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

[Continued on next page]

(54) **Title**: CELL LINES THAT SECRETE ANTI-ANGIOGENIC ANTIBODY-SCAFFOLDS AND SOLUBLE RECEPTORS AND USES THEREOF

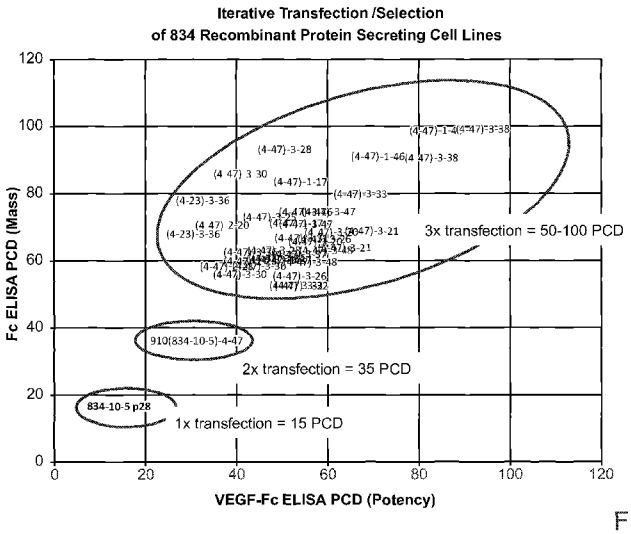

FIG. 9

(57) **Abstract**: The invention provides nucleic acid and polypeptide sequences encoding antibody based scaffolds such as full antibodies, antibody Fab fragments, single chain antibodies, soluble VEGF receptor-Fc fusion proteins, and/or anti-angiogenic PDGF receptors. Also encompassed are cell lines encoding such anti-angiogenic antibody scaffolds, VEGF receptors, and/or PDGF receptors. The invention also provides encapsulated cell therapy devices that are capable of delivering such anti-angiogenic antibody scaffolds, VEGF receptors, and/or PDGF receptors as well as methods of using these devices to deliver the anti-angiogenic antibody scaffolds, VEGF receptors, and/or PDGF receptors to medically treat disorders in patients, including ophthalmic, vascular, inflammatory, and cell proliferation diseases.

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INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12P 21/00; C12N 15/85 (2012.01)
USPC - 435/69.6; 435/70.3
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(8): C12P 21/00; C12N 15/85 (2012.01)
USPC: 435/69.6; 435/70.3

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 435/69.1; 435/70.1

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST (PGPB,USPT,EPAB,JPAB); Google Scholar; esp@cent; GenCore 6.3: ARPE-19, antibody, scaffold, transfection, vector, VEGF, matrix, semi-permeable membrane, monofilaments, yarn, MWCO, tether, anchor, aqueous humor, periocular, posterior chamber, anterior chamber, permselective, ultrafiltration, hydrogel, methyl methacrylate, Neurotech, Ling, ARPE,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y ----- A	US 2009/0269319 A1 (TAO et al.) 29 October 2009 (29.10.2009), abstract; para [0006], [0026], [0027], [0028], [0038], [0045], [0046], [0047], [0065], [0066], [0067], [0071],[0072], [0083], [0092]; claim 1; claim 5.	1, 11, 20-22, 25, 26, 29, 30, 37, ---------- 2-7, 10, 12-19, 23, 24, 27, 28, 31-36, 38 ---------- 8 and 9
Y	US 2006/0239966 A1 (TORNOE et al.) 26 October 2006 (26.10.2006) Fig. 7; para [0053]; [0055]	2-7, 10
Y	US 2010/0272780 A1 (LING et al.) 28 October 2010 (28.10.2010), abstract; para [0042], [0046], [0047], [0049], [0051], [0089], [0100], [0108], [0109], [0116], [0131], [0132].	12-19, 23, 24, 27, 28, 31, 33-36, 38
Y	US 2009/0136465 A1 (MERENICK et al.) 28 May 2009 (28.05.2009), para [0159], [0167], [0173].	32
A	US 2005/0175610 A1 (WIEGAND et al.) 11 August 2005 (11.08.2005), abstract; para [0004], SEQ ID NO: 15; SEQ ID NO: 16.	8 and 9

☐ Further documents are listed in the continuation of Box C. ☐

* 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
19 June 2012 (19.06.2012)	29 JUN 2012
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

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/62704

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 1-10, directed to a cell line comprising an ARPE-19 cell genetically engineered to produce a therapeutically effective amount of one or more anti-angiogenic antibody-scaffold or anti-angiogenic molecules, wherein the one or more anti-angiogenic antibody-scaffold or anti-angiogenic molecules are introduced into the ARPE-19 cell by an iterative transfection process, wherein the iterative transfection comprises one transfection, two transfections, or three transfections.

- Please see extra sheet for continuation -

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.:
1-38

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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/62704

Continuation of Box III: Lack of Unity of Invention

Group II: claims 11-38 directed to an implantable cell culture device, the device comprising:
a. a core comprising the cell line of claim 1 or the cell line of claim 10; and
b. a semi-permeable membrane surrounding the cell line or the cell, wherein the membrane permits the diffusion of the one or more anti-angiogenic antibody scaffold or anti-angiogenic molecules therethrough.

Group III: claim 39, directed to use of the device of claim 11 to deliver an appropriate therapeutic dose of the one or more anti-angiogenic antibody-scaffolds or anti-angiogenic molecules to an eye of a subject, wherein the therapeutic dose is at least 100 ng/day/eye.

Group IV: claims 40-47, directed to a method for treating ophthalmic disorders, comprising implanting the implantable cell culture device of claim 11 into the eye of a patient and allowing the one or more anti-angiogenic antibody-scaffolds or anti-angiogenic molecules to diffuse from the device and bind to VEGF, PDGF, or both VEGF and PDGF in the eye, thereby treating the ophthalmic disorder.

Group V: claims 48-50, directed to a method of delivering an anti-angiogenic antibody-scaffold or an anti-angiogenic molecule to a recipient host, comprising implanting the implantable cell culture device of claim 11 into a target region of the recipient host, wherein the encapsulated one or more ARPE-19 cells secrete the anti-angiogenic antibody-scaffold or the antiangiogenic molecule at the target region.

Group VI: claims 51 and 52, directed to a method for making the implantable cell culture device of claim 11, comprising:
a. genetically engineering at least one ARPE-19 cell to secrete one or more antiangiogenic antibody-scaffolds or anti-angiogenic molecules, and
b. encapsulating said genetically modified ARPE-19 cells within a semipermeable membrane, wherein said membrane allows the diffusion of the one or more anti-angiogenic antibody-scaffolds or anti-angiogenic molecules therethrough.

The inventions listed as Groups I - VI do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature of the claims of Groups I-VI are indicated above in the Group descriptions. The claims of all Groups share in common the technical elements of claim 1. Groups II-VI further share in common the technical elements of claim 11. Groups III-V also share a common technical element of treatment of a host, wherein, in Groups III and IV the treatment is related to the eye.

However, these common technical elements do not represent an improvement over the prior art of US 2009/0269319 A1 to TAO et al. (hereinafter Tao), which discloses (as to claim 1) a cell line comprising an ARPE-19 cell genetically engineered to produce a therapeutically effective amount of one or more anti-angiogenic molecules (abstract; para [0006]; claim 1), wherein the one or more anti-angiogenic molecules are introduced into the ARPE-19 cell by an iterative transfection process, wherein the iterative transfection comprises one transfection (para [0026]). Tao further discloses (as to claim 11) an implantable cell culture device (para [0065]), the device comprising: a. a core comprising the cell line of claim 1 (para [0006], [0065]); and b. a semi-permeable membrane surrounding the cell line or the cell, wherein the membrane permits the diffusion of the one or more anti-angiogenic antibody scaffold or anti-angiogenic molecules therethrough (para [0065], claim 5). Additionally, Tao teaches the treatment of eye (ophthalmic) disorders (para [0092]) in recipients of the cells (para [0097], [0098]).

Therefore, the inventions of Groups I - VI lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.