Title: DUAL VARIABLE DOMAIN IMMUNOGLOBIN AND USES THEREOF

Abstract: The present invention relates to engineered multivalent and multispecific binding proteins, methods of making, and specifically to their uses in the prevention and/or treatment of acute and chronic inflammatory and other diseases.
INTERNATIONAL SEARCH REPORT

A CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 51/00; A61M 36/14; C12Q 1/68 (2008.04)
USPC - 424/1.49

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 424/1.49

Documentation searched other than minimum documentation to the extent that such document; are included in the fields searched

USPC 424/155 1, 178 1, 435/6, 69 1, 252 3, 254 21, 326, 348, 530/388 22, 388 8, 391 1, 536/23 53

text search see search terms below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PubWEST/PGPB,USPTO,USOC,EPAB,JPAB, Google, PubMed NCBI Blast

Search terms scDb, diabody, bispecific bivalent antibody, aktpkleegefeasr, crystal, controlled release, heavy chain, light chain variable domain, constant domain, Fc, SEQ ID NO 33, SEQ ID NO 35

C DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>ALT et al Novel tetravalent and bispecific IgG-like antibody molecules combining single-chain diabodig frac with the immunoglobulin gamma Fc or CH3 region FEBS Lett, 2 July 1999, Vol 454, No 1-2, pp 90-94, Fig 1, pg 90, para 3, 8, pg 91, para 1</td>
<td>1-7, 9, 12-17, 19-20, 23-30, 32-33, 35-37, 39-43 and 52-63</td>
</tr>
<tr>
<td>Y</td>
<td>Li et al Genetically engineered brain drug delivery vectors cloning, expression and in vivo application of an anti-transferrin receptor single chain antibody-streptavidin fusion gene and protein Protein Eng, September 1999, Vol 12, No 9, pp 787-796, Fig 4, amino acids 137-152</td>
<td>8, 10-11, 18, 21-22, 48-51</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C

Date of the actual completion of the international search
18 July 2008 (18 07 2008)

Date of mailing of the international search report
18 AUG 2008

Name and mailing address of the ISA/US
Mail Stop PCT, Attn ISA/US, Commissioner for Patents
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PCT/US 06/32398

Form PCT/ISA/210 (second sheet) (April 2007)
INTERNATIONAL SEARCH REPORT

**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 44-47 and 66-76 because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 64(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:

Sea extra 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 1-43 and 48-65, limited to the linker AKTTPKLEEDEPSEAR and SEQ ID No 33, namely claims 1-33, 35-37, 39-43, and 48-65

**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

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2007)
Inventions 1-990 claims 1-43 and 48-65, directed to a binding protein comprising a polypeptide chain, wherein said chain comprises VD1-(X1)n-VD2-C-(X2)n. wherein VD1 is a first variable domain, VD2 is a second variable domain. C is a constant domain. X1 represents an amino acid or polypeptide. X2 represents an Fc region and n is Oor 1 X1 can be a linker which is selected from the group consisting of 30 different polypeptide sequences as described in claim 8 (and 18) In addition, the binding protein comprises a DVD (heavy chain and light chain) amino acid sequence selected from the group consisting of 33 SEQ ID Nos as described in claims 31, 34 and 38

It will be readily apparent that the 30 polypeptide sequences of claim 8 (and 18) do not share any significant structural element and cannot be considered as having the same or corresponding technical feature. In addition, the amino acids having the 33 SEQ ID Nos as described in claims 31, 34 and 38 also do not share any significant structural element and cannot be considered as having the same or corresponding technical feature. Thus, inventions 1-990 (30 x 33) do not share any underlying common technical feature and therefore lack unity of invention as required under Rule 64 (a)

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13 1

In this case, first named species is the binding protein, etc with the first linker listed in claim 8, namely AKTTPKLEEGEFEAR along with SEQ ID NO 33 applicable to claims 1-43 and 48-65

In order for more than one species to be examined, the appropriate additional examination fees must be paid and the desired species specified. The species are as follows
The species pertaining to additional linkers described in claim 8, 1e AKTTPKLEEGEFEARV, AKTTPKLG, etc
Additional species include
The species pertaining to the DVD heavy and light chain amino acid sequences SEQ ID No 37, SED ID No 41, etc as described in claims 31, 34 and 38

Claims 44-47 and 66-76 are improper multiple dependent claims because they are dependent claims and do not comply with the second and third sentences of Rule 64 (a)