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(54) Title: COMPOSITIONS AND METHODS FOR GENERATING MUSCULOSKELETAL TISSUE

(57) Abstract: The present disclosure provides compositions comprising musculoskeletal cells and mesenchymal stem cells in discrete regions. The present disclosure provides systems comprising a subject composition; and methods of using a subject composition to generate cartilage, bone, tendon, muscle, intervertebral disc, or other musculoskeletal tissues.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/03189

<p>A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - C12N 5/08 (2009.01) USPC - 435/372 According to International Patent Classification (IPC) or to both national classification and IPC</p>												
<p>B. FIELDS SEARCHED</p> <p>Minimum documentation searched (classification system followed by classification symbols) IPC8 : C12N 5/08 (2009.01) USPC : 435/372</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched IPC8 : C12N 5/00, A61K 35/12, A61L 27/00, A61L 27/38, A61L 27/40 (2009.01) USPC : 424/93.1, 424/93.2, 424/93.7, 424/520, 424/548, 424/549, 424/572, 435/325, 435/377, 435/405, 435/366</p> <p>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:density, ratio, envelop\$, encapsulat\$, spher\$, globular, circular, cube, cuboid, cubic, mesenchymal stem cell, nucleus pulposus, chondroblast, chondrocyte, osteoblast, osteocyte, myoblast, myocyte, tenocyte, multilayer\$, bilayer, plural\$, composition, pellet,construct\$, matrix</p>												
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X --- Y</td> <td>US 2005/0069572 A1 (WILLIAMS et al) 31 March 2005 (31.03.2005) see especially para [0049]-[0051], [0053], [0057], [0059], [0091], [0092], [0102], [0103], [0132], [0188], [0191], [0195]</td> <td>1-3, 7, 10, 11 ----- 4-6, 8, 9, 50</td> </tr> <tr> <td>Y</td> <td>US 2007/0292514 A1 (CHAN PUI et al) 20 December 2007 (20.12.2007) see especially para [0015], [0027], [0029], [0040], [0042], [0043], [0052], [0057], [0059], [0072], [0077]</td> <td>4-6, 8, 9, 50</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X --- Y	US 2005/0069572 A1 (WILLIAMS et al) 31 March 2005 (31.03.2005) see especially para [0049]-[0051], [0053], [0057], [0059], [0091], [0092], [0102], [0103], [0132], [0188], [0191], [0195]	1-3, 7, 10, 11 ----- 4-6, 8, 9, 50	Y	US 2007/0292514 A1 (CHAN PUI et al) 20 December 2007 (20.12.2007) see especially para [0015], [0027], [0029], [0040], [0042], [0043], [0052], [0057], [0059], [0072], [0077]	4-6, 8, 9, 50	
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<p><input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/></p>												
<p>* Special categories of cited documents:</p> <table border="0"> <tr> <td>“A” document defining the general state of the art which is not considered to be of particular relevance</td> <td>“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</td> </tr> <tr> <td>“E” earlier application or patent but published on or after the international filing date</td> <td>“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</td> </tr> <tr> <td>“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)</td> <td>“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</td> </tr> <tr> <td>“O” document referring to an oral disclosure, use, exhibition or other means</td> <td>“&” document member of the same patent family</td> </tr> <tr> <td>“P” document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </table>			“A” document defining the general state of the art which is not considered to be of particular relevance	“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	“E” earlier application or patent but published on or after the international filing date	“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	“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)	“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	“O” document referring to an oral disclosure, use, exhibition or other means	“&” document member of the same patent family	“P” document published prior to the international filing date but later than the priority date claimed	
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<p>Date of the actual completion of the international search 9 October 2009 (09.10.2009)</p>		<p>Date of mailing of the international search report 22 OCT 2009</p>										
<p>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</p>		<p>Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774</p>										

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/03189

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 continuation 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.:
1-11, 50

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.

Box III - Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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 1-11 and 50, drawn to a multi-layer three-dimensional cell composition and method of making said multi-layer three-dimensional cell composition.

Group II, claims 12-28 and 36-49, drawn to a cartilage and/or musculoskeletal tissue production composition, comprising said multi-layer three-dimensional cell composition.

Group III, claims 29-35, drawn to a system for delivering a musculoskeletal tissue-producing composition to a treatment site in an individual, the system comprising said multi-layer cell composition.

The common technical feature of the listed groups is:

A multi-layer three-dimensional cell composition comprising:

- a) a first layer comprising a plurality of cells, wherein at least about 85% of the cells in the first layer are nucleus pulposus cells (NPC), chondroblasts, chondrocytes, osteoblasts, osteocytes, myoblasts, myocytes, or tenocytes; and
- b) a second layer comprising a plurality of cells, wherein at least about 85% of the cells in the second layer are mesenchymal stem cells (MSC).

However, this is not an improvement over the teachings of the prior art US 2005/0069572 A1 (Williams et al.), which teaches:

A multi-layer three-dimensional cell composition (para [0051], [0103], [0154]) comprising:

- a) a first layer comprising a plurality of cells (para [0051]), wherein at least about 85% of the cells in the first layer are nucleus pulposus cells (NPC), chondroblasts, chondrocytes, osteoblasts, osteocytes, myoblasts, myocytes, or tenocytes (para [0059]--first cell layer comprised entirely of chondrocytes, which inherently is at least about 85%; [0103], [0154]); and
- b) a second layer comprising a plurality of cells (para [0051]), wherein at least about 85% of the cells in the second layer are mesenchymal stem cells (MSC) (para [0059]--second cell layer comprised entirely of mesenchymal stem cells OR embryonic stem cells [emphasis added]--inherently teaches 100% mesenchymal stem cells, which is at least about 85%; [0103], [0154]).

Accordingly, unity of invention is lacking under PCT Rule 13.1.