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(54) Title: METHODS OF GENERATING MULTISPECIFIC, MULTIVALENT AGENTS FROM V_H AND V_L DOMAINS

(57) Abstract: This invention relates to multi-specific, multivalent binding proteins and methods of generating these agents from V_H and V_L domains. The binding protein has three or more binding sites where at least one binding site binds with a hapten moiety and at least two sites bind with target antigens. The present invention further relates to bispecific, trivalent heterodimers that have at least one binding site with affinity towards molecules containing a histamine-succinyl-glycyl (HSG) moiety and at least two binding sites with affinity towards carcinoembryonic antigen (CEA), and to trispecific, trivalent heterodimers that have at least one binding site with affinity towards molecules containing a HSG moiety, at least one binding sites with affinity towards CEA, and at least one binding site having affinity towards a metal-chelate complex indium-DTPA. Moreover, this invention relates to recombinant vectors useful for the expression of these functional heterodimers in a suitable host.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/38985

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 15/85, 5/12, 15/63; A61K 39/395; C07K 16/00
 US CL : 530/387.3, 388.1, 388.85, 391.7; 435/320.1, 325; 424/133.1, 135.1, 156.1

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)
 U.S. : 530/387.3, 388.1, 388.85, 391.7; 435/320.1, 325; 424/133.1, 135.1, 156.1

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)
 Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,837,242 A (HOLLIGER et al.) 17 November 1998 (17.11.1998), see entire document, especially figure 1, column 8, 16, 22, 23, 26.	1-7, 18, 35-47
Y	US 6,121,424 A (WHITLOW et al.) 19 September 2000 (19.09.2000), see entire document, especially Figure 4B, 6A, 6B.	1-7, 18, 35-47
Y	US 6,096,289 A (GOLDENBERG) 01 August 2000 (01.08.2000), see entire document, especially column 15, lines 25-35, column 16, 18, 19, 22.	1-7, 18, 35-47
Y	PLUCKTHUN et al. New protein engineering approaches to multivalent and bispecific antibody fragments. Immunotechnology. 1997, Vol.3, pages 83-105, especially Figure 3.	1-7, 18, 35-47
Y	US 5,693,762 A (QUEEN et al.) 02 December 1997 (02.12.1997), see entire document, especially abstract.	6

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent published on or after the international filing date	"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
"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)	"&" document member of the same patent family
"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	

Date of the actual completion of the international search

11 September 2003 (11.09.2003)

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/38985

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claim Nos.: 8-17, 19-34 and 48-52
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:
Claims 8-17, 19-34, 48-52 were not searched because the claims recite SEQ ID in figures but there is no correspondence between the SEQ ID Nos and the figures.

3. Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

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.

INTERNATIONAL SEARCH REPORT

PCT/US02/38985

Continuation of B. FIELDS SEARCHED Item 3:

CAPLUS, WEST, MEDLINE CANCERLIT BIOSIS USPATFUL

SEARCH TERMS: inventor name, scfv, diabody, tumor, triabody, CEA, label, MRI, hMN-14