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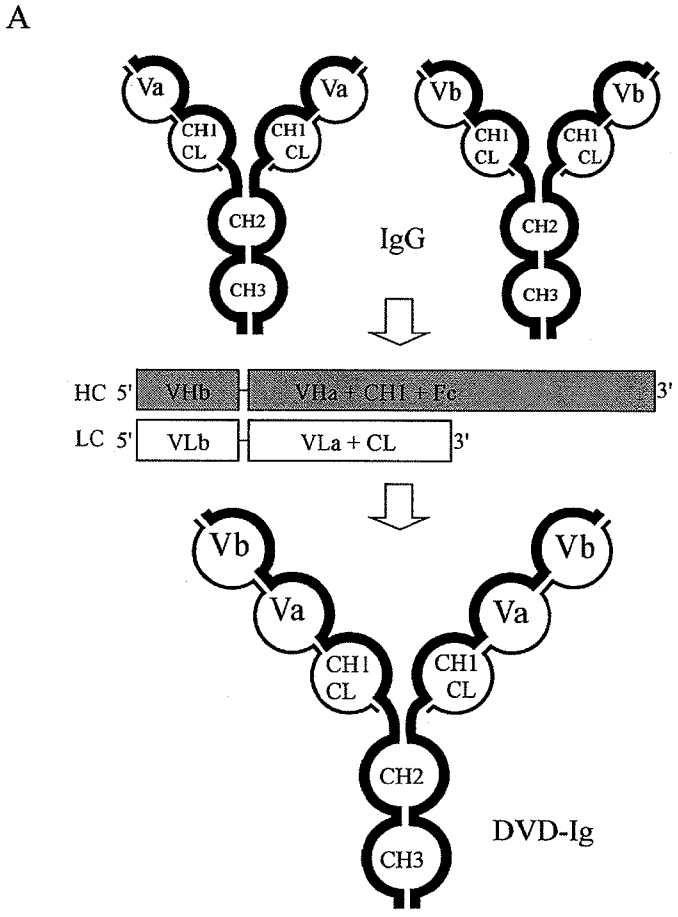
[Continued on next page]

(54) Title: DUAL VARIABLE DOMAIN IMMUNOGLOBULINS AND USES THEREOF

(57) Abstract: Engineered multivalent and multispecific binding proteins, methods of making, and their uses in the prevention, diagnosis, and/or treatment of disease are provided.

Figure 1



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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:
10 May 2012

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/49147

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/00; C07K 16/00 (2011.01)
USPC - 424/136.1; 530/388.15
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 39/00; C07K 16/00 (2011.01)
USPC - 424/136.1; 530/388.15

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)
PubWEST(PGPB,USPT,USOC,EPAB,JPAB); Google Scholar: binding, antibod$, antigen, polypep$, peptid$, protein, oligopept$, immunog$, tnf, tnf$, ngf, ngfb, nerve growth factor, fc, linker, cdr, heavy, variable, TVAPP, TVAPP$, ASTKGPS$.
GenCore 6.3: SEQ ID NO:21, 14, 28-31

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009/0215992 A1 (WU, et al.) 27 August 2009 (27.08.2009) para [0013]; [0015]-[0018]; [0024]-[0029]; [0031]-[0032]; [0052]; [0072]; [0073]; [0110]; [0126]; [0198]; [0209]-[0210]	1-4, 7-30, 59
X	US 2009/0311253 A1 (GHAYUR, et al.) 17 December 2009 (17.12.2009) para [0012]; [0015]; [0018]; [0019]; [0105]; [0160]; [0250]; Table 2; SEQ ID NO: 14, 21, 32, 33, 36, 37.	1, 5-6

☐ 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
13 March 2012 (13.03.2012)	21 MAR 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 11/49147

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.: 31-41, 46-58
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 1-30, 59, drawn to a binding protein capable of binding two antigens and that comprises a first and a second polypeptide chain, wherein said first polypeptide chain comprises a first VD1-(Xl)n-VD2-C(X2)n. The first invention is restricted to X1, X2 of SEQ ID NO:21, 14, 28-31. Should an additional fee(s) be paid, Applicant is invited to elect an additional SEQ ID NO(s) to be searched. Claims searched will depend on Applicant's election.

----------*continued on first blank sheet attached hereto*----------

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.:
1-30, 59, restricted to SEQ ID NO:21, 14, 28-31

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 Box **********

continuation of Box No. III: Observations where unity of invention is lacking

Group II: claims 42-45, 60, drawn to a method for generating a binding protein capable of binding two antigens by
a) obtaining a first parent antibody or antigen binding portion thereof, capable of binding a first antigen;
b) obtaining a second parent antibody or antigen binding portion thereof, capable of binding a second antigen;
c) constructing first and third polypeptide chains comprising VDI-(XI)n-VD2-C-(X2)n,
d) constructing second and fourth polypeptide chains comprising VDI-(XI)nVD2-C-(X2)n,
e) expressing the first, second, third and fourth polypeptide chains such that a binding protein capable of binding two antigens is generated.

The inventions listed as Groups I+ and 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 method for generating a binding protein capable of binding two antigens, as required by Group II.

The inventions of Group I+ share the technical feature of a binding protein of claim 1. However, this shared technical feature does not represent a contribution over prior art as being anticipated by US 2009/0215992 A1 to Wu et al. (hereinafter "Wu") that teaches a binding protein capable of binding two antigens and that comprises a first and a second polypeptide chain (para [0017]), wherein said first polypeptide chain comprises a first VD1-(X1)n-VD2-C-(X2)n (para [0013] and [0017]), wherein
VD1 is a first heavy chain variable domain (para [0013]);
VD2 is a second heavy chain variable domain (para [0013]);
C is a heavy chain constant domain (para [0013]);
X1 is a linker with the proviso that it is not CH1 (para [0013]); and
X2 is an Fc region (para [0013]); and
wherein said second polypeptide chain comprises a second VD1-(X1)n-VD2-C-(X2)n (para [0016]-[0017]), wherein
VD1 is a first light chain variable domain (para [0016]);
VD2 is a second light chain variable domain (para [0016]);
C is a light chain constant domain (para [0016]);
X1 is a linker (para [0016]);
X2 does not comprise an Fc region (para [0016]); and
wherein n is 0 or 1 (para [0110]), and
wherein the binding protein is capable of binding TNF and NGF (para [0018] and [0072]); wherein:
(a) X1 between the first and second heavy chain variable domains is ASTKGP (SEQ ID NO: 21) (para [0013]), and X1 between the first and second light chain variable domains is TVAAPSVFIFPP (SEQ ID NO: 14) (para [0016] and [0073]). As said method would have been obvious to one of ordinary skill in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Another special technical feature of the inventions listed as Group I+ is X1 of the specific amino acids sequence recited therein. The inventions do not share a special technical feature, because 1) no significant structural similarities can readily be ascertained among the sequences, and 2) Wu discloses that X1 between the first and second heavy chain variable domains is ASTKGP (SEQ ID NO: 21) (para [0013]), and X1 between the first and second light chain variable domains is TVAAPSVFIFPP (SEQ ID NO: 14) (para [0016] and [0073]). Without a shared special technical feature, the inventions lack unity with one another.

Another special technical feature of the inventions listed as Group I+ is CDRs of the specific amino acids sequence recited therein. The inventions do not share a special technical feature, because 1) no significant structural similarities can readily be ascertained among the sequences, and 2) US 2003/0092059 A1 to Salfeld, et al discloses the claimed SEQ ID NO: 28 (SEQ ID NO: 2, 100% identity) and US 2009/0304693 A1 to GHAYUR, et al. discloses the claimed SEQ ID NO: 29 (SEQ ID NO 35, 100% identity). Without a shared special technical feature, the inventions lack unity with one another.

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