PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	02 AUG 2007
Applicant's or agent's file reference 48169.000009	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US06/14790	19 April 2006	20 April 2005

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61M 31/00 (2007.01)
USPC - 604/522

Applicant Medtronic, Inc.

1. This opinion contains indications relating to the following items:

- [X] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [X] Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	05 June 2007	Blaine Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US06/14790

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing

      ☐ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US06/14790

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	2, 6-8, 12-13, 20	YES
	Claims	1, 3-5, 9-11, 14-19, 21-23	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-23	NO
Industrial applicability (IA)	Claims	1-23	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1, 3-5, 9-11, 14-19, 21-23 lack novelty under PCT Article 33(2) as being anticipated by 5,840,059 to March et al.

Regarding claim 1, March et al disclose a method for delivering therapeutic cells to the heart of a subject (Abstract), comprising: a) forming one or more channels (Col. 2, lines 49-60) within a region of a wall of the subject's heart which includes a myocardial layer (Col. 5, lines 15-18); and b) delivering to said region a composition comprising living cells (Col. 3, lines 40-45) and a biocompatible matrix (Col. 3, lines 20-25, Col. 7, lines 25-35) that forms in situ upon exposure to a physiological condition, wherein said living cells provide a therapeutic effect (Abstract).

Regarding claim 3, March et al disclose that as applied above and further teach wherein the cells are recombinantly engineered to provide the therapeutic effect (Abstract).

Regarding claim 4, March et al disclose that as applied above and further teach wherein the therapeutic cells secrete a growth factor (Col. 6, lines 40-45).

Regarding claim 5, March et al disclose that as applied above and further teach wherein the growth factor is selected from the group consisting of vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF-BB, PDGF-CC or PDGF-DD), angiopoietin-I (Ang-1), acidic fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF), and transforming growth factor (TGF-f) (Col. 6, lines 40-45).

Regarding claim 9, March et al disclose that as applied above and further teach wherein the physiological condition is selected from the group consisting of temperature, pH, water content and ion concentration (Col. 7, lines 25-45). It is noted that the biodegradable polymer matrix becomes viscous upon the action of that action of the body by any one or combination of the above.

Regarding claim 10, March et al disclose that as applied above and further teach wherein the biocompatible matrix is selected from the group consisting of a thermoplastic paste, an in situ crosslinked system, such as a thermoset or an ion-mediated gelating system; an in situ precipitating system with a sol-gel transition induced by solvent removal, temperature or pH; and an organogel (Col. 3, lines 20-25, Col. 7, lines 25-45).

Regarding claim 11, March et al disclose that as applied above and further teach wherein the biocompatible matrix comprises components selected from the group consisting of O,L-lactide, glycolide, c-caprolactone, trimethylene carbonate, dioxanone, ortho esters, poly (ethylene glycol) , alginate, sucrose acetate isobutyrate, poly(lactide-co-glycolide}, poly(acrylic acid}, poly (N-isopropylacrylamide) (PNIPAAM), methylcellulose (MC), MC-grafted PNIPAAM, poly(ethylene glycol}-poly(lactic acid)poly(ethyleneglycol} triblocks (PEG-PLA-PEG), PEG-PLA diblock copolymers, poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide} (PEO-PPO-PEO) triblocks (Pluronics® or Poloxamer®), capped PEO-PPO-PEO, PEO-poly (L-lactic acid-eo-glycolic acid) (PEO-PLLGA) , PEO-poly (Ollactic acid-eo-glycolic acid (PEO-PLGA) block and graft copolymers, PEG-PLGA-PEG, PLGA-PEG-PLGA, poly(organophosphazene)s, chitosan-based and silk-elastin polymers, hydroxypropyl-cellulose (Carbopol®) , chitosan, peanut oil and waxes (Col. 3, lines 20-25, Col. 7, lines 25-45).

Regarding claim 14, March et al disclose that as applied above and further teach wherein the composition further comprises one or more therapeutic agents (Col. 5, lines 62-67).

Regarding claim 15, March et al disclose that as applied above and further teach wherein the therapeutic agent or agents is selected from the group consisting of vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF-BB, PDGF-CC or PDGF-DD), angiopoietin-I (Ang-I), acidic fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF), and transforming growth factor (TGF) , estrogen, heparin sulphates and oligomeric regenerating agents (RGTAs) (Col. 5, lines 62-67)..

Regarding claim 16, March et al disclose that as applied above and further teach wherein the subject is a patient suffering from heart disease (Col. 1, lines 5-20).

Regarding claim 17, March et al disclose a system for delivering therapeutic cells to the heart of a subject (Abstract), comprising: a) means for forming one or more channels (Col. 2, lines 49-60) within a region of a wall of the subject' s heart which includes a myocardial layer (Col. 5, lines 15-18); (b) means for introducing into said region a composition comprising living cells (Col. 3, lines 40-45) and a biocompatible matrix (Col. 3, lines 20-25, Col. 7, lines 25-35) that forms in situ upon exposure to a physiological condition, wherein said living cells provide a therapeutic effect (Abstract).

Regarding claim 18, March et al disclose that as applied above and further teach wherein the channel forming means is selected from the group consisting of laser transmyocardial revascularization, high frequency current transmyocardial revascularization, percutaneous laser myocardial revascularization, high frequency current myocardial revascularization, mechanical transmyocardial revascularization and mechanical percutaneous myocardial revascularization (Col2, lines 60-63).

Regarding claim 19, March et al disclose that as applied above and further teach wherein the channel forming means comprises a catheter (10).

Continued in Supplemental Box

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V

Regarding claim 21, March et al disclose that as applied above and further teach wherein the composition introducing means comprises a catheter (10).
Regarding claim 22, March et al disclose that as applied above and further teach wherein the composition introducing means further comprises a delivery element selected from the group consisting of a hollow needle, a coated delivery surface, a perfusion port and a delivery lumen (Col. 4, lines 1-5).
Regarding claim 23, March et al disclose that as applied above and further teach wherein the subject is a patient suffering from heart disease (Col. 1, lines 5-20).

Claims 2, 6-8, 12-13, and 20 lack an inventive step under PCT Article 33(3) as being obvious over United States patent number 5,840,059 to March et al in view of United States patent number 6,151,525 to Soykan et al.
Regarding claim 2, March et al disclose that as applied above. March et al does not show wherein the cells provide the therapeutic effect naturally. Soykan et al show wherein the cells provide the therapeutic effect naturally (Abstract). It would have been obvious at the time the invention was made to a person having ordinary skill in the art to employ natural cells as taught by Soykan et al in the process of March et al in order to provide a more effective range of medical treatment because different patients will respond differently to the presence of differentiated cells and cells harvested from the individual will produce a neutral antibody response.
Regarding claim 6, March et al disclose that as applied above. March et al does not show wherein the therapeutic cells are contractile cells. Soykan et al show wherein the therapeutic cells are contractile cells (Abstract). It would have been obvious at the time the invention was made to a person having ordinary skill in the art to employ natural cells as taught by Soykan et al in the process of March et al in order to provide a more effective range of medical treatment because different patients will respond differently to the presence of differentiated cells and cells harvested from the individual will produce a neutral antibody response.
Regarding claim 7, March et al disclose that as applied above. March et al does not show wherein the therapeutic cells are selected from the group consisting of hematopoietic stem cells (including bone marrow, circulating and umbilical cells), mesenchymal stem cells, myoblasts (including skeletal and cardiac myoblasts), satellite cells, embryonic stem cells or progenitor cells (including endothelial progenitor cells and cardiac progenitor cells), cardiomyocytes, fibroblasts and skeletal myocytes. Soykan et al show , wherein the therapeutic cells are selected from the group consisting of hematopoietic stem cells (including bone marrow, circulating and umbilical cells), mesenchymal stem cells, myoblasts (including skeletal and cardiac myoblasts), satellite cells, embryonic stem cells or progenitor cells (including endothelial progenitor cells and cardiac progenitor cells), cardiomyocytes, fibroblasts and skeletal myocytes (Col. 6, lines 5-15). It would have been obvious at the time the invention was made to a person having ordinary skill in the art to employ natural cells as taught by Soykan et al in the process of March et al in order to provide a more effective range of medical treatment because different patients will respond differently to the presence of differentiated cells and cells harvested from the individual will produce a neutral antibody response.
Regarding claim 8, March et al disclose that as applied above. March et al does not show wherein the therapeutic cells are obtained from allogeneic, xenogeneic, transgeneic, or autogeneic sources. Soykan et al show wherein the therapeutic cells are obtained from allogeneic, xenogeneic, transgeneic, or autogeneic sources (Col. 7, lines 5-10). It would have been obvious at the time the invention was made to a person having ordinary skill in the art to employ natural cells as taught by Soykan et al in the process of March et al in order to provide a more effective range of medical treatment because different patients will respond differently to the presence of differentiated cells and cells harvested from the individual will produce a neutral antibody response.
Regarding claim 12, March et al disclose that as applied above. March et al does not show wherein the components are modified to facilitate cell adhesion and cell growth. Soykan et al show wherein the components are modified to facilitate cell adhesion and cell growth (Col. 12, lines 40-50). It would have been obvious at the time the invention was made to a person having ordinary skill in the art to employ natural cells as taught by Soykan et al in the process of March et al in order to provide a more effective range of medical treatment because different patients will respond differently to the presence of differentiated cells and cells harvested from the individual will produce a neutral antibody response.
Regarding claim 13, March et al disclose that as applied above. March et al does not show wherein the modification includes the introduction of RGD-sites. Soykan et al show wherein the modification includes the introduction of RGD-sites (Col. 12, lines 40-50). It is noted that sites promoting cell adhesion and growth are obviously RGD-sites. It would have been obvious at the time the invention was made to a person having ordinary skill in the art to employ natural cells as taught by Soykan et al in the process of March et al in order to provide a more effective range of medical treatment because different patients will respond differently to the presence of differentiated cells and cells harvested from the individual will produce a neutral antibody response.
Regarding claim 20, March et al disclose that as applied above. March et al does not show wherein the channel forming means comprises a hollow needle. Soykan et al show wherein the channel forming means comprises a hollow needle (Col. 16, lines 15-20). It would have been obvious at the time the invention was made to a person having ordinary skill in the art to employ natural cells as taught by Soykan et al in the device of March et al in order to provide a more effective range of medical treatment because different patients will respond differently to the presence of differentiated cells and cells harvested from the individual will produce a neutral antibody response.

Claims 1-23 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.