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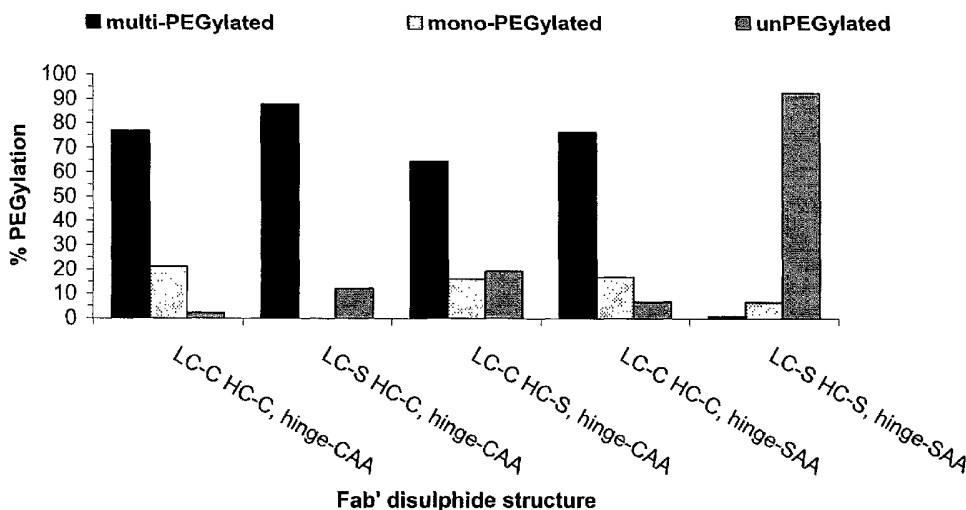
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(54) Title: MODIFIED ANTIBODY FRAGMENTS



(57) Abstract: The present invention relates to a new class of antibody fragments including antibody Fab and Fab' fragments in which the heavy chain is not covalently bonded to the light chain and two or more effector molecules are attached to the fragment, of which at least one of said molecules is attached to a cysteine in the heavy or light chain constant region.

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# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB2004/002871

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 C07K16/00 A61K39/395

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 7 C07K A61K

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 practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, Sequence Search

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No.    |
|------------|---|--------------------------|
| X          | WO 98/37200 A (GENENTECH, INC; HSEI, VANESSA; KOUMENIS, IPHIGENIA; LEONG, STEVEN, R;) 27 August 1998 (1998-08-27)<br>"ANTIBODY FRAGMENT-POLYMER CONJUGATES AND HUMANIZED ANTI-IL-8 MONOCLONAL ANTIBODIES"<br>page 21, line 4 - line 9<br>page 23, line 9 - page 27, line 18<br>page 30, line 30 - page 31, line 10<br>page 42, line 29 - line 37<br>claim 14<br><div style="text-align: center; margin-top: 20px;">-----<br/>-/--</div> | 1-23,<br>31-38,<br>41-43 |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

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- \*E\* earlier document 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

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- \*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
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- \*&\* document member of the same patent family

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INTERNATIONAL SEARCH REPORT

International Application No  
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| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT |  |                                   |
|--|--|-----------------------------------|
| Category *   | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No.             |
| X  | <p>WO 97/36932 A (PHARMACIA &amp; UPJOHN AB;<br/>ANTONSSON, PER; HANSSON, JOHAN; BJOERK,<br/>PER; DO) 9 October 1997 (1997-10-09)<br/>"MODIFIED/CHIMERIC SUPERANTIGENS AND THEIR<br/>USE"<br/>page 14, line 28 - line 33<br/>page 19, line 1 - line 11<br/>claim 27</p> <p style="text-align: center;">-----</p>   | <p>1-23,<br/>31-38,<br/>41-43</p> |
| X  | <p>WO 99/15549 A (CELLTECH THERAPEUTICS LTD ;<br/>HUMPHREYS DAVID PAUL (GB))<br/>1 April 1999 (1999-04-01)<br/>"PEPTIDE SEQUENCES AS HINGE REGIONS IN<br/>PROTEINS LIKE IMMUNOGLOBULIN FRAGMENTS AND<br/>THEIR USE IN MEDICINE"<br/>page 15, line 16 - line 26<br/>page 30; table II</p>   | <p>1-23,<br/>31-38,<br/>41-43</p> |
| Y  | <p>page 20, line 22 - line 32</p> <p style="text-align: center;">-----</p>   | <p>32-38</p>                      |
| Y  | <p>BURMEISTER GETZ E ET AL: "COMPARISON<br/>BETWEEN THE SULFHYDRYL REDUCTANTS<br/>TRIS(2-CARBOXYETHYL)PHOSPHINE AND<br/>DITHIOTHREITOL FOR USE IN<br/>PROTEINBIOCHEMISTRY"<br/>ANALYTICAL BIOCHEMISTRY, ACADEMIC PRESS,<br/>SAN DIEGO, CA, US,<br/>vol. 273, 15 August 1999 (1999-08-15),<br/>pages 73-80, XP000946001<br/>ISSN: 0003-2697<br/>abstract<br/>page 73, right-hand column, last paragraph<br/>- page 74, paragraph 3<br/>discussion</p> <p style="text-align: center;">-----</p>                                  | <p>32-38</p>                      |
| X  | <p>SINGH RAJEEVA ET AL: "Labeling of<br/>antibodies by in situ modification of<br/>thiol groups generated from<br/>selenol-catalyzed reduction of native<br/>disulfide bonds"<br/>ANALYTICAL BIOCHEMISTRY, ACADEMIC PRESS,<br/>NEW YORK, NY, US,<br/>vol. 304, no. 2, 2002, pages 147-156,<br/>XP001165655<br/>ISSN: 0003-2697<br/>abstract<br/>figure 1<br/>page 155, left-hand column, paragraph 2 -<br/>right-hand column, paragraph 1</p> <p style="text-align: center;">-----</p> <p style="text-align: center;">-/--</p> | <p>24-41,43</p>                   |

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB2004/002871

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT |  |                       |
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| Category *   | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
| X  | LEONG S R ET AL: "Adapting pharmacokinetic properties of a humanized anti-interleukin-8 antibody for therapeutic applications using site-specific pegylation"<br>CYTOKINE, ACADEMIC PRESS LTD,<br>PHILADELPHIA, PA, US,<br>vol. 16, no. 3,<br>7 November 2001 (2001-11-07), pages<br>106-119, XP002314089<br>ISSN: 1043-4666 | 41                    |
| A  | the whole document   | 20-40,43              |
| P,X  | WO 2004/043492 A (BRACCO IMAGING S.P.A; DE<br>HAEN, CHRISTOPH; MAISANO, FEDERICO)<br>27 May 2004 (2004-05-27)<br>abstract<br>page 11, line 20 - page 12, line 12<br>page 23; examples 3-5<br>claim 1   | 24-41,43              |

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB2004/002871

## Box 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 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:

see additional 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 an additional fee, this Authority did not invite payment of any additional fee.
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.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-23 and 42 (completely) and 31-38, 41 and 43 (in part)

Antibody Fab' or Fab fragment, characterized in that the interchain cysteine of CH1, CL or both have been replaced by another amino acid.

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2. claims: 24-30, 39 and 40 (completely) and 31-38, 41 and 43 (in part)

Antibody Fab or fab' fragment, characterized in that the heavy chain is not covalently bonded to the light chain, and to which two or more effector molecules are attached, at least one to each of the interchain cysteines

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## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/GB2004/002871

| Patent document cited in search report |            | Publication date | Patent family member(s) | Publication date |
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