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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 March 2007 (08.03.2007)

PCT

(10) International Publication Number
WO 2007/027505 A1

(51) International Patent Classification:
A61N 1/05 (2006.01) *C12N 5/06* (2006.01)
A61N 1/362 (2006.01) *A61N 1/32* (2006.01)
A61M 5/14 (2006.01)

(21) International Application Number:
PCT/US2006/033107

(22) International Filing Date: 23 August 2006 (23.08.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
11/216,295 31 August 2005 (31.08.2005) US

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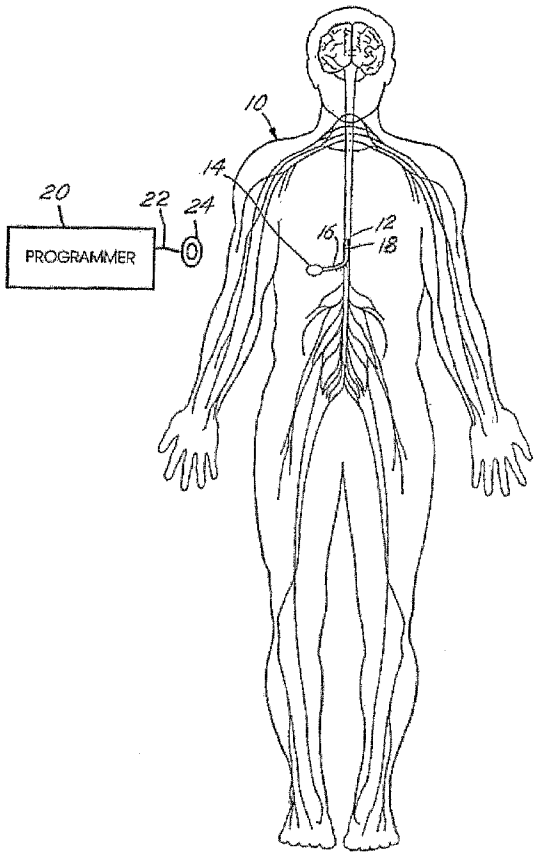
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ,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

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

[Continued on next page]

(54) Title: CELLULAR INTERVENTION TO TREAT DAMAGED MYOCARDIUM



(57) Abstract: A system and method for treating damage myocardial tissue includes delivering replacement cells to the myocardium of a patient and electrically stimulating the spinal column of the patient to affect a cellular environment within the myocardium.

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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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

CELLULAR INTERVENTION TO TREAT DAMAGED MYOCARDIUM

BACKGROUND OF THE INVENTION

The present invention relates generally to systems and methods for treating coronary heart disease. In particular, the present invention relates to repopulating and/or regenerating damaged or diseased myocardial tissue with introduced replacement cells.

Coronary Artery Disease (CAD) is a major health problem worldwide. In persons having CAD, the formation of plaque narrows the coronary artery and reduces the supply of oxygen and nutrients to the heart, which can cause acute myocardial infarction (AMI). AMI is a condition of irreversible necrosis of the heart muscle that results from prolonged ischemia. Over time, the damaged or diseased regions of the myocardium associated with AMI are replaced with scar tissue, which decreases the contraction of the heart and can create electrical abnormalities. As a result, survivors of AMI have an increased risk of developing heart failure.

Current treatments for AMI survivors focus on pharmacological and surgical approaches that are designed to achieve reperfusion and minimize ventricular damage. These therapies, however, do not address myocardial necrosis and its effects on heart function. Cellular replacement techniques to address myocardial necrosis and/or myocardial depressed contractility (akynesia) are under clinical investigation. These techniques entail supplying replacement cells to repair or enhance damaged or diseased portions of the myocardium. Preliminary results suggest that this form of therapy may positively impact the functioning of the heart.

These conventional cellular replacement techniques, however, have yielded low survival rates for the introduced replacement cells, as well as poor engraftment, when introduced into the myocardial tissue of patients. Cell survival rates are poor, with typically about 20 percent of the replacement cells surviving 1 week after being delivered to the myocardium. One report indicates survival rates for the replacement cells of less than 1 percent. See Taylor, *Int'l Journal of Cardiology*, 95 Suppl. 1 (2004): S13-S15. While the precise reasons for the low survival rates are not known, they may be associated with a lack of necessary nutrients and gaseous exchange.

Thus, among other things a need exists for improved apparatus and methods for addressing myocardial necrosis for survivors of AMI and other subjects having scars or lesions that interfere with conduction and/or mechanical electrical contraction of the heart.

BRIEF SUMMARY OF THE INVENTION

The present invention treats damaged myocardial tissue in a patient with a combination of replacement cells delivered to the myocardium and electrical stimulation applied to the spinal column. The electrical stimulation affects a cellular environment for the replacement of cells within the myocardium.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic representation of a nerve stimulator system applying electrical stimulation to the spine of a patient.

FIG. 2 is a schematic representation of a cell delivery device delivering replacement cells to a damaged myocardial tissue region of the patient of FIG. 1.

FIG. 3 is a cross-sectional view of the spinal column of the patient of FIG. 1 showing placement of a stimulation electrode within the epidural space.

DETAILED DESCRIPTION

FIGs. 1 and 2 illustrate a method and system for treating a patient 10 having AMI with a combination of replacement cells delivered to the myocardium and electrical stimulation applied to the spinal column. The present invention combines cell-replacement with electrical stimulation of the spinal column of a patient to affect the cellular environment of the myocardium and form a more hospitable cellular environment for replacement cells. The beneficial effects of modifying the cellular environment may include, for example, enhanced cell survival of replacement cells, enhanced host myocardial tissue, enhanced ability of replacement cells to differentiate into more suitable cell types, and/or enhanced ability of replacement cells to bond (or engraft) with host myocardial tissue or structural matrixes.

The more hospitable cellular environment may result from improvements in myocardial blood flow caused by spinal cord stimulation (SCS). SCS has been employed to treat various conditions, including angina pectoris, which is a symptom of myocardial

ischemia. SCS has been demonstrated to improve myocardial blood flow at the microvascular level in angina patients using positron emission tomography (PET), with improvement in regional blood flow to ischemic areas. See Latif, et al., *Clinical Cardiology* 24: 533-541 and Hautvast, et al., *The American Journal of Cardiology* 77 (1996): 462 – 467. For further discussion regarding the effects of SCS on myocardial blood flow, see also Jessurun, et al., *European Journal of Pain* 7 (2003): 507-512. SCS has been documented to have numerous positive effects on patients suffering from angina pectoris, including both antianginal and anti-ischematic effects. See Aronow, et al., *Current Treatment Options in Cardiovascular Medicine* 6: 79-83. Improved blood flow as a result of SCS may play a key role in mediating these positive effects in angina pectoris patients.

FIG. 1 is a schematic view of patient 10 that illustrates electrical stimulation being applied to spine 12. Nerve stimulator 14 supplies electrical stimulation pulses via lead 16 to electrode 18. These electrical stimulation pulses are applied to spine 12 by electrode 18, which is located within, or adjacent to, spine 12.

Nerve stimulator 14 may be programmed to provide a predetermined stimulation dosage in terms of pulse amplitude, pulse width, pulse frequency, or duty cycle. Programmer 20, in conjunction with conductor 22 and antenna 24, may be used to provide stimulation parameters to nerve stimulator 14 via telemetry. This permits attending medical personnel to provide stimulation parameters to nerve stimulator 14 after implantation using radio frequency communication.

Nerve stimulator 14 may be implanted in the abdomen or any other portion of the body of patient 10. In some embodiments, nerve stimulator 14 is located outside patient 10. Nerve stimulator 14 can be an implantable pulse generator with one or more implanted leads 16, a partially implantable nerve stimulation system including an external transmitter and an implantable receiver powered by the transmitter, or an external stimulation system having an external pulse generator and leads. Examples of suitable nerve stimulators 14 include, but are not limited to, Model 7425 Itrel® 3 neurostimulators, Model 7427 Synergy® neurostimlators, Model 7479 SynergyPlus® neurostimulators, Model 7479B SynergyCompact® neurostimulators, 3271 Mattrix® receivers, and 3271 Mattrix® receivers – all of which are commercially available from Medtronic, Inc.

Any type of lead 16 with any number and configuration of electrodes 18 may be used to apply electrical stimulation to the spinal column. Examples of suitable leads include percutaneous leads, surgical leads, and transcutaneous leads.

FIG. 2 is a schematic view illustrating the delivery of replacement cells to heart 30 of patient 10. Heart 30 has a right ventricle RV, a left ventricle LV, a right atrium RA, and a left atrium LA. In the example of FIG. 2, left ventricle LV has a damaged myocardial tissue region 32. Cell delivery device 34 (which includes replacement cell source 36 and delivery conduit 38) delivers replacement cells to damaged myocardial tissue region 32. To affect the cellular environment for the replacement cells in myocardial tissue region 32, nerve stimulator 14 applies electrical stimulation to spine 12. The timing of the electrical stimulation with respect to the delivery of replacement cells is selected to produce the cellular environment that is more hospitable for the replacement cells.

Cell delivery device 34 can take various forms and use various methods to deliver replacement cells to damaged myocardial tissue region 32. Such cell delivery devices and methods are well known in the art. See, for example, U.S. Pat. No. 6,805,860 and U.S. Pat. App. 2004/0158289 (Application Serial No. 722,115) by Girouard, et al. As shown in FIG. 2, cell delivery device 34 is a catheter-based delivery system in which replacement cell source 36 comprises a pump or syringe and delivery conduit 38 comprises a catheter. In other embodiments, replacement cell source 36 comprises a syringe and delivery conduit 38 comprises a needle.

The replacement cells may be delivered to the myocardium via any route, including intravenously, transvenuously, intramyocardially, or other routes known in the art. After being located in close proximity to heart 30, the replacement cells can be delivered to the myocardium by either injecting cells directly into the myocardium or by introducing the replacement cells into a vessel supplying blood to the myocardium.

To inject cells into the myocardium, delivery conduit 38 may be positioned, for example, in or adjacent to the left ventricle, the right ventricle, the left atrium, or the right atrium. In some embodiments, the replacement cells are injected near, and/or into, an infarcted region of the myocardium (e.g., myocardial region 32) or other damaged or diseased region of the myocardium. The replacement cells may be injected into the myocardium using a single injection or a plurality of injections. In some embodiments,

injections may be separated from each other in time by hours, days, weeks, months, or years.

Various methods may be employed to locate damaged myocardial tissue regions 32. For example, electrophysiology (e.g., electrocardiograms) or any other locating methods known in the art may be used to locate damaged myocardial tissue. See U.S. Pat. App. 2004/0158289 (Application Serial No. 722,115) by Girouard, et al.

The application of the electrical stimulation by nerve stimulator 14 has a temporal relationship to the delivery of the replacement cells to the myocardium. For example, the electrical stimulation may be applied prior to delivery of the replacement cells, during delivery of the replacement cells, after delivery of the replacement cells, or any combination of these. The timing of the delivery of the replacement cells to the myocardium by cell delivery device 34 may be determined as a function of the timing of the application of electrical stimulation to the spinal column by nerve stimulator 14.

In one embodiment, nerve stimulator 14 is initiated at a given time (e.g., about 1 month) prior to delivery of replacement cells to the myocardium. SCS delivered by nerve stimulator 14 may be continued and/or modified after delivery of the replacement cells by cell delivery device 34. In some embodiments, SCS is continued for a set period of time after delivery of the replacement cells (e.g., about 1 month), while in other embodiments SCS is continued indefinitely.

The nature of the electrical stimulation applied to the spinal column by nerve stimulator 14 may vary. The electrical stimulation can be applied to the spinal column using any SCS stimulus parameters known in the art, such as amplitude, pulse width, and pulse rate. In one embodiment, the stimulation parameters include a pulse amplitude of about 5 volts (V), a pulse width between about 10 microseconds and about 1,000 microseconds, and a pulse rate between about 30 Hertz (Hz) and about 80 Hz. The electrical stimulation can be applied in a continuous mode (i.e., continuous stimulation), a cycling mode (i.e., on for a set period of time and off for a set period of time), pursuant to any other mode known in the art, or in any combination of these.

In some embodiments, the nature of the electrical stimulation applied to the spinal column may be varied by nerve stimulator 14 during the course of treatment as a function of various factors. For example, in one embodiment, a first stimulation protocol is used by nerve stimulator 14 before delivery of the replacement cells to the myocardium, a second

stimulation protocol is used during delivery of the replacement cells to the myocardium by cell delivery device 34, and a third stimulation protocol is used after delivery of the replacement cells to the myocardium.

In some embodiments, lead(s) 16 are placed in the epidural space of the spinal column so that one or more electrodes 18 are located close enough to the dorsal horn to stimulate specific large nerve fibers. FIG. 3 shows a cross sectional view of spine 12 and adjacent tissue of patient 10 of FIGs. 1 and 2, with lead 16 and electrode 18 implanted in epidural space 50. Subdural space 54 located between dura mater 52 and arachnoid membrane 60 are included in FIG. 3 purposes of orientation.

Lead 16 and electrode 18 can be placed in epidural space 50 either surgically or percutaneously through a needle (e.g., a Tuohy needle). Optimal lead placement sites for angina pectoris patients include upper thoracic or lower cervical spinal locations. See U.S. Pat. No. 5,085,584. Thus, in some embodiments, lead 16 is positioned so that one or more electrodes are located in epidural space 50 of the upper thoracic or lower cervical vertebrae. In one embodiment, electrode(s) 18 is located in the epidural space of thoracic vertebrae T1, T2, and/or T3.

In other embodiments, SCS is accomplished by nerve stimulator 14 through transcutaneous electrical nerve stimulation (TENS). One or more electrodes are placed on skin that overlies, or is near to, the spinal column, and electrical stimulation is applied from the electrodes to the spinal column through the skin.

Any variety or combination of suitable replacement cells known in the art may be utilized in conjunction with the present invention. In some embodiments, the replacement cells are autologous to help avoid host rejection. In other embodiments, the replacement cells may be allogenic, xenogenic, or a combination of any of these (including autologous). While a risk of cell rejection is associated with allogenic and xenogenic cells, the use of such cells, when taken from established cell lines, overcomes the need to harvest and expand cells. Allogenic and xenogenic cells may be treated to reduce the risk of rejection.

Other examples of cell types useful in this invention include, but are not limited to, stem cells and progenitor cells derived from bone marrow and from blood; skeletal muscle progenitor cells (skeletal muscle myoblasts or adult stem cells derived from skeletal muscle are synonyms); cardiac progenitor cells (c-kit +); other stem cells; satellite cells;

other cells; and any combination of these in any proportion. For further discussion of replacement cells, see, for example, U.S. Pat. No. 6,671,558, U.S. Pat. No. 6,805,860, and U.S. Pat. App. 2004/0158289 (Application Serial No. 722,115) by Girouard, et al.

In some embodiments, cells are harvested from a patient and cultured outside the patient for a period of days or weeks to produce a population of replacement cells for delivery to the myocardium of the patient. In one embodiment, one or more electrodes 18 are implanted into, or near, the spinal column of the patient during the same procedure in which the cells are harvested from the patient.

A variety of exogenous stimuli may be applied to the replacement cells being delivered to the myocardium. For instance, the replacement cells may be conditioned *in vitro* with mechanical stimuli (e.g., applying cyclical mechanical stress to replacement cells to simulate the cyclical contraction of cardiac muscle cells *in vivo*), electrical stimuli (e.g., subjecting replacement cells to electrical conditions that simulate the electrical conditions in the myocardium which result in contraction of the heart muscle), or biological stimuli (e.g., exposure to differentiation factors, growth factors, angiogenic proteins, survival factors, and/or cytokines). See, for example, U.S. Pat. App. 2004/0158289 (Application Serial No. 722,115) by Girouard, et al. The conditioning may include continuous or intermittent exposure to the exogenous stimuli.

In some embodiments, the replacement cells may also be transfected *ex vivo* or *in vitro* to express one or more desired proteins (e.g., connexins and/or sodium channel subunits and/or calcium channel subunits).

The replacement cells can be coated or otherwise incorporated into a carrier to, for example, assist in localizing the replacement cells in the myocardium. In some embodiments, the replacement cells are delivered to the myocardium in a polymeric matrix made up of one or more synthetic or natural polymers compatible with the replacement cells. See, for example, U.S. Patent No. 6,671,558. In one embodiment, the polymeric matrix can be in the form of a porous scaffold, whereby the polymer matrix is seeded with replacement cells. See U.S. Patent No. 6,671,558.

In some embodiments, one or more growth factors or other chemical or biological agents may be injected into the myocardium before, after, and/or simultaneous with delivery of the replacement cells to help provide a more optimal environment for survival, engraftment, and/or differentiation of the replacement cells.

Thus, as described above, the present invention includes a system and method for delivering replacement cells to myocardial tissue of a patient and electrically stimulating the spinal column of the patient to affect a cellular environment for the replacement cells within the myocardium.

Although the present invention has been described with reference to preferred embodiments, workers skilled in the art will recognize that changes may be made in form and detail without departing from the metes and bounds and scope of the invention.

CLAIMS

1. A system for treating a myocardium of a patient, the system comprising:
a cell delivery device for delivering cells to the myocardium of the patient; and
a nerve stimulator for applying electrical stimulation to a spinal column of the patient, wherein the application of the electrical stimulation has a temporal relationship to the delivery of the cells to myocardium.

2. A system according to claim 1, wherein the nerve stimulator is programmed to apply electrical stimulation to the spinal column before the cells are delivered to the myocardium.

3. A system according to claim 1, wherein the nerve stimulator is programmed to apply electrical stimulation to the spinal column after the cells are delivered to the myocardium.

4. A system according to claim 1, wherein the nerve stimulator is programmed to apply electrical stimulation to the spinal column both before and after the cells are delivered to the myocardium.

5. A system according to claim 1, wherein the nerve stimulator is programmed to apply electrical stimulation to the spinal column while the cells are being delivered to the myocardium.

6. A system according to claim 1, wherein the nerve stimulator applies electrical stimulation to the spinal column through skin of the patient.

7. A system according to claim 1, wherein the nerve stimulator includes an electrode implanted into or near the spinal column.

8. A system according to claim 1, wherein the cell delivery device is configured to inject the cells into the myocardium.

9. A system according to claim 8, wherein the cell delivery device is configured to inject the cells into an infarcted region of the myocardium.

10. A system according to claim 1, wherein the cell delivery device is configured to introduce the cells into a vessel supplying blood to the myocardium.

11. A system according to claim 1, wherein the cells comprise stem cells.

12. A system according to claim 1, wherein the cells comprise myoblasts.

13. A system according to claim 1, wherein the nerve stimulator is programmed to apply the electrical stimulation during a period of time ranging from about a month prior to delivering the cells to the myocardium to about a month after the cell delivery device delivers the cells.

14. A method for treating damaged myocardial tissue of a myocardium of a patient, the method comprising:

preparing cells capable of enhancing myocardial tissue;

delivering the cells to the damaged myocardial tissue; and

electrically stimulating a spinal column of the patient to affect a cellular environment within the myocardium.

15. A method according to claim 14, wherein at least a portion of the electrical stimulation is applied during a period of time ranging from about a month prior to delivering the cells to the myocardium to about a month after delivering the cells.

16. A method according to claim 14, wherein preparing the cells comprises harvesting the cells from the patient and culturing the cells outside the patient.

17. A method according to claim 14, and further comprising:

delivering a growth factor to the damaged myocardial tissue.

18. A method according to claim 14, wherein the cells delivered to the damaged myocardial tissue are dispersed in a carrier material.

19. A method for treating a myocardium of a patient, the method comprising:

delivering cells to the myocardium of the patient; and

applying, to a spinal column of the patient, electrical stimulation capable of affecting myocardial blood flow.

20. A method according to claim 19, wherein applying electrical stimulation occurs during a time period between about one month prior to delivering cells and about one month subsequent to delivering cells.

FIG. 1

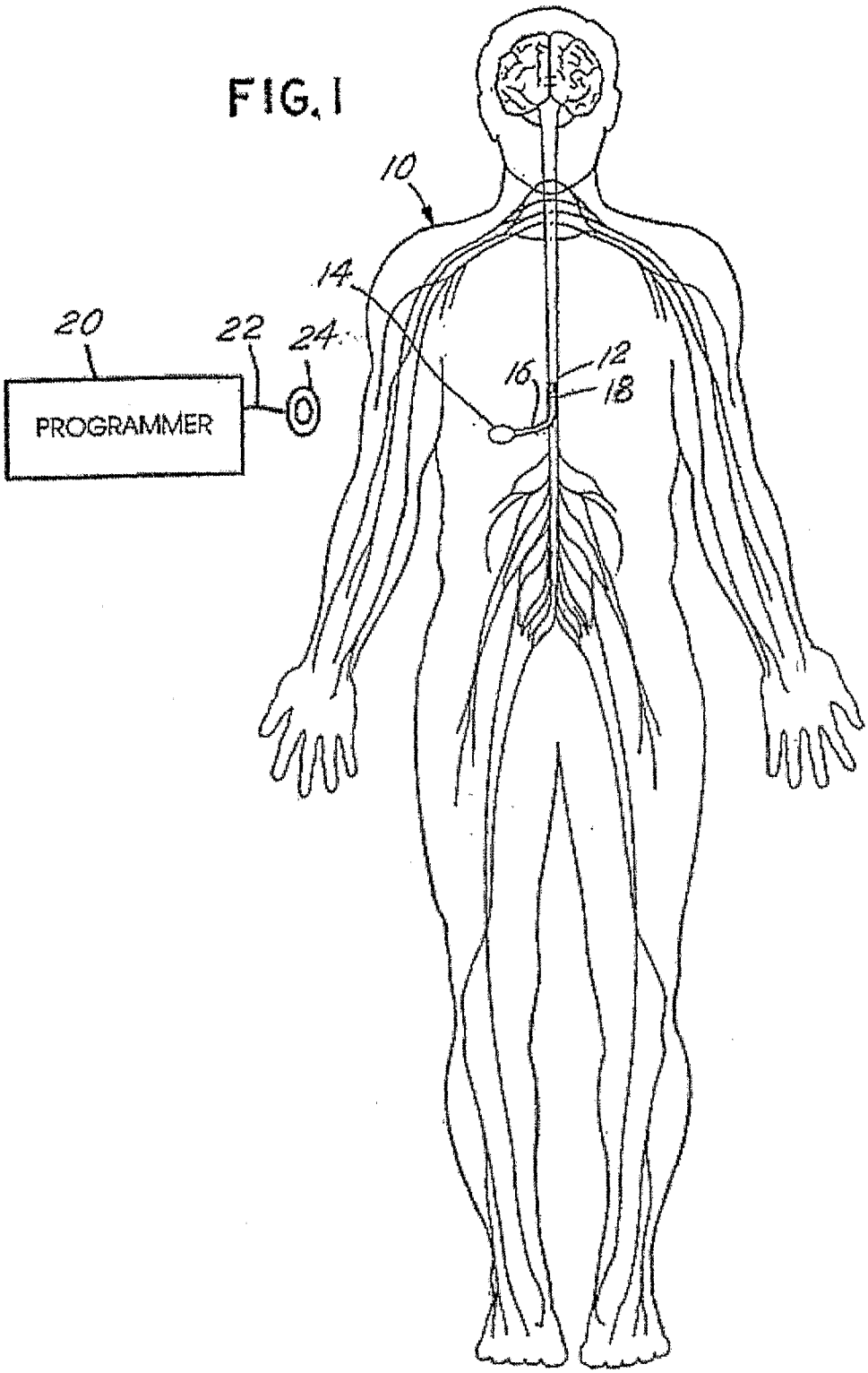
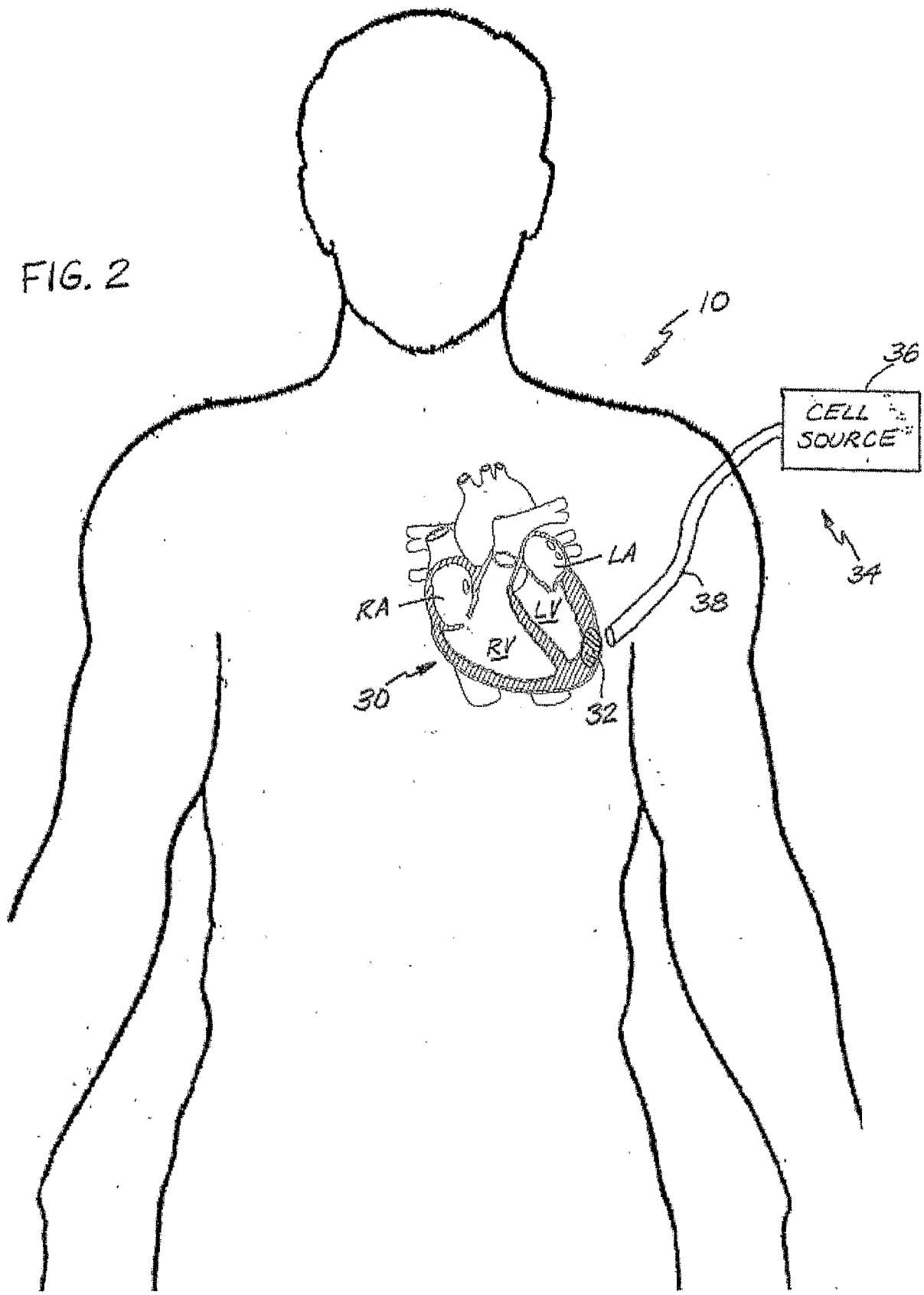


FIG. 2



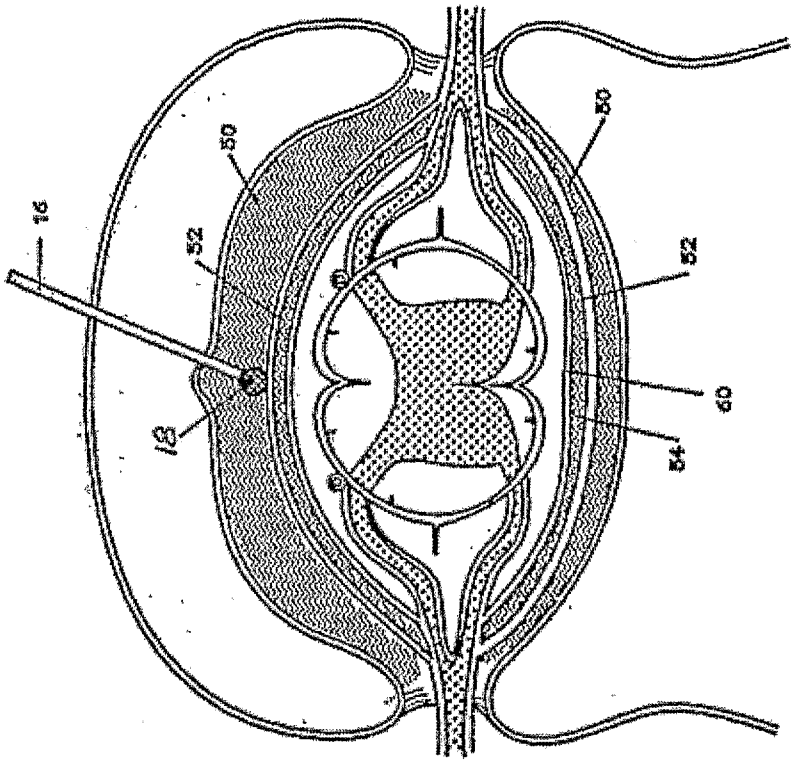


FIG. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/033107

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61N1/05 A61N1/362 A61M5/14 C12N5/06
ADD. A61N1/32

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)
A61N C12N A61M

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 practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/26319 A (MEDTRONIC INC [US]) 4 April 2002 (2002-04-04) figures 1,2 page 2, line 2 - page 4, line 5 page 5, line 4 - page 6, line 22 page 11, line 24 - page 12, line 14 page 15, line 3 - page 17, line 6 page 22, line 12 - page 25, line 7	1-10
A	WO 03/064637 A1 (MEDTRONIC INC [US]) 7 August 2003 (2003-08-07) page 7, line 9 - page 14, line 14 page 27, line 2 - page 28, line 12	1-13
A	US 2004/158289 A1 (GIROUARD STEVEN D [US] ET AL) 12 August 2004 (2004-08-12) cited in the application the whole document	1-13

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[X] Further documents are listed in the continuation of Box C.

[X] 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 document 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
17 January 2007	26/01/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ließmann, Frank

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/033107

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/082007 A2 (REGENT OF THE UNIVERSITY OF CA [US]; SEN LUYI [US]; CUI GUANGGEN [US];) 9 October 2003 (2003-10-09) the whole document	1-13
A	US 2004/162590 A1 (WHITEHURST TODD K [US] ET AL) 19 August 2004 (2004-08-19) the whole document	1-13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/033107

Box 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. [X] Claims Nos.: 14-20
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 therapy and/or 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 III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/033107

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 6487446 B1	26-11-2002
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US 2004162590 A1	19-08-2004	NONE	