(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 September 2010 (23.09.2010)

PCT

(10) International Publication Number
WO 2010/108048 A3

(51) International Patent Classification:
A61K 39/00 (2006.01) *C07H 21/04* (2006.01)
C12N 15/00 (2006.01)

(21) International Application Number:
PCT/US2010/027882

(22) International Filing Date:
18 March 2010 (18.03.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/161,320 18 March 2009 (18.03.2009) US

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(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, BR, BW, BY, BZ, CA, CH, CL, 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, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, 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, 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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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:
11 November 2010

WO 2010/108048 A3

(54) Title: COMPOSITIONS AND METHODS FOR BLOOD-BRAIN BARRIER DELIVERY OF IGG-DECOY RECEPTOR FUSION PROTEINS

(57) Abstract: Provided herein are compositions and related methods for delivering an IgG-decoy receptor to the CNS. The methods include systemic administration of a bifunctional decoy receptor-BBB receptor antibody fusion antibody comprising a receptor extracellular domain (ECD) covalently linked to an antibody to a receptor expressed on the surface of the blood-brain barrier (BBB receptor). In some embodiments, the compositions described herein are administered to treat a subject suffering from a CNS condition.

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A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/00; C12N 15/00; C07H 21/04 (2010.01)
USPC - 424/133.1; 435/320.1; 536/23.4
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)
USPC- 424/133.1; 435/320.1; 536/23.4

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 435/325; 514/2 (text search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic data bases searched: PubWEST (PGPB, UPST, EPAB, JPAB); Google Scholar: blood brain barrier (BBB), transport,central nervous system (CNS), extracellular domain (ECD), decoy receptor, antibody fusion, [receptors: TNF, TRAIL, TWEAK, VEGF, ephrin, insulin, transferring, IGF, lipoprotein]. GenCore Sequence Search: SEQ ID NO: 3-7

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2007/0280940 A1 (WINKLES et al.) 6 December 2007 (06.12.2007) para [0036], [0095], sheet 12 fig 11	1-4, 6-11, 30-46
Y	US 2008/0170994 A1 (PARDRIDGE et al.) 17 July 2008 (17.07.2008) para [0069], [0094], [0101], [0132], [0236], sheet 45 fig 44, sheet 48 fig 47, SEQ ID NO: 22	1-4, 6-11, 30-46
X,P	BOADO et al. Selective targeting of a TNFR decoy receptor pharmaceutical to the primate brain as a receptor-specific IgG fusion protein. J Biotechnol ePub 25 January 2010, 146(1-2):84-91	1-11, 30-46

☐ 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
11 August 2010 (11.08.2010)	07 SEP 2010
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)

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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:

Group I: claims 1-11, 30-46, drawn to a bifunctional decoy receptor fusion antibody comprising the amino acid sequence of a heavy chain immunoglobulin or a light chain immunoglobulin covalently linked to the amino acid sequence of a receptor extracellular domain, wherein the fusion antibody binds to a receptor expressed on the BBB and a ligand for the receptor extracellular domain, and a method of using said bifunctional decoy receptor fusion antibody.

--------continued on Separate 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.:
Claims 1-11, 30-46

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.

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********** Supplementsl Box **********

Continuation of Box III (Lack of Unity of Invention):

Group II, claims 12-29, 47-55, drawn to a nucleic acid comprising:
(i) a first sequence encoding a heavy chain immunoglobulin and a receptor extracellular domain in frame with the heavy chain immunoglobulin;
(ii) a second sequence encoding a light chain immunoglobulin and a receptor extracellular domain in frame with the light chain immunoglobulin; or
(iii) the complementary sequence of (i) or (ii); wherein the heavy chain and light chain immunoglobulin are from an antibody against a BBB receptor, and a method of using said nucleic acid for manufacturing a bifunctional decoy receptor fusion antibody

The inventions listed as Groups I-II 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 inventions of Group I do not include the inventive concept of a nucleic acid, as required by Group II.
The inventions of Group II do not include the inventive concept of a bifunctional decoy receptor fusion antibody as required by Group I.

The inventions of Groups I-II share the technical feature of a fusion antibody comprising the amino acid sequence of a heavy chain immunoglobulin or a light chain immunoglobulin covalently linked to the amino acid sequence of a receptor extracellular domain, wherein the fusion antibody binds to a receptor expressed on the BBB and a ligand for the receptor extracellular domain. However, this shared technical feature does not represent a contribution over prior art. Specifically, a paper titled "Fusion Antibody for Alzheimer?s Disease with Bi-Directional Transport Across the Blood-Brain Barrier and Abeta Fibril Disaggregation" by BOADO et al. (Bioconjug Chem. 2007, 18(2):447?455) discloses a bifunctional fusion antibody comprising the amino acid sequence of a heavy chain immunoglobulin (pg 3, top para - 'universal chimeric HIRMAb heavy chain') linked to the amino acid sequence of a second antibody/protein fragment (pg 3, top para - 'The engineering of the gene encoding the heavy chain of the fusion antibody was done in 2 steps: (a) PCR cloning of the anti-A?ScFv and (b) insertion of this cDNA into the universal chimeric HIRMAb heavy chain expression vector'),
---wherein the fusion antibody binds to a receptor expressed on the BBB (pg 2, middle para - 'the ?head? of the fusion antibody binds the human insulin receptor (HIR). The insulin receptor is highly expressed at the human BBB'; pg 3, last para - 'Binding to the HIR extracellular domain (ECD) was measured as described') and a ligand (pg 3, last para - 'Binding of fusion antibody to A? and to HIR', wherein A.beta is the ligand). As said fusion antibody was known at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Groups I-II therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.