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- (71) **Applicant (for all designated States except US):** **THE J. DAVID GLADSTONE INSTITUTES** [US/US]; 1650 Owens Street, San Francisco, California 94158 (US).
- (72) **Inventors; and**
- (75) **Inventors/Applicants (for US only):** **SRIVASTAVA, Deepak** [US/US]; 619 Marina Boulevard, San Francisco, California 94123 (US). **IVEY, Kathryn Nicole** [US/US]; 451 Kansas Street #490, San Francisco, California 94107 (US).
- (74) **Agent:** **BORDEN, Paula, A.**; Bozicevic, Field & Francis LLP, 1900 University Avenue, Suite 200, East Palo Alto, California 94303 (US).
- (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, 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, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
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(54) **Title:** METHODS OF GENERATING CARDIOMYOCYTES AND CARDIAC PROGENITORS AND COMPOSITIONS

(57) **Abstract:** The present disclosure provides methods of inducing cardiomyogenesis in a stem cell or progenitor cell, or in a population of stem cells or progenitor cells; and methods for expansion of (increasing the numbers of) cardiac progenitors. Cell compositions are also provided.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/31288

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - C12Q 1/68; A61K 31/7105 (2009.01) USPC - 435/6, 514/44 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) IPC: C12Q 1/68 USPC: 435/6, 514/44 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched IPC: A61K 31/7105 USPC: 514/453, 42, 23 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PubWest(PGPB,USPT,EPAB,JPAB); Google Scholar Search Terms: stem cell, matrix, cardiomyocyte, biocompatible substrate, isolate, microRNA-1, microRNA1, or microRNA 1, induced, pluripotent stem cell, miR-1, miR1		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2006/0246491 A1 (SRIVASTAVA) 2 Nov 2006 (02.11.2006) para [0007], [0008], [0015], [0021], [0049], [0055], [0085], [0106], [0129]	1, 2, 5, 7-10, 20-26
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Y		3, 4, 6, 11-13, 27-29
Y	US 2005/0059005 A1 (TUSCHL, ET AL.) 17 March 2005 (17.03.2005) SEQ ID NO: 283	3, 4, 6
Y	US 2004/0126879 A1 (SCHEIDER, ET AL.) 1 July 2004 (01.07.2004) para [0128]	11
Y	US 2007/0031389 A1 (MICKLE, ET AL.) 8 Feb 2007 (08.02.2007) para [0022]	12, 13
Y	US 2007/0212423 A1 (EPSTEIN, ET AL.) 13 Sept 2007 (13.09.2007) para [0050] and [0133]	13, 27-29
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/>		
* 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 28 May 2009 (28.05.2009)		Date of mailing of the international search report 12 JUN 2009
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201		Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

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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:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I claims 1-13 are directed to a method of inducing cardiomyogenesis in an induced pluripotent stem (iPS) cell wherein the miR-1 nucleic acid comprises a nucleotide sequence having at least about 85% nucleotide sequence identity to nucleotides 7-69 of the nucleotide sequence set forth in SEQ ID NO: 1.

Group II claims 14-19 are directed to a method of inducing expansion of a cardiac progenitor cell wherein the miR-133 nucleic acid comprises a nucleotide sequence having at least 75% nucleotide sequence identity with nucleotides 7-83 of the nucleotide sequence set forth in SEQ ID NO:5.

****Con't on Extra 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 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.: 1-13 and 20-29

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.

INTERNATIONAL SEARCH REPORT

International application No.

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Con't of Box III

Claims 20-29 are generic for both Groups I and II.

Groups I and II have the shared technical feature of inducing expansion of a cardiac progenitor cell by introducing microRNAs. However, this is not an improvement over the prior art of US 2006/0246491 A1 to Srivastava (2 November 2006) that teaches inducing expansion of a cardiac progenitor cell by introducing microRNAs (abstract, para [0008] specifically teaching miR-1 and miR-133 nucleic acids). Further, the nucleotides represented by the unique sequences as designated SEQ ID NO:1 and SEQ ID NO:5 do not relate to a single general inventive concept because, under PCT Rule 13.2, the different nucleotides represented by the sequences are not common to one another but are different because they are composed of unique nucleic acid sequences. (Note that SEQ ID NO:2 is a smaller, wholly contained fragment of SEQ ID NO:1 and SEQ ID NO:8 is a smaller, wholly contained fragment of SEQ ID NO:5).