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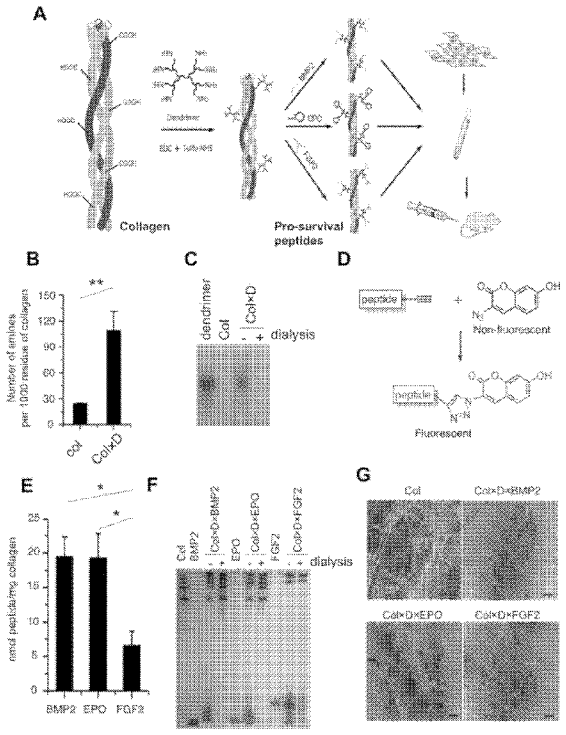
(54) Title: IMPLANTABLE BIOMATERIALS THAT ENHANCE STEM CELL SURVIVAL AND FUNCTION

FIG. 1



(57) Abstract: The present invention is directed to formulations comprising implantable or injectable biomaterials and methods for transplantation using the biomaterials to support enhanced survival of stem cells in tissues or organs after transplantation. In one embodiment, an implantable biomaterial comprises a scaffold comprising a matrix and one or more dendrimers crosslinked to the matrix. One more or peptides or peptide analogs are crosslinked to the dendrimers, or the matrix, or both. The matrix itself comprises one or more of a collagen, a hyaluronic acid, a chondrointin sulfate, or an extracellular matrix component. The biomaterials and the methods for administering them disclosed herein facilitate a slow release of the peptides or peptide analogs to prolong the stem cell survival, cell growth or both.

WO 2019/148140 A3

[Continued on next page]

GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

— *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))*

(88) Date of publication of the international search report:
19 September 2019 (19.09.2019)

INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61L 27/52; A61K 31/74, 47/34; C07K 16/18 (2019.01)

CPC - A61L 27/52; A61K 31/74, 47/34; C07K 16/18

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)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	WO 2017/196986 A1 (MASSACHUSETTS INSTITUTE OF TECHNOLOGY) 16 November 2017; page 23, lines 6-25; page 24, lines 14-17; page 29, line 16; page 31, lines 7-10; page 38, lines 16-21; page 40, lines 3-4; claims 1, 27, 42	1-4, 16-20, 23-32, 36-37, 51-52 ---------- 7, 10-12, 14, 21-22, 33-35, 40, 43-45, 47, 49-50
Y	EP 1 288 228 B1 (NISHIMURA, Y et al.) 5 March 2003; paragraphs [0037], [0041]	7, 10, 40, 43
Y	(DYER, LA et al.) The Role of BMPs in Endothelial Cell Function and Dysfunction. Trends in Endocrinology and Metabolism. 4 June 2014; Vol. 25, No. 9; pages 1-20; page 7, paragraph 4; DOI: 10.1016/j.tem.2014.05.003	11-12, 14, 44-45, 47
Y	WO 2011/087768 A1 (STRYKER CORPORATION) 21 July 2011; paragraph [0084]	21, 49
Y	US 2014/0220688 A1 (MEDTRAIN TECHNOLOGIES LLC.) 7 August 2014; abstract; paragraph [0005]	22, 50
Y	(DING, X et al.) Increased Stem Cells Delivered using a Silk Gel/Scaffold Complex for Enhanced Bone Regeneration. Scientific Reports. 19 May 2017; Vol. 7, No. 1; pages 1-10; abstract; page 2, paragraph 3; DOI: 10.1038/s41598-017-02053-z	33
Y	WO 2016/025394 A2 (BOARD OF SUPERVISORS OF LOUISIANA STATE UNIVERSITY AND AGRICULTURAL AND MECHANICAL COLLEGE) 18 February 2016; abstract; claim 1	34

☒ 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
10 July 2019 (10.07.2019)	18 JUL 2019
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US19/15482

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☒ furnished subsequent to the international filing date for the purposes of international search only:

      ☒ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☒ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US19/15482

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:
-***-Please See Supplemental Page-***-

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.:
Group 1+ Claims 1-4, 7, 10-12, 14, 16-37, 40, 43-45, 47 and 49-52; BMP2 encompassing SEQ ID NO: 7 (peptide)

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.
PCT/US19/15482

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2012/0009249 A1 (MATTERN, C) 12 January 2012; claim 47	35

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US19/15482

-***-Continued from Box III: Observations where unity of invention is lacking-***-

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.

Groups I+, Claims 1-52 and BMP2 encompassing SEQ ID NO: 7 (peptide) are directed toward an implantable biomaterial and a method for transplantation therewith.

The implantable biomaterial and method will be searched to the extent they encompass BMP2 encompassing SEQ ID NO: 7 (first exemplary peptide). Applicant is invited to elect additional peptide(s), with, where applicable, specified SEQ ID NO: for each, or with specified substitution(s) at specified site(s) of a SEQ ID NO:, such that the sequence of each elected species is fully specified (i.e. no optional or variable residues or substituents), to be searched. Additional peptide(s) and, where applicable, associated sequence(s) will be searched upon the payment of additional fees. It is believed that claims 1-3, 4 (in-part), 7 (in-part), 10 (in-part), 11, 12 (in-part), 14 (in-part), 16-36, 37 (in-part), 40 (in-part), 43 (in-part), 44, 45 (in-part), 47 (in-part), and 49-52 encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass BMP2 encompassing SEQ ID NO: 7 (peptide). Applicants must specify the claims that encompass any additionally elected peptide(s) and/or associated sequence(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be BMP2 encompassing SEQ ID NO: 8 (peptide).

No technical features are shared between the peptides of Groups I+ and, accordingly, these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features including: an implantable biomaterial comprising: a scaffold comprising a matrix and one or more dendrimers crosslinked to the matrix; and one more or peptides or peptide analogs crosslinked to the dendrimers or the matrix, or both; wherein the matrix comprises a collagen, a hyaluronic acid, a chondroitin sulfate, an extracellular matrix component, or combinations thereof; and a method for transplantation comprising: preparing a scaffold comprising a matrix and one or more dendrimers crosslinked to the matrix, wherein the matrix comprises one or more of a collagen, a hyaluronic acid, a chondrointin sulfate, or an extracellular matrix component; crosslinking one more or peptides or peptide analogs to the dendrimers or the matrix, or both, to yield an implantable biomaterial; and administering the biomaterial to a tissue or an organ site; these shared technical features are previously disclosed by US 2008/0031916 A1 to Sheardown et al. (hereinafter 'Sheardown').

Sheardown discloses an implantable biomaterial (a material suitable for use as a tissue engineering scaffold in vivo (an implantable biomaterial); paragraph [0008]) comprising: a scaffold comprising a matrix (comprising: a scaffold comprising a matrix; paragraph [0008]) and one or more dendrimers crosslinked to the matrix (one or more dendrimers crosslinked to the matrix; paragraph [0008]); and one more or peptides or peptide analogs (one more or peptides or peptide analogs; paragraphs [0008], [0037]) crosslinked to the dendrimers or the matrix (covalently attached (crosslinked) to the dendrimers; paragraphs [0006], [0087]); wherein the matrix comprises a collagen (wherein the matrix comprises a collagen; paragraph [0008]); and a method comprising: preparing a scaffold comprising a matrix and one or more dendrimers crosslinked to the matrix (a method comprising: preparing a scaffold comprising a matrix and one or more dendrimers crosslinked to the matrix; paragraph [0010]), wherein the matrix comprises a collagen (wherein the matrix comprises a collagen; paragraph [0008]); crosslinking one more or peptides or peptide analogs to the dendrimers (covalently attaching (crosslinking) one more or peptides or peptide analogs to the dendrimers; paragraphs [0006], [0008], [0037], [0087]), to yield an implantable biomaterial (to yield a material suitable for use as a tissue engineering scaffold in vivo (an implantable biomaterial); paragraphs [0008], [0010], [0087]). Sheardown further discloses use of the biomaterial for the delivery of biomolecules to a desired site in vivo (use of the biomaterial for the delivery of biomolecules to a desired site in vivo; paragraphs [0008], [0035]).

Sheardown does not disclose: a method for transplantation; and administering the biomaterial to a tissue or an organ site. However, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the disclosure of Sheardown to have included the transplantation of the implantable biomaterial disclosed by Sheardown at a desired tissue or organ site to accomplish the biomolecule delivery disclosed by Sheardown.

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Sheardown reference, unity of invention is lacking.