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[Continued on next page]

(54) Title: DUAL PDGF/VEGF ANTAGONISTS

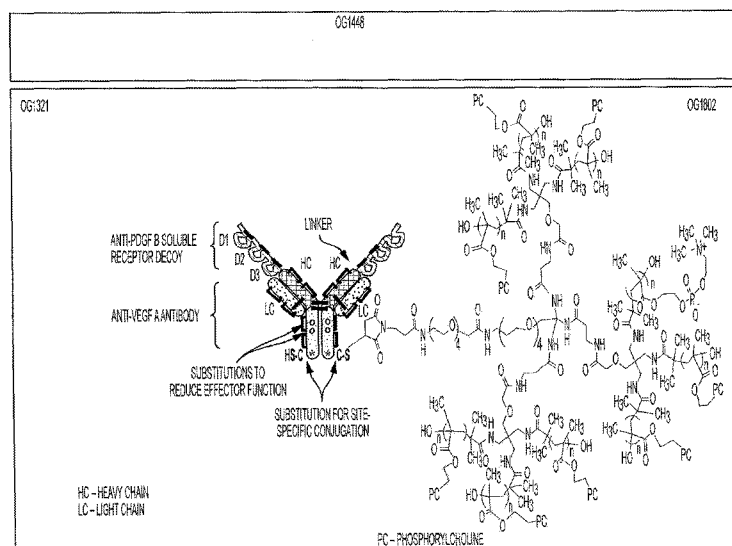


FIG. 39

(57) Abstract: The invention provides a dual VEGF/PDGF antagonist comprising a VEGF antagonist linked to a PDGF antagonist. The VEGF antagonist is an antibody to a VEGF or VEGFR or is a VEGFR extracellular trap segment (i.e., a segment from the extracellular region of one or more VEGFR receptors that inhibits binding of at least one VEGFR to at least one VEGF). The PDGF antagonist is an antibody to a PDGF or PDGFR or is a PDGFR extracellular trap segment (i.e., segment from the extracellular region of one or more PDGFRs, which inhibits binding of at least one PDGFR and at least one PDGF). The dual antagonist is preferably conjugated to a half-life extending moiety, such as a HEMA-PC polymer. The dual antagonist is particularly useful for treating wet aged related macular degeneration.



Declarations under Rule 4.17:

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

— *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:

18 February 2016

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 15/38203

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 38/00, A61K 38/16, A61K 38/18, C07K 14/47, C07K 14/475, A61K 39/395, A61P 35/00 (2015.01)

CPC - A61K 38/00, A61K 38/1709, A61K 38/177, A61K 38/17, A61K 38/18, A61K 38/1808, A61K 38/19

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) - A61K 38/00, A61K 38/16, A61K 38/18, C07K 14/47, C07K 14/475, A61K 39/395, A61P 35/00 (2015.01)

CPC - A61K 38/00, A61K 38/1709, A61K 38/177, A61K 38/17, A61K 38/18, A61K 38/1808, A61K 38/19

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
 CPC- A61K 38/1709, A61K 31/195, C07K 14/71, C07K 14/78, C07K 14/52, C07K 14/47, C07K 14/475, C07K 14/57545, C07K 14/705, C07K 7/06, C07K 7/08, C07K 7/22, C07K 2319/00, C07K 2317/73, C07K 16/18, C07K 2316/96, A61K 2039/505, C07K 2317/24...

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 PubWEST(PGPB,USPT,USOC,EPAB,JPAB); PatBase, Google/Scholar: Diabody, dual antagonist, PDGF/VEGF, platelet-derived growth factor, Aflibercept, VEGF-Trap, decoy, soluble, extracellular, ECD, ectodomain, inhibit, binding, PDGF-AB, PDGF-BB, PDGF-DD....

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Mabry, et al. A dual-targeting PDGFRbeta/VEGF-A molecule assembled from stable antibody fragments demonstrates anti-angiogenic activity in vitro and in vivo. MAbs 2010, 2(1):20-34; Abstract, pg 21; pg 22, Fig 1 and its legend	1-5, 106-108
Y	Kuhnert, et al. Soluble receptor mediated selective inhibition of VEGFR and PDGFRbeta signaling during physiologic and tumor angiogenesis. Proceedings of the National Academy of Sciences of the United States of America 2008, 105(29):10185-10190; Abstract, pg 10188, col 1	1-5, 106-108
X	US 7,855,178 B2 (Alitalo, et al.) 21 December 2010 (21.12.2010) claims 2, 10 [meet instant claim 1 limitation comprising VEGFR extracellular trap and PDGF antibody]	1

☐ 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

07 November 2015 (07.11.2015)

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Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 15/38203

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.: 6-27, 42-62, 116-145
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.

Group I+: claims 1-5, 28-41, 63-108, directed to a dual VEGF/PDGF antagonist comprising a VEGF antagonist linked to a PDGF antagonist. The dual VEGF/PDGF antagonist will be searched to the extent that the VEGF antagonist encompasses an antibody and the PDGF antagonist encompasses the PDGFRalpha extracellular trap segment. It is believed that claims 1-5, 106-108 encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass a dual VEGF/PDGF antagonist comprising an anti-VEGF antibody and the PDGFRalpha extracellular trap segment. Additional VEGF and/or PDGF antagonist(s) will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected VEGF and/or PDGF antagonist(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. An exemplary election would be a dual VEGF/PDGF antagonist comprising the VEGF extracellular trap segment antagonist linked to the PDGF extracellular trap segment, i.e. claims 1, 84-105.

***** See Supplemental Sheet to continue *****

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.:
1-5, 106-108 limited to VEGF antibody and PGFR extracellular trap

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.

***** Supplemental Sheet *****

In Continuation of Box III. Observations where unity of invention is lacking:

Group II: claims 109-112, directed to a method of purifying a dual VEGF/PDGF antagonist.

Group III: claims 113-115, directed to a pharmaceutical composition comprising at least one dual VEGF/PDGF antagonist.

The inventions listed as Groups I+, II, and III 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:

Special Technical Features

The inventions of Groups I+ and II do not include the technical feature of a pharmaceutical composition comprising at least one dual VEGF/PDGF antagonist, as required by Group III.

The inventions of Group III do not include the technical feature of a dual VEGF/PDGF antagonist comprising a VEGF antagonist linked to a PDGF antagonist, wherein the VEGF and PDGF antagonists are not both antibodies, as required by Group I+; or a method of purifying a dual VEGF/PDGF antagonist, as required by Group II.

The inventions of Group I+ do not include the technical feature of a method of purifying a dual VEGF/PDGF antagonist, as required by Group II.

The inventions of Group II do not include the technical feature of a dual VEGF/PDGF antagonist comprising a VEGF antagonist linked to a PDGF antagonist, wherein the VEGF and PDGF antagonists are not both antibodies, as required by Group I+.

The special technical feature of each invention of Group I+ is a specific combination of a VEGF antagonist and a PDGF antagonist, because said antagonists were known in the art at the time of the invention.

Specifically, US 2011/0177074 A1 to Sivakumar, et al. discloses "antagonists of PDGF receptor .beta. (PDGFR.beta.) and VEGF-A, including neutralizing anti-PDGFR.beta. and anti-VEGF-A antibodies... Anti-PDGFR.beta. and anti-VEGF-A antibodies disclosed herein include bispecific antibodies capable of binding and neutralizing both PDGFR.beta. and VEGF-A" (Abstract); a paper titled "Vascular endothelial growth factor A competitively inhibits platelet-derived growth factor (PDGF)-dependent activation of PDGF receptor and subsequent signaling events and cellular responses" by Pennock, et al. (Mol Cell Biol. 2012, 32(10):1955-66) discloses a PDGFRalpha extracellular trap segment (pg 1956, col 2, "TRAP, a chimera consisting of the extracellular domain of PDGFR[alpha] fused to human IgG Fc5...").

Common Technical Features

The inventions of Groups I+, II, and III share the technical feature of a dual VEGF/PDGF antagonist. However, this shared technical feature does not represent a contribution over prior art as being anticipated by a paper titled "A dual-targeting PDGFRbeta/VEGF-A molecule assembled from stable antibody fragments demonstrates anti-angiogenic activity in vitro and in vivo" by Mabry, et al. (MABS 2010, 2(1):20-34) (hereinafter "Mabry").

Mabry discloses a dual VEGF/PDGF antagonist (Abstract, "Single-chain antibody fragments (scFvs) targeting PDGFRbeta and VEGF-A were selected for superior stability. The scFvs were fused to both termini of human Fc to generate a bispecific, tetravalent molecule. The resulting molecule displays potent activity, binds both targets simultaneously, and is stable in serum. The assembly of a bsAb using stable monomeric units allowed development of an anti-PDGFRbeta/VEGF-A antibody capable of attenuating angiogenesis through two distinct pathways"; pg 22, Figure 1, and its legend, "DSC analysis of the scFvs and scFv-Fc-scFv constructs"). As said technical feature was known in the art at the time of the invention, this cannot be considered special technical feature that would otherwise unify the groups.

The inventions of Group I+ share the technical feature of a dual VEGF/PDGF antagonist, wherein the VEGF and PDGF antagonists are not both antibodies. However, this shared technical feature does not represent a contribution over prior art as being obvious over Mabry, as above, in view of a paper titled "VEGF-Traps: a VEGF blocker with potent antitumor effects" by Holash, et al. (Proc Natl Acad Sci USA 2002, 99(17):11393-8) (hereinafter "Holash").

Mabry discloses a dual VEGF/PDGF antagonist, wherein the VEGF and PDGF antagonists are both antibodies (Abstract, "Single-chain antibody fragments (scFvs) targeting PDGFRbeta and VEGF-A were selected for superior stability. The scFvs were fused to both termini of human Fc to generate a bispecific, tetravalent molecule. The resulting molecule displays potent activity, binds both targets simultaneously, and is stable in serum. The assembly of a bsAb using stable monomeric units allowed development of an anti-PDGFRbeta/VEGF-A antibody capable of attenuating angiogenesis through two distinct pathways"; pg 22, Figure 1, and its legend, "DSC analysis of the scFvs and scFv-Fc-scFv constructs").

Mabry does not provide a motivation to one of ordinary skill in the art to modify said scFv-Fc-scFv construct by substituting either anti-PDGFRbeta or anti-VEGF-A by a corresponding extracellular trap segment. The motivation to do so is provided by Holash disclosing that "one of the most effective ways to block the VEGF-signaling pathway is to prevent VEGF from binding to its normal receptors by administering decoy-soluble receptors. The highest-affinity VEGF blocker described to date is a soluble decoy receptor created by fusing the first three Ig domains of VEGF receptor 1 to an Ig constant region; however, this fusion protein has very poor in vivo pharmacokinetic properties. By determining the requirements to maintain high affinity while extending in vivo half life, we were able to engineer a very potent high-affinity VEGF blocker that has markedly enhanced pharmacokinetic properties. This VEGF-Traps effectively suppresses tumor growth and vascularization in vivo, resulting in stunted and almost completely avascular tumors. VEGF-Traps-mediated blockade may be superior to that achieved by other agents, such as monoclonal antibodies targeted against the VEGF receptor" (Abstract). It would have been obvious to one of ordinary skill in the art to combine, in the course of routine experimentation and with a reasonable expectation of success, Mabry and Holash, by substituting the anti-VEGF-A antibody in the scFv-Fc-scFv construct of Mabry by the VEGF-Traps disclosed by Holash, to improve efficiency of suppression of tumor growth and vascularization in vivo (Holash, Abstract).

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

***** See Supplemental Next Sheet to continue *****

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 15/38203

***** Second Supplemental Sheet *****

Note re claims 5, 108, 139:

Claim 5 is objected to as unclear with regard to the element "of any preceding claim 1." For the purpose of this lack of Unity analysis, this ISA/USA has construed claim 5 to be dependent from claim 1.

Claim 108 is objected to as self-referring. For the purpose of this lack of Unity analysis, this ISA/USA has construed claim 108 to be dependent from claim 107.

Claim 139 is objected to, because claim 140 is its parent claim and also its dependent claim. For the purpose of this lack of Unity analysis, this ISA/USA has construed claim 139 to be dependent from claim 138.

Note re item 4:

Claims 6-27, 42-62, 116-145 are not drafted in accordance with the second and third sentences of Rule 6.4 (a). These claims are improper multiple dependent claims.