionally or alternatively include one or more of fibronectin, laminin, collagens I, III, V, IV, VII, and XI, elastin, other ECM-related molecules, and combinations thereof.

[0029] The overall dimensions of the elongated member 102 may vary according to particular anatomical conditions where the device is expected to be utilized. In some embodiments, the elongated member 102 may have an overall longitudinal length of about 2 mm to 8 mm, more typically within a range of about 3 mm to 6 mm. The diameter at the distal end 106 may be about 0.5 to 3 mm, or about 1 mm to 2 mm. The outer wall may taper at about 10 to 35 degrees to form the cone shape. Other embodiments having differently shaped elongated members (i.e., non-cone-shaped) may have similar dimensions, albeit with a few differences dictated by the different shape of the elongated member. For example, a cylindrical embodiment will not include a taper and will instead have a substantially uniform diameter of about 0.5 to 3 mm, or about 1 mm to 2 mm.

[0030] The wall of the elongated member 102 is preferably about 40 μm thick (e.g., about 20 μm to 75 μm or about 30 μm to 55 μm). The outer perforations may have a diameter of about 50 μm (e.g., about 25 μm to 75 μm or about 35 μm to 65 μm) and may be included at a density of about 100 to 350, or about 150 to 250 perforations per mm^2 . The ECM layer coating/covering the outer perforations 110 may have a thickness of about 20 μm to 40 μm .

[0031] To allow for effective communication between the pacemaker cells of the proximal section 112 and the cardiac myocytes of the distal section 114, the barrier 116 is preferably thinner than the outer wall of the elongated member 102, with larger perforations 118, and with a thinner ECM layer. For example, the barrier 116 may have a thickness of about 30 μm (e.g., about 15 μm to 45 μm or about 20 μm to 40 μm), the perforations 118 may have a diameter of about 100 μm (e.g., about 50 μm to about 200 μm or about 75 μm to 150 μm), and the ECM layer may have a thickness of about 10 μm (e.g., about 3 μm to 20 μm or about 5 μm to 15 μm).

[0032] The foregoing dimensional ranges, including wall thicknesses, perforation diameters, overall device length and diameter, etc., are exemplary only. Other dimensional ranges may also be utilized according to particular application needs. However, devices within the foregoing ranges are presently preferred because of the effective balancing of size, structural strength, deliverability, and alignment to the anatomy of a typical patient.

[0033] The cannula assembly 108 provides access to the proximal section 112 and allows for the flushing of cells, the removal of blood and tissue debris, the introduction of new or additional pacemaker cells, and the injection of growth factors, epinephrine, hormones, other therapeutic and/or signaling agents (e.g., sonic hedgehog expression signals, Klotho expression signals, etc.), and combinations thereof. These types of therapeutic agents may be utilized to maintain desired cell phenotypes and promote sufficient growth of the pacemaker cells. The access to the proximal section 112 provided by the cannula assembly 108 also allows for sample collection, cell phenotype monitoring (e.g., via RNA profiling or other suitable technique), and other monitoring of implant status. In some embodiments, the cannula assembly 108 may also be utilized to deliver optical signals to the cells within the proximal section 112.

[0034] Following implantation of the scaffold 100, the cannula assembly 108 may remain in place coupled to the elongated member 102 at one end and extending to a proximal end external to the patient (e.g., through a transthoracic access site). This allows caretakers to continue to inject cells or therapeutic agents and/or to remove blood, debris, cells, or other materials until the implant is determined to be self-sufficiently functional. Once such a determination has been made, the cannula assembly may be removed while the remainder of the implant remains in place within the subject.

[0035] In some embodiments, the pacemaker cells may be autologous pacemaker cells obtained from the patient. Such cells beneficially avoid immune reactions. Some embodiments may additionally or alternatively utilize a patient's stem cells (e.g., pluripotent stem cells derived from the patient's blood and/or cardiomyocytes) that are then transformed into pacemaker cells. The foregoing types of cells have been shown to preserve membrane channels and receptors and to allow modulation by parasympathetic and sympathetic signals. Some embodiments may additionally or alternatively utilize optogenetically modified pacemaker cells designed to allow action potential modulation in response to applied light signals.

[0036] Figures 4A through 4C illustrate expanded views of the proximal end 104 of the elongated member with the cannula assembly 108 connected. Figure 4A illustrates transfer of fluid moving toward the implant in one cannula and moving out of and away from the implant in another cannula. As described above the fluid may be a wash media and/or may include one or more therapeutic agents. Figure 4B illustrates the same concept showing the transfer of cells. As shown in Figure 4C, after the cells and/or media

reach the desired location, positive pressure may be added to both cannula lines to provide for insertion into the proximal section of the scaffold device.

[0037] Figures 5A through 5C illustrate an exemplary implantation procedure using the scaffold device 100. Initially, as shown in Figure 5A, a small incision may be made through the epicardium to provide access to an implant site. Access to the patient's heart may be accomplished through open-heart surgery, but more preferably is accomplished via a laparoscopic approach. A preparation composition may be applied to the implant site to better prepare the surrounding tissue for receiving the implant. For example, the preparation composition may include a vascularization promoter (such as a vascularization gel known in the art) and/or cardiomyocyte cells (e.g., transformed from pluripotent stem cells of the patient).

[0038] As shown in Figure 5B, the scaffold device 100 may then be delivered to the prepared implant site using a suitable needle 121, catheter, or other delivery device. The delivery device preferably has a size similar to that of the scaffold 100 to allow the scaffold 100 to be driven into the cardiac muscular tissue surrounding the implant site. Figure 5B also illustrates that the scaffold 100 may include one or more hooks 120 and/or other frictional structures to help maintain the scaffold 100 in position at the implant site.

[0039] Figure 5C illustrates the scaffold 100 after implantation and removal of the delivery needle 121. As shown, one or more electrodes 122 (preferably 2 to 4 electrodes) may also be integrated with or attached to the proximal section of the scaffold 100. The leads of the electrodes may pass out with the cannula assembly out of a suture 124 and to the exterior of the patient. The electrodes 122 may be utilized to measure/monitor electrical activity of the cells within the scaffold. The electrodes 122 may additionally or alternatively be utilized, when necessary or desirable, to provide a pacing/training signal to the pacemaker cells of the implant during an initial training phase following implantation. As with the cannula assembly 108, the electrodes 122 may be removed once it is determined that the implanted pacemaker cells have reached a self-sufficient level of function.

[0040] Figures 6A through 6C illustrate an alternative embodiment of a scaffold device 200 having a cylindrical shape, and also illustrate an exemplary implantation procedure similar to that shown in Figures 5A through 5C. Initially, as shown in Figure 6A, a biopsy and/or incision is made to provide access to the targeted implant site. A preparation composition (e.g., vascularization gel) may be applied to the implant site as shown in Figure 6B.

[0041] As shown in Figure 6C, the scaffold device 200 may then be delivered to the prepared implant site using a suitable delivery device. As with the embodiment of Figures 5A through 5C, the assembly may include one or more electrodes 222 coupled to the scaffold device 200 and a multi-lumen cannula (not shown). As above, the electrodes
5 222 may measure/monitor electrical activity of the cells within the scaffold and/or may be used to provide a pacing/training signal to the pacemaker cells of the implant during an initial training phase following implantation. The cannula may be used as described above. The illustrated embodiment also includes an accessory electrode 223 which may be utilized for additional measurement/monitoring of the heart during an initial phase
10 following implantation. For example, the accessory electrode 223 may be utilized to record beating of the pacemaker device and check for electrical coupling of the pacemaker cells with the existing cardiac musculature. It is typically removed following the startup/training phase.

[0042] Biological pacemaker devices described herein may be formed using one or
15 more suitable (e.g., biocompatible) materials known in the art. Examples of such suitable materials particularly include biocompatible polymers such as polystyrene, polycarbonate, polyethylene, and the like. One or more tissue compatibility enhancers, such as the poly(p-xylene) polymers sold under the trade name Parylene, may also be included with the device (e.g., coated onto the device). Fabrication of the device(s) may
20 also be carried out using any suitable manufacturing microfabrication or nanofabrication process known in the art. Exemplary fabrication methods that may be utilized include 3D printing, photolithography, electron beam lithography, and the like.

[0043] Additional examples utilizing certain embodiments of the biological pacemaker devices described herein are described in the attached Appendix.

25 [0044] The terms “approximately,” “about,” and “substantially” as used herein represent an amount or condition close to the stated amount or condition that still performs a desired function or achieves a desired result. For example, the terms “approximately,” “about,” and “substantially” may refer to an amount or condition that deviates by less than 10%, or by less than 5%, or by less than 1%, or by less than 0.1%,
30 or by less than 0.01% from a stated amount or condition.

[0045] It will be understood that elements described in relation to any embodiment depicted and/or described herein may be substituted for or combined with elements described in relation to any other embodiment depicted and/or described herein.

CLAIMS

1. A biological pacemaker device, comprising:
 - an elongate member extending between a closed proximal end and an open distal end along a longitudinal axis, the elongate member having an outer wall that defines an
 - 5 inner lumen;
 - a plurality of perforations extending through the outer wall; and
 - an outer wall ECM layer covering the perforations of the outer wall, the outer wall ECM layer enabling the restriction of cell dispersion while also allowing the diffusion of gases through the perforations.
- 10 2. The pacemaker device of claim 1, wherein the distal end of the elongate member has a diameter larger than a diameter of the proximal end to enable amplification of an action potential as it propagates distally.
3. The pacemaker device of claim 1 or claim 2, wherein the elongate member encloses a plurality of pacemaker cells.
- 15 4. The pacemaker device of claim 3, wherein the pacemaker cells are autologous pacemaker cells obtained from a patient or are derived from pluripotent stem cells.
5. The pacemaker device of any one of claims 1 through 4, wherein the elongate member has a cone shape.
6. The pacemaker device of any one of claims 1 through 5, further comprising a
- 20 barrier disposed within the lumen of the elongate member, the barrier extending in a direction transverse to the longitudinal axis of the elongate member and separating a proximal section within the elongate member from a distal section within the elongate member.
7. The pacemaker device of claim 6, wherein a plurality of pacemaker cells are
- 25 enclosed in the proximal section of the elongate member.
8. The pacemaker device of any one of claims 1 through 7, wherein the perforations of the outer wall have a diameter of about 25 μm to 75 μm or about 35 μm to 65 μm .
9. The pacemaker device of any one of claims 1 through 8, wherein the perforations are included at a density of about 100 to 350 per mm^2 , or about 150 to 250 per mm^2 .
- 30 10. The pacemaker device of any one of claims 1 through 9, wherein the outer wall has a thickness of about 20 μm to 75 μm or about 30 μm to 55 μm .
11. The pacemaker device of any one of claims 6 through 10, wherein the barrier is thinner than the outer wall.

12. The pacemaker device of any one of claims 6 through 11, wherein the barrier includes a plurality of barrier perforations.
13. The pacemaker device of claim 12, wherein the barrier perforations are larger than perforations of the outer wall.
- 5 14. The pacemaker device of claim 12 or claim 13, further comprising a barrier ECM layer disposed on the barrier and covering the perforations of the barrier.
15. The pacemaker device of claim 14, wherein the ECM layer of the barrier is thinner than the ECM layer of the outer wall.
16. The pacemaker device of any one of claims 6 through 15, wherein the barrier has
10 a thickness of about 15 μm to 45 μm or about 20 μm to 40 μm
17. The pacemaker device of any one of claims 1 through 16, wherein the outer wall ECM layer and/or the barrier ECM layer includes one or more of ECM derived from cardiac tissues, fibronectin, laminin, collagen, elastin, and combinations thereof.
18. The pacemaker device of any one of claims 1 through 17, further comprising a
15 cannula assembly coupled at the proximal end of the elongate member, the cannula assembly including one or more cannula members in communication with the inner lumen of the elongate member.
19. The pacemaker device of claim 18, wherein the cannula assembly includes a plurality of cannula members.
- 20 20. The pacemaker device of claim 18 or claim 19, wherein the cannula assembly is selectively detachable from the elongate member.
21. The pacemaker device of any one of claims 1 through 20, further comprising one or more frictional members disposed at the distal end of the elongate member for engaging with tissue during implantation of the device.
- 25 22. The pacemaker device of any one of claims 1 through 21, further comprising an electrode assembly having one or more electrodes in electrical communication with the inner lumen and one or more leads extending proximally therefrom.
23. The pacemaker device of claim 22, wherein at least the one or more leads of the electrode assembly are selectively detachable from the elongate member.
- 30 24. A method of implanting a biological pacemaker device, comprising:
providing a pacemaker device as in any one of claims 1 through 23; and
implanting the pacemaker device at an implant site within a subject in need thereof.

25. The method of claim 24, further comprising preparing the implant site by applying a vascularization promoting agent and/or cardiomyocytes.

26. The method of claim 25, wherein the cardiomyocytes are derived from pluripotent stem cells.

5 27. The method of any one of claims 24 through 26, wherein the pacemaker device is implanted such that cardiac muscle tissue at the implant site resides within the distal section and contacts the barrier to allow communication with pacemaker cells within the proximal section.

28. The method of any one of claims 24 through 27, further comprising injecting cells
10 and/or a therapeutic agent through the cannula assembly and into the inner lumen.

29. The method of any one of claims 24 through 28, further comprising operating the electrode assembly to train pacemaker cells within the inner lumen.

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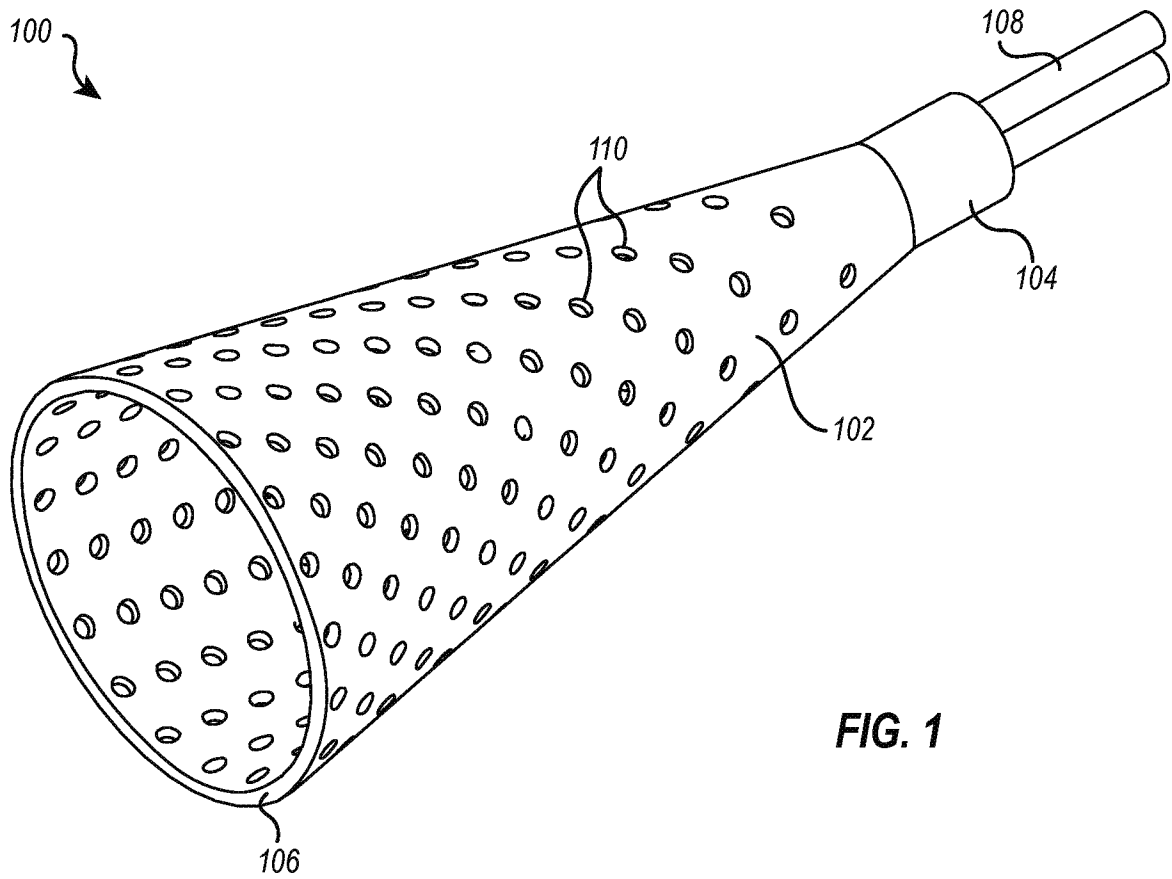


FIG. 1

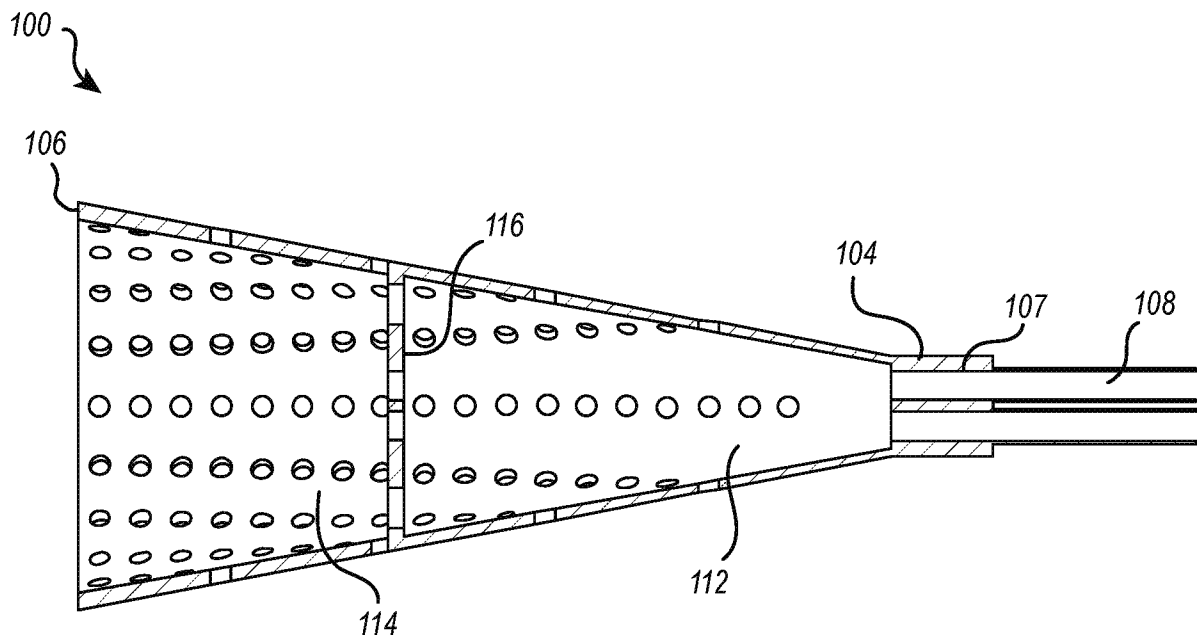


FIG. 2

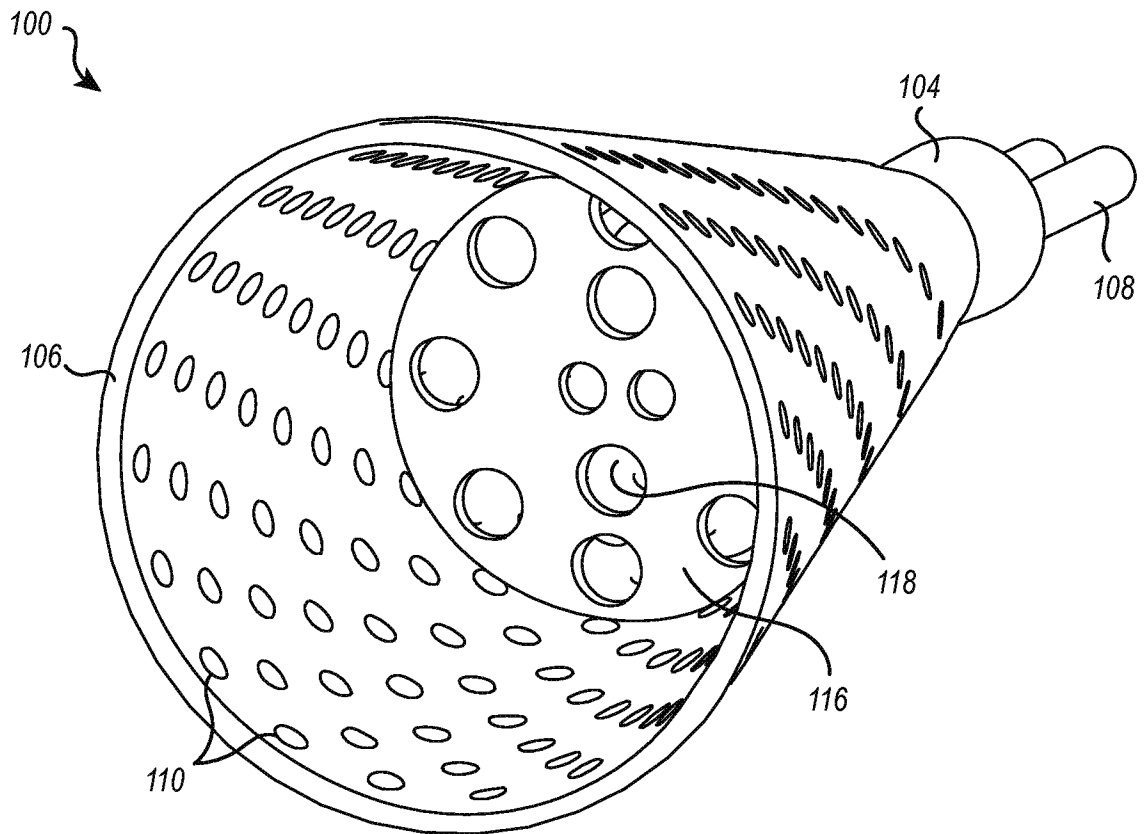


FIG. 3

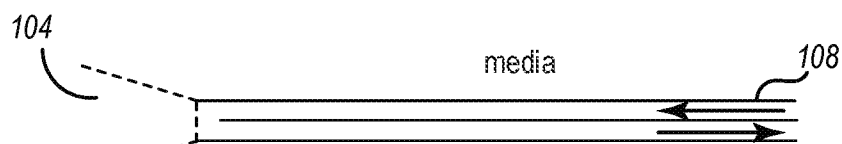


FIG. 4A

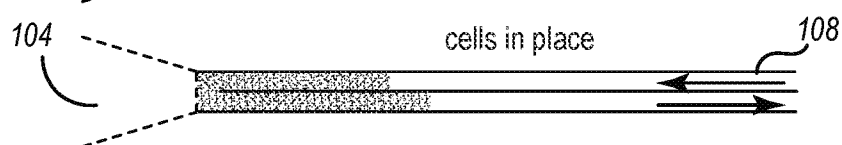


FIG. 4B

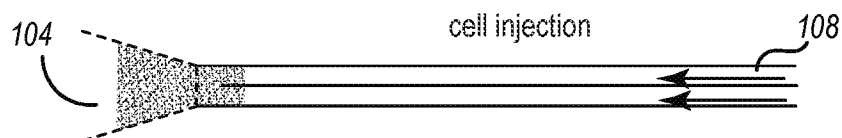


FIG. 4C

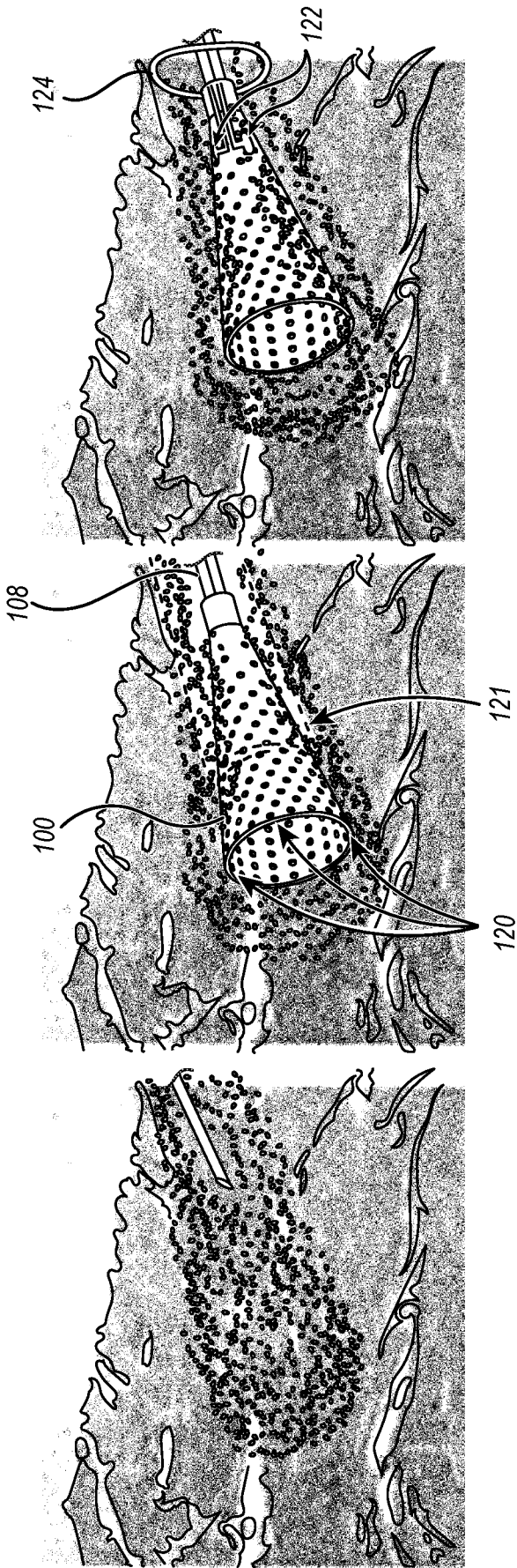


FIG. 5A

FIG. 5B

FIG. 5C

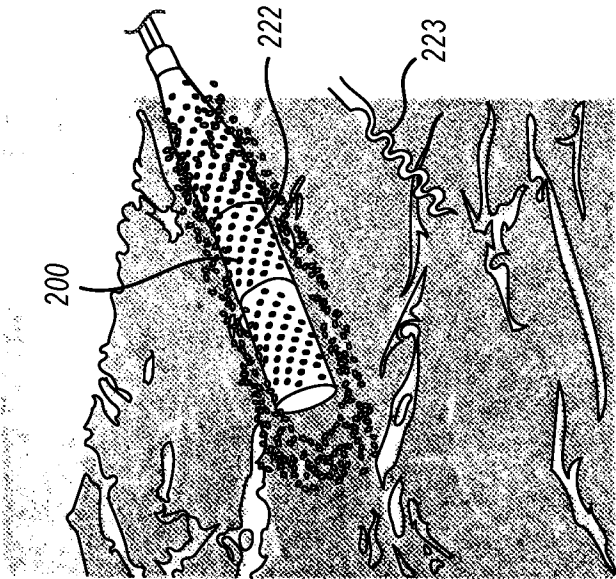


FIG. 6C

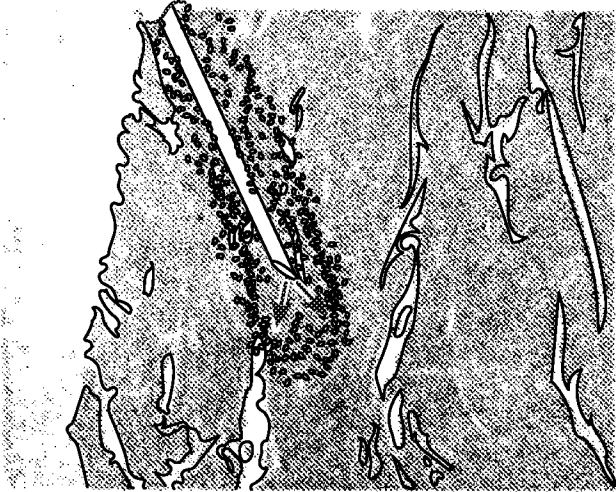


FIG. 6B

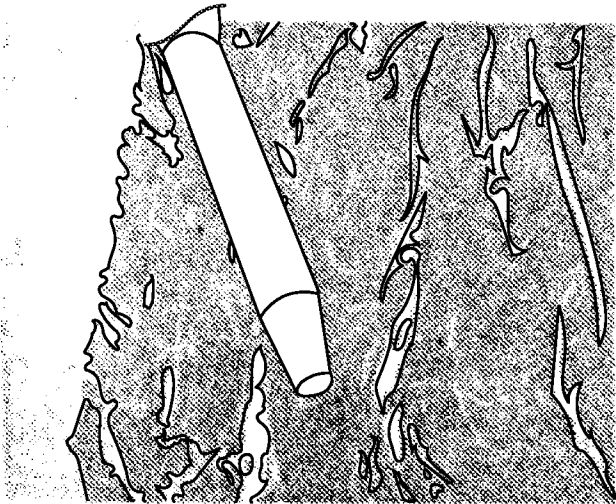


FIG. 6A

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/044915

A. CLASSIFICATION OF SUBJECT MATTER INV. A61L27/36 A61L27/56 A61K35/28 A61K35/34 A61K35/545 ADD. A61N1/362 A61N1/05																				
According to International Patent Classification (IPC) or to both national classification and IPC																				
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61L A61K A61N Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data																				
C. DOCUMENTS CONSIDERED TO BE RELEVANT <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 2015/297798 A1 (BADYLAK STEPHEN F [US] ET AL) 22 October 2015 (2015-10-22)</td> <td>1,2,5, 8-10,17, 21</td> </tr> <tr> <td>Y</td> <td>paragraphs [0003], [0030], [0053], [0071], [0196]; figures 3, 11, 12</td> <td>3,4</td> </tr> <tr> <td>Y</td> <td>US 2005/283218 A1 (WILLIAMS MICHAEL S [US]) 22 December 2005 (2005-12-22) abstract; figure 3 paragraphs [0009], [0066] - [0070], [0076]</td> <td>3,4</td> </tr> <tr> <td>A</td> <td>US 2009/171406 A1 (FOLEY JOHN [US] ET AL) 2 July 2009 (2009-07-02) paragraphs [0113] - [0118]; figure 1 the whole document</td> <td>1-5, 8-10,17, 21</td> </tr> <tr> <td></td> <td>-/--</td> <td></td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	US 2015/297798 A1 (BADYLAK STEPHEN F [US] ET AL) 22 October 2015 (2015-10-22)	1,2,5, 8-10,17, 21	Y	paragraphs [0003], [0030], [0053], [0071], [0196]; figures 3, 11, 12	3,4	Y	US 2005/283218 A1 (WILLIAMS MICHAEL S [US]) 22 December 2005 (2005-12-22) abstract; figure 3 paragraphs [0009], [0066] - [0070], [0076]	3,4	A	US 2009/171406 A1 (FOLEY JOHN [US] ET AL) 2 July 2009 (2009-07-02) paragraphs [0113] - [0118]; figure 1 the whole document	1-5, 8-10,17, 21		-/--	
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.																		
X	US 2015/297798 A1 (BADYLAK STEPHEN F [US] ET AL) 22 October 2015 (2015-10-22)	1,2,5, 8-10,17, 21																		
Y	paragraphs [0003], [0030], [0053], [0071], [0196]; figures 3, 11, 12	3,4																		
Y	US 2005/283218 A1 (WILLIAMS MICHAEL S [US]) 22 December 2005 (2005-12-22) abstract; figure 3 paragraphs [0009], [0066] - [0070], [0076]	3,4																		
A	US 2009/171406 A1 (FOLEY JOHN [US] ET AL) 2 July 2009 (2009-07-02) paragraphs [0113] - [0118]; figure 1 the whole document	1-5, 8-10,17, 21																		
	-/--																			
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.																				
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family																				
Date of the actual completion of the international search		Date of mailing of the international search report																		
24 October 2019		16/01/2020																		
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Pfeiffer, Uwe																		

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2019/044915

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2013/330378 A1 (PARKER KEVIN KIT [US] ET AL) 12 December 2013 (2013-12-12) paragraphs [0005] - [0007], [0036] - [0039], [0069], [0093] - [94115] -----	1-5, 8-10,17, 21
A	WO 2018/017611 A1 (COOK BIOTECH INC [US]) 25 January 2018 (2018-01-25) pages 26, 27; figure 1A -----	1-5, 8-10,17, 21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/044915

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

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

1. ☒ Claims Nos.: 24-29
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-5, 8-10, 17, 21

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-5, 8-10, 17, 21

Biological pacemaker comprising perforated wall covered by an ECM layer and defining a lumen that comprises pacemaker cells for solving the problem of providing stimulation

2. claims: 6, 7, 11-16

Elongate member comprising perforated wall covered by an ECM layer and defining a lumen that comprises a transverse barrier for solving the problem of providing a separated compartment.

3. claims: 18-20

Elongate member comprising perforated wall covered by an ECM layer and defining a lumen, further comprising a cannula in communication with the lumen for solving the problem of delivering substances into the lumen

4. claims: 22, 23

Elongate member comprising perforated wall covered by an ECM layer and defining a lumen, further comprising an electrode for solving the problem of sensing electrical signals.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2019/044915

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2015297798	A1	22-10-2015	NONE
US 2005283218	A1	22-12-2005	AU 2005258205 A1 05-01-2006 CA 2565340 A1 05-01-2006 EP 1773446 A2 18-04-2007 JP 2008503328 A 07-02-2008 US 2005283218 A1 22-12-2005 WO 2006002306 A2 05-01-2006
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WO 2018017611	A1	25-01-2018	US 2019351241 A1 21-11-2019 WO 2018017611 A1 25-01-2018