

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
6 December 2007 (06.12.2007)

PCT

(10) International Publication Number
WO 2007/138098 A3

(51) International Patent Classification:
C12N 5/00 (2006.01) *G01N 33/50* (2006.01)

(21) International Application Number:
PCT/EP2007/055345

(22) International Filing Date: 31 May 2007 (31.05.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/809,306 31 May 2006 (31.05.2006) US

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(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
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, 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, SV, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL,
PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

(88) Date of publication of the international search report:
17 April 2008

(54) Title: ANIMAL MODELS OF TUMOUR METASTASIS AND TOXICITY

(57) Abstract: The present invention relates to a methodology designed to convert an animal into appropriate recipients of tumour cells derived from a different species. Animals thereof are immuno-incompetent animals that are doubly grafted with orthotopic tissues: One grafted tissue (i.e. breast) is from an organ of the same class as the tumour of origin (graft A). The second grafted tissue (i.e. bone) is from an organ of the same class as a target organ for metastasis (graft B). These dual grafted animals can be used to model human diseases. A preferred model will be one in which human tumour cells are orthotopically seeded in graft A in order to analyze the occurrence of metastasis in graft B. Also in this invention are included methods and compositions to create a multiorgan human environment in mice. This will be achieved by grafting human stem cells (mesenchymal, embryonic or others) into mice. Mice in this invention can be conveniently injured to enhance tissue specific engraftment. As in double grafted mice, such chimeric mice can be used to grow human tumours and to study the occurrence of metastasis.



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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2007/055345

A. CLASSIFICATION OF SUBJECT MATTER

INV. C12N5/00 G01N33/50

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)

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 practical, search terms used)

EPO-Internal, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ERDÖ F, ET AL.: "HOST-DEPENDENT TUMORIGENESIS OF EMBRYONIC STEM CELL TRANSPLANTATION IN EXPERIMENTAL STROKE" JOURNAL OF CEREBRAL BLOOD FLOW AND METABOLISM, vol. 23, 2003, pages 780-785, XP009091152 the whole document	53-88
X	SVENDSEN C N ET AL: "LONG-TERM SURVIVAL OF HUMAN CENTRAL NERVOUS SYSTEM PROGENITOR CELLS TRANSPLANTED INTO A RAT MODEL OF PARKINSON'S DISEASE" EXPERIMENTAL NEUROLOGY, ACADEMIC PRESS, NEW YORK, NY, US, vol. 148, 1997, pages 135-146, XP001126943 ISSN: 0014-4886 the whole document	53-88

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☒ 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 document but published on or after the international filing date

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"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

12 February 2008

Date of mailing of the international search report

06/03/2008

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/055345

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	SCHWARZ ET AL: "Transplantation of human neural precursor cells in the 6-OHDA lesioned rats: Effect of immunosuppression with cyclosporine A" PARKINSONISM AND RELATED DISORDERS, ELSEVIER SCIENCE, OXFORD, GB, vol. 12, no. 5, June 2006 (2006-06), pages 302-308, XP005481540 ISSN: 1353-8020 the whole document	53-56, 58-69, 71,83-85
A	US 2002/199212 A1 (SONE SABURO [JP] ET AL) 26 December 2002 (2002-12-26) abstract paragraphs [0002], [0007], [0009] - [0057], [0074] - [0079]	1-34, 42-88
P,A	US 2006/123494 A1 (WU MIN [US] ET AL) 8 June 2006 (2006-06-08) abstract paragraphs [0003], [0004], [0007] - [0010], [0019], [0024], [0050]	1-34, 42-88
Y	US 5 643 551 A (NAMIKAWA REIKO [US] ET AL) 1 July 1997 (1997-07-01) abstract column 2, lines 8-47 column 3, line 11 - column 4, line 34	35-42, 44-52
Y	US 2005/132427 A1 (NAKAMURA MASATO [JP] ET AL) 16 June 2005 (2005-06-16) abstract paragraphs [0003], [0009], [0010], [0020] - [0029], [0054], [0060] - [0062]	35-42, 44-52
Y	RYAN JENNIFER M ET AL: "Mesenchymal stem cells avoid allogeneic rejection" JOURNAL OF INFLAMMATION, BIOMED CENTRAL, LONDON, GB, vol. 2, no. 1, 26 July 2005 (2005-07-26), page 8, XP021008620 ISSN: 1476-9255 the whole document	35-42, 44-52
Y	DJOUAD F, ET AL.: "IMMUNOSUPPRESSIVE EFFECT OF MESENCHYMAL STEM CELLS FAVORS TUMOR GROWTH IN ALLOGENEIC ANIMALS" BLOOD, vol. 102, no. 10, 2003, pages 3837-3844, XP002468564 the whole document	35-42, 44,52

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/055345

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 allsearchable 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 reportcovers 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.:

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: 1-34, 43 and 53-88 (completely), 42 and 44-52 (partially)

Method for obtaining an animal model comprising inflicting damage leading to cellular death to at least one tissue or organ in a recipient animal, implanting into the recipient animal a composition comprising precursor or stem cells from a donor animal from a different species and allowing them to differentiate into the at least one tissue or organ that has been damaged. Non-human animal obtainable by this method, use of this animal to study metastasis or the effect of a compound of interest. Identification, determination or evaluation methods on metastasis based on the use of this animal.

2. claims: 35-41 (completely), 42 and 44-52 (partially)

Method for obtaining an animal model for tumour metastasis comprising implanting into a recipient animal a composition comprising mesenchymal stem cells from a donor animal from a different species and allowing them to differentiate into cells of mesenchymal tissues, implanting into the recipient animal a composition comprising precursor or stem cells from a donor animal from the same species as the donor of mesenchymal stem cells, implanting into the recipient animal cells derived from a tumour from the donor animal. Non-human animal obtainable by this method, use of this animal to study metastasis. Identification, determination or evaluation methods on metastasis based on the use of this animal.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2007/055345

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