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A61P 3/10 (2006.01)

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

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[Continued on next page]

(54) Title: PANCREATIC DUCT PROGENITOR CELLS AND MICRORNA OBTAINED THEREFROM FOR USE IN TISSUE REGENERATION

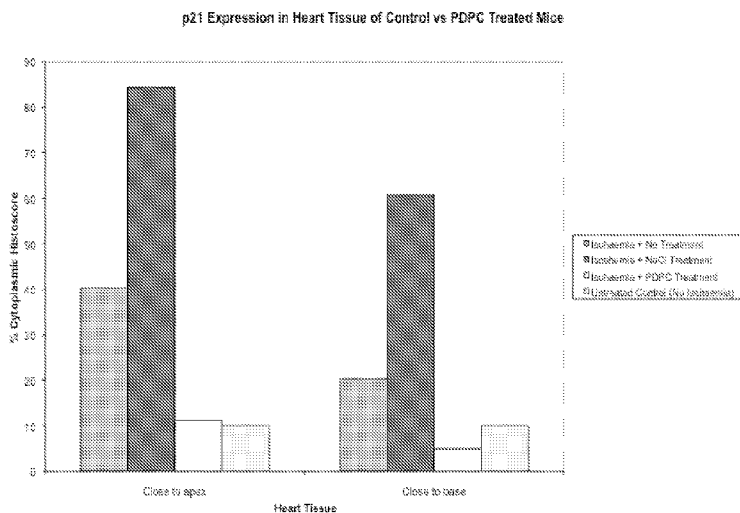


Figure 3

(57) Abstract: The present invention provides, among other things, improved compositions and methods for the treatment of tissue damage (e.g., acute or chronic) and related diseases, disorders or conditions based on the use of pathfinder cells, extracellular secretomes thereof, and/or pathfinder cell-associated micro RNAs. In some embodiments, the present invention provides a method for treating tissue damage (e.g., acute or chronic) comprising a step of administering a population of cells to an individual suffering from a disease, disorder or condition characterized by acute damage to one or more tissues, wherein the cells are originated from an adult tissue and wherein the cells induce tissue repair, regeneration, remodeling, reconstitution or differentiation. In some embodiments, the present invention provides a method for treating inflammation comprising a step of administering a population of cells, or extracellular secretomes thereof, to an individual suffering from a disease, disorder or condition characterized by inflammation of one or more tissues, wherein the cells are originated from an adult tissue and wherein the cells induce an anti-inflammatory response.

WO 2012/020308 A3

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

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11 April 2013

INTERNATIONAL SEARCH REPORT

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| International application No PCT/IB2011/002048 |
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|---|--|--|--|--|
| A. CLASSIFICATION OF SUBJECT MATTER | | | | |
| INV. A61K35/22 | A61K35/39 | G01N33/50 | | |
| A61P13/12 | C12N15/113 | A61P3/10 | | |
| A61P9/10 | | | | |
| ADD. | | | | |
| 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) A61K C12N G01N | | | | |
| 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, BIOSIS, EMBASE | | | | |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT | | | | |
| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. | | |
| A | WO 2006/120476 A1 (UNIV GLASGOW [GB]; SHIELS PAUL G [GB]; DAVIES R WAYNE [GB]) 16 November 2006 (2006-11-16) cited in the application the whole document ----- -/-- | 1-4, 7-14, 16-22, 26-33, 38-43, 47-49 | | |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex. | | | | |
| * Special categories of cited documents : <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> "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 </td> <td style="width: 50%; border: none; vertical-align: top;"> "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 </td> </tr> </table> | | | "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 |
| "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 | | | |
| 27 July 2012 | 14/02/2013 | | | |
| 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 Hars, Jesko | | | |

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/002048

| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT | | |
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| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| X,P | <p>anonymous: "Pathfinder Cells Demonstrate Ability to Regenerate Damaged Tissue and Restore Pancreatic Function in a Diabetic Mouse Model", 29 March 2011 (2011-03-29), pages 1-4, XP002680741, Retrieved from the Internet: URL:http://www.prnewswire.com/news-releases/pathfinder-cells-demonstrate-ability-to-regenerate-damaged-tissue-and-restore-pancreatic-function-in-a-diabetic-mouse-model-118833319.html [retrieved on 2012-07-24] the whole document</p> | <p>1-4, 7-14, 16-22, 26-33, 38-43, 47-49</p> |
| A,P | <p>STEVENSON KAREN ET AL: "Pancreatic-derived pathfinder cells enable regeneration of critically damaged adult pancreatic tissue and completely reverse streptozotocin-induced diabetes", REJUVENATION RESEARCH,, vol. 14, no. 2, 19 March 2011 (2011-03-19) , pages 163-171, XP009159613, ISSN: 1557-8577 the whole document</p> | <p>1-4, 7-14, 16-22, 26-33, 38-43, 47-49</p> |

INTERNATIONAL SEARCH REPORT

International application No
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| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT | | |
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| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| A | <p>LEO A. B. JOOSTEN ET AL: "Role of interleukin-4 and interleukin-10 in murine collagen-induced arthritis. Protective effect of interleukin-4 and interleukin-10 treatment on cartilage destruction", ARTHRITIS & RHEUMATISM, vol. 40, no. 2, 1 February 1997 (1997-02-01), pages 249-260, XP055033715, ISSN: 0004-3591, DOI: 10.1002/art.1780400209 the whole document</p> | <p>1-4, 7-14, 16-22, 26-33, 38-43, 47-49</p> |
| T | <p>----- anonymous: "Pathfinder Cell Therapy, Inc. - FORM 10-K - March 30, 2012", 30 March 2012 (2012-03-30), pages 1-65, XP002680742, Retrieved from the Internet: URL:http://www.faq.s.org/sec-filings/120330/SyntheMed-Inc 10-K/ [retrieved on 2012-07-24] page 6</p> | |
| X | <p>----- K. E.A. VAN DER BOGT ET AL: "Comparison of Different Adult Stem Cell Types for Treatment of Myocardial Ischemia", CIRCULATION, vol. 118, no. 14 suppl 1, 30 September 2008 (2008-09-30), pages S121-S129, XP055033790, ISSN: 0009-7322, DOI: 10.1161/CIRCULATIONAHA.107.759480 the whole document & Koen Van Der Bogt: "SUPPLEMENT METHODS", 30 September 2008 (2008-09-30), pages 1-5, XP055033793, Retrieved from the Internet: URL:http://circ.ahajournals.org/content/suppl/2008/09/29/118.14_suppl_1.S121.DC1/Koen_Online_Supplement_Final.pdf [retrieved on 2012-07-25] the whole document</p> | <p>1-4, 7-14, 16-22, 26-33, 38-43, 47-49</p> |
| A | <p>----- WO 2010/056737 A2 (MIRNA THERAPEUTICS INC [US]; PATRAWALA LUBNA [US]; TANG DEAN G; KELNAR) 20 May 2010 (2010-05-20) the whole document</p> | <p>1-4, 7-14, 16-22, 26-33, 38-43, 47-49</p> |
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INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2011/002048

| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT | | |
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| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| A | <p>HU, SHIJUN ET AL.: "Abstract 3981: MicroRNA-210 as a Novel Therapy for Treatment of Ischemic Heart Disease", CIRCULATION</p> <p>, vol. 120, no. 18 MeetingAbstracts 3 November 2009 (2009-11-03), pages 1-1, XP002680934, Retrieved from the Internet: URL:http://circ.ahajournals.org/cgi/content/meeting_abstract/120/18_MeetingAbstracts/S899-b [retrieved on 2012-07-26] the whole document</p> | <p>1-4, 7-14, 16-22, 26-33, 38-43, 47-49</p> |
| A,P | <p>S. HU ET AL: "MicroRNA-210 as a Novel Therapy for Treatment of Ischemic Heart Disease", CIRCULATION, vol. 122, no. 11 suppl 1, 14 September 2010 (2010-09-14), pages S124-S131, XP055029627, ISSN: 0009-7322, DOI: 10.1161/CIRCULATIONAHA.109.928424 the whole document</p> | <p>1-4, 7-14, 16-22, 26-33, 38-43, 47-49</p> |
| A | <p>----- DATABASE miRBase [Online]</p> <p>2007, "Stem-loop sequence hsa-mir-210", XP002680935, Database accession no. MI0000286 the whole document</p> | <p>1-4, 7-14, 16-22, 26-33, 38-43, 47-49</p> |
| A | <p>----- DATABASE miRBase [Online]</p> <p>2007, "Stem-loop sequence mmu-mir-210", XP002680936, Database accession no. MI0000695 the whole document</p> <p>-----</p> | <p>1-4, 7-14, 16-22, 26-33, 38-43, 47-49</p> |

INTERNATIONAL SEARCH REPORT

Information on patent family members

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| International application No PCT/IB2011/002048 |
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| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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| | | WO 2010056737 A2 | 20-05-2010 |
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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.:
because they relate to subject matter not required to be searched by this Authority, namely:

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.:

4(completely); 1-3, 7-14, 16-22, 26-33, 38-43, 47-49(partially)

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: 4(completely); 1-3, 7-14, 16-22, 26-33, 38-43, 47-49(partially)

Treatment of acute tissue damage or repairing / regenerating tissue with cells originated from adult tissue, wherein the cells induce tissue repair, regeneration, remodeling, reconstitution or differentiation and wherein the acute damage is ischemic damage as associated with myocardial infarct or acute renal failure .

2. claims: 5, 37(completely); 1-3, 8-14, 16-22, 26-33, 38-43, 47-49(partially)

Treatment of acute tissue damage or repairing / regenerating tissue with cells as defined in invention 1, wherein the acute damage is associated with tissue transplantation , or a method oforgan transplantation comprising administering to an organ transplant recipient said cells.

3. claims: 1-3, 6, 8-14, 16-22, 26-33, 38-43, 47-49(all partially)

Treatment of acute tissue damage or repairing / regenerating tissue with cells as defined in invention 1, wherein the acute damage is associated with radiation injury or therapy.

4. claims: 1-3, 6, 8-14, 16-22, 26-33, 38-43, 47-49(all partially)

Treatment of acute tissue damage or repairing / regenerating tissue with cells as defined in invention 1, wherein the acute damage is associated with chemical injury or therapy.

5. claims: 1-3, 7-14, 16-22, 26-33, 38-43, 47-49(all partially)

Treatment of acute tissue damage or repairing / regenerating tissue with cells as defined in invention 1, wherein the acute damage is characteristic of type I diabetes.

6. claims: 15(completely); 16-22, 26-33(partially)

Treatment of acute tissue damage with cells as defined in invention 1, wherein the cells are first treated to reduce a telomeric attrition rate before the cultivating step.

- 7-616. claims: 23-25, 34-36, 44-46, 50, 51(completely); 26-33, 38-43, 47-49(partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Treatment of acute tissue damage or repairing / regenerating tissue with microRNA of any of SEQ ID NO:1-610, optionally present within cells as defined in invention 1, wherein each individual microRNA sequence of SEQ ID NO:1-610 represents a single invention.

617. claims: 52, 54-73(all partially)

A method of treating inflammation by administering cells that originate from an adult tissue and induce an anti-inflammatory response.

618. claims: 53(completely); 52, 54-73(partially)

A method of treating inflammation by administering extracellular secretomes of cells that originate from an adult tissue and induce an anti-inflammatory response.
