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- (71) Applicant: **VIERA BIOSCIENCE, INC.** [US/US]; PO Box 829, Rancho Santa Fe, CA 92067 (US).
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- (74) Agent: **MALLON, Joseph J.**; Knobbe, Martens, Olson & Bear, LLP, 2040 Main Street, 14th Floor, Irvine, CA 92614 (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, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, 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.

- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, 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:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

[Continued on next page]

(54) Title: STIMULATION OF THERAPEUTIC ANGIOGENESIS BY T REGULATORY CELLS

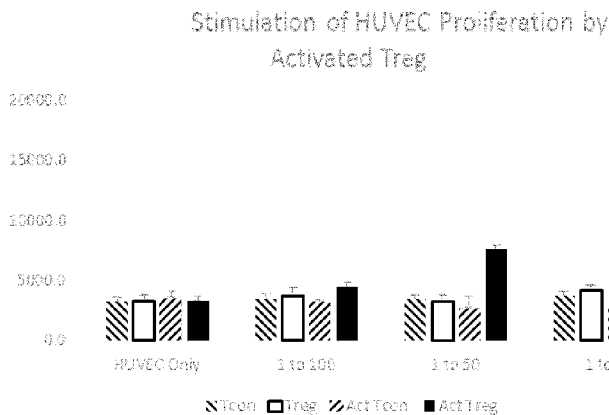


FIGURE 1

(57) Abstract: Disclosed herein are new, useful, and non-obvious means of stimulating therapeutic angiogenesis, or conditions favorable for stimulation of therapeutic angiogenesis utilizing T regulatory cells. One disclosed method includes administering a population of T regulatory cells into an area of hypoxia to stimulate angiogenesis. T regulatory cells are generated and expanded by culture with mesenchymal stem cells, with either population or both populations together administered into the hypoxic area.





— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))* — *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))*

Published:

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

(88) Date of publication of the international search report:
28 September 2017

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K35/17 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 A61P

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, BIOSIS, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FRANCO R. D'ALESSIO ET AL: "Lung Angiogenesis Requires CD4 + Forkhead Homeobox Protein-3 + Regulatory T Cells", AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR BIOLOGY., vol. 52, no. 5, 1 May 2015 (2015-05-01), pages 603-610, XP055368292, NEW YORK, NY, US ISSN: 1044-1549, DOI: 10.1165/rcmb.2014-02780C the whole document ----- -/--	1-17

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 2 August 2017	Date of mailing of the international search report 21/08/2017
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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 Schnack, Anne
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/018417

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	<p>JAKUB TOLAR ET AL: "Immune regulatory cells in umbilical cord blood: T regulatory cells and mesenchymal stromal cells", BRITISH JOURNAL OF HAEMATOLOGY, vol. 147, no. 2, 1 October 2009 (2009-10-01), pages 200-206, XP055368434, GB ISSN: 0007-1048, DOI: 10.1111/j.1365-2141.2009.07781.x abstract</p>	1-17
X	<p>ZHAN HAI-LUN ET AL: "Presence of tumour-infiltrating FOXP3+ lymphocytes correlates with immature tumour angiogenesis in renal cell carcinomas.", 2012, ASIAN PACIFIC JOURNAL OF CANCER PREVENTION : APJCP 2012, VOL. 13, NR. 3, PAGE(S) 867 - 872, XP002769774, ISSN: 2476-762X *Discussion*</p>	1-17
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X	<p>DAVID BREA ET AL: "Regulatory T cells modulate inflammation and reduce infarct volume in experimental brain ischaemia", JOURNAL OF CELLULAR AND MOLECULAR MEDICINE, vol. 18, no. 8, 30 May 2014 (2014-05-30), pages 1571-1579, XP055368478, RO ISSN: 1582-1838, DOI: 10.1111/jcmm.12304 *Discussion*</p>	1-17
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/018417

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	ZOU GGARI Y ET AL: "D022 Natural CD4/CD25/Foxp3 regulatory t cells modulate post-ischemic inflammatory response: role in neovascularization", ARCHIVES OF CARDIOVASCULAR DISEASE, ELSEVIER, AMSTERDAM, NL, vol. 102, 1 March 2009 (2009-03-01), page S44, XP026054615, ISSN: 1875-2136, DOI: 10.1016/S1875-2136(09)72232-6 [retrieved on 2009-03-01] the whole document	1-17
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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2017/018417

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J.-S. SILVESTRE ET AL: "Post-ischaemic neovascularization and inflammation", CARDIOVASCULAR RESEARCH, vol. 78, no. 2, 19 February 2008 (2008-02-19), pages 242-249, XP055368561, GB ISSN: 0008-6363, DOI: 10.1093/cvr/cvn027 5. Type of inflammatory cells and mechanisms of pro-angiogenic/pro-arteriogenic activities -----	1-17
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X	A. FACCIABENE ET AL: "T-Regulatory Cells: Key Players in Tumor Immune Escape and Angiogenesis", CANCER RESEARCH, vol. 72, no. 9, 1 May 2012 (2012-05-01), pages 2162-2171, XP055044575, ISSN: 0008-5472, DOI: 10.1158/0008-5472.CAN-11-3687 the whole document -----	1-10
X,P	QIONG ZHONG ET AL: "Effector T Cells and Ischemia-Induced Systemic Angiogenesis in the Lung", AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR BIOLOGY., vol. 54, no. 3, 1 March 2016 (2016-03-01), pages 394-401, XP055368783, NEW YORK, NY, US ISSN: 1044-1549, DOI: 10.1165/rcmb.2015-00870C *Discussion* ----- -/--	1-17

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/018417

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GIATROMANOLAKI A ET AL: "The presence of tumor-infiltrating FOXP3<+> lymphocytes correlates with intratumoral angiogenesis in endometrial cancer", GYNECOLOGIC ONCOLOGY, ACADEMIC PRESS, LONDON, GB, vol. 110, no. 2, 1 August 2008 (2008-08-01), pages 216-221, XP022940944, ISSN: 0090-8258, DOI: 10.1016/J.YGYNO.2008.04.021 [retrieved on 2008-06-03] cited in the application the whole document	1-10
Y	Miltenyi Biotech ET AL: "Treg Expansion kit", 1 January 2013 (2013-01-01), XP055395416, Retrieved from the Internet: URL:https://www.miltenyibiotec.com/~/media/ /Images/Products/Import/0001800/IM0001831. ashx?force=1 [retrieved on 2017-08-02] the whole document	19,20
Y	WO 2013/082543 A1 (ADVANCED CELL TECH INC [US]) 6 June 2013 (2013-06-06) figures 14, 15; examples 8-10	20
X	Miltenyi Biotech ET AL: "CD4+CD25+ Regulatory T Cell Isolation Kit", 1 January 2015 (2015-01-01), pages 1-4, XP055395397, Retrieved from the Internet: URL:http://www.miltenyibiotec.com/~/media/ /Images/Products/Import/0001100/IM0001159.a shx?force=1 [retrieved on 2017-08-02] the whole document	18
Y		19

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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.:

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: 1-17

A method of stimulating angiogenesis, comprising:obtaining a population of cells comprising T regulatory cells;selecting said T regulatory cells from said population of cells;activating said T regulatory cells to enhance angiogenic activity of said T regulatory cells; andadministering said T regulatory cells to a patient in need of therapy.

A method of stimulating angiogenesis comprising administering a T regulatory cell into an ischemic tissue.

2. claims: 18-20

A method of expanding T regulatory cells, comprising: culturing a population of cells comprising T regulatory cells; and enriching CD25+ cells.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2017/018417

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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