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27 November 2008

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(54) **Title:** ANTI-CHEMOKINE (CCL2, CCL3, CCL5, CXCLI l, CXCL12) SINGLE-DOMAIN ANTIBODIES

(57) **Abstract:** The present invention relates to amino acid sequences that are directed against chemokines, as well as to compounds or constructs, and in particular proteins and polypeptides, that comprise or essentially consist of one or more such amino acid sequences. The invention also relates to nucleic acids encoding such amino acid sequences and polypeptides; to methods for preparing such amino acid sequences and polypeptides; to host cells expressing or capable of expressing such amino acid sequences orpolypeptides; to compositions, and in particular to pharmaceutical compositions, that comprise such amino acid sequences, polypeptides, nucleic acids and/or host cells; and to uses of such amino acid sequences or polypeptides, nucleic acids, host ceils and/or compositions, in particular for prophylactic, therapeutic or diagnostic purposes.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/064466

A; CLASSIFICATION OF SUBJECT MATTER
INV . C07K16/24

According to International Patent Classification (IPC) or Io both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K

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-Interπai, WPI Data, BIOSIS, Sequence Search

C. DOCUMENTS CONSIDERED VO BE RELEVANT

Category*	Citation of document, with Indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/02640 A (NOVARTIS AG [CH]; NOVARTIS ERFIND VERWALT GMBH [AT]; HIESTAND PETER [C) 10 January 2002 (2002-01-10) abstract claims 1-13	1-324
X	WO 2006/085961 A (CENTOCOR INC [US]; DAS ANUK [US]; CARTON JILL M [US]) 17 August 2006 (2006-08-17) the whole document claims 1-4,9-15	1-324
X	US 2006/246069 Al (SUGIHURA KAZUHISA [CH] SUGIMURA KAZUHISA [JP] ET AL) 2 November 2006 (2006-11-02) abstract; claims 1-37,41,42	1-324

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* 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 document but published on or after ltie international filing date

'L" document which may throw doubts on priority claimfs) 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 docu- ments, such combination being obvious to a person skilled in the art

'S" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 June 2008	26/09/2008
Name and mailing address of the ISA/ European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx. 31 651 epo nl, Fax. (+31-70)340-3016	Authorized officer Lechner, Oskar

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International application No
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C(ContInuatIo π). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with Indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/016769 A (ABGENIX INC [US]; GUDAS JEAN M [US]; HAAK-FRENDSCHO MARY [US]; FOORD 0) 26 February 2004 (2004-02-26) the whole document	1-324
A	RUDIKOFF S ET AL: "Single amino acid substitution altering antigen-binding specificity" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE, WASHINGTON, DC, vol. 79, 1 March 1982 (1982-03-01), pages 1979-1983, XP007901436 ISSN: 0027-8424 the whole document	1-324
A	HOLLIGER PHILIPP ET AL: "ENGINEERED ANTIBODY FRAGMENTS AND THE RISE OF SINGLE DOMAINS" NATURE BIOTECHNOLOGY, NATURE PUBLISHING GROUP, NEW YORK, NY, US, VOl . 23, no. 9 , 1 September 2005 (2005-09-01), pages 1126-1136, XP008076746 ISSN: 1087-0156 the whole document	1-324
A	REVETS H ET AL: "NANOBODIES AS NOVEL AGENTS FOR CANCER THERAPY" €XPERT OPINION ON BIOLOGICAL · THERAPY, ASHLEY, LONDON, GB, vol. 5 , no. 1 , 1 January 2005 (2005-01-01), pages 111-124, XP009076361 ISSN: 1471-2598 the whole document	1-324
A	ELS CONRATH K ET AL: "Camel single-domain antibodies as modular building units in bispecific and bivalent antibody constructs" JOURNAL OF BIOLOGICAL CHEMISTRY, AL, vol . 276, no. 10, 9 March 2001 (2001-03-09), pages 7346-7350, XP002248402 ISSN: 0021-9258 the whole document	1-324

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/064466

C(Contlnuatlo π). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication where appropriate of the relevant passages	Relevant to claim No
A	**RIECHMANN L ET AL: "Single domain antibodies: comparison of camel VH and camel ised human VH domains"** **JOURNAL OF IMMUNOLOGICAL** METHODS, **ELSEVIER SCIENCE PUBLISHERS B .V . .AMSTERDAM,** NL, **vol. 231, no.** 1-2, **10 December 1999** (1999-12-10), **pages** 25-38, **XP004187632** **ISSN: 0022-1759** **the whole document**	**1-324**
A	**CONRATH K ET AL: "Antigen Binding and** Solubility **Effects upon the Veneering of a Camel VHH in Framework-2 to Mimic a VH"** **JOURNAL OF MOLECULAR** BIOLOGY, LONDON, GB, **vol.** 350, **no. 1, 1 July 2005** (2005-07-01), **pages** 112-125, **XP004918534** **ISSN: 0022-2836** **the whole document**	**1-324**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/064466

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. [MM] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 267-270 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2 [X] 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:

see FURTHER INFORMATION sheet PCT/ISA/210

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 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:

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 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. [y] 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.:

1-324 (all in part and only as far as and if relating to antiCCL2(=MCPl) VH H according to SeqID 126)

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 trie payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box II. 1

Although claims 267-270 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II. 2

Claims Nos.: 1-324 (all only in part and only as far as relating to invention 1)

The majority of claims 1-324 are unclear (Art. 6 PCT) as they attempt to define the subject-matter in terms of the result to be achieved, i.e. amino acid sequence, compounds etc. directed against and/or specifically binding to a chemokine, i.e. in terms of functional features only defining the problem which is to be solved without giving any (structural) element of the solution to the problem. The claims do not provide any criterion to discriminate between known and novel compounds. Thus, the lack of clarity is to such an extent that a meaningful search over the entire scope of said claims cannot be carried out.

Apart from that, the present application contains 324 claims ({75 independent claims, most of them being compound claims). There are so many independent and dependent claims, and they are drafted in such a way that the claims as a whole are not in compliance with the provisions of clarity and conciseness of Art. 6 PCT, as they erect a smoke screen in front of the skilled reader when assessing what should be the claimed subject-matter and could be the contribution over the prior art.

In addition, some of the claims contain typographical errors, which makes them not fully readable (c.f. e.g. claims 54-74 and many others).

Consequently, a meaningful search and examination could only be carried out in light of the molecules which are sufficiently defined by structural and functional features, i.e. anti-chemokine antibodies as well as methods and uses relating to said anti-chemokine antibodies.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no International search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome .

FURTHER INFORMATION CONTINUED FROM PCT/1S/W 210

This International Searching Authority found multiple (group!S Of) - inventions in this international application, as follows:

1. claims: 1-324 (all in part and only as far as and if relating to antiCCL2 (= MCPl) VHH according to SeqID 126)

antiCCL2 (= GDCF2; GDCF2 HCIl; HSMCR30 ; MCAF; MCPl; FIGC9434; SCYA2; SMC CF) VHH according to SeqID L26

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2. claims: 1-324 (all in part and only as far as and if relating to antiCCL2 (= MCPl) VHH according to SeqID 127)

antiCCL2 VHH according to SeqID 127

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3. claims: 1-324 (all in part and only as far as and if relating to ant1CCL2 (= MCPl) VHH according to SeqID 128)

antiCCL2 VHH according to SeqID 128

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4. claims: 1-324 (all in part and only as far as and if relating to antiCCL2 (= MCPl) VHH according to SeqID 129)

antiCCL2 VHH according to SeqID 129

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5. claims: 1-324 (all in part and only as far as and if relating to antiCCL2 (= MCPl) VHH according to SeqID 130)

aπtiCCL2 VHH according to SeqID 130

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6. claims: 1-324 (all In part and only as far as and if relating to antiCCL2 (= MCPl) VHH according to SeqID 131)

antiCCL2 VHH according to SeqID 131

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7. claims: 1-324 (all in part and only as far as and if relating to antiCCL2 (= MCPl) VHH according to SeqID 132)

antiCCL2 VHH according to SeqID 132

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8. claims: 1-324 (all in part and only as far as and if relating to

FURTHERINFORMATIONCONTINUEDFROM PCT/ISA/ 210

ant1CCL2 (= MCPl) VHH according to SeqID 133)

antiCCL2 VHH according to SeqID 133

9. claims: 1-324 (all in part and only as far as and if relating to antiCCL2 (= MCPl) VHH according to SeqID 134)

antiCCL2 VHH according to SeqID 134

10. claims: 1-324 (all in part and only as far as and if relating to antiCCL2 (= MCPl) VHH according to SeqID 135)

antTCCL2 VHH according to SeqID 135

11. claims: 1-324 (all in part and only as far as and if relating to antiCCL2 (= WCPl) VHH according to SeqID 136)

antiCCL2 VHH according to SeqID 136

12. claims: 1-324 (all in part and only as far as and if relating to antiCCL2 (= MCPl) VHH according to SeqID 137)

antiCCL2 VHH according to SeqID 137

13. claims: 1-324 (all in part and only as far as and if relating to antiCCL2 (= MCPl) VHH according to SeqID 138)

ant1CCL2 VHH according to SeqID 138

14. claims: 1-324 (all in part and only as far as and if relating to antiCCL2 (= MCPl) VHH according to SeqID 139)

antiCCL2 VHH according to SeqID 139

15. claims: 1-324 (all in part and only as far as and if relating to antiCCL2 (= MCPl) VHH according to SeqID 140)

antiCCL2 VHH according to SeqID 140

FURTHER INFORMATION CONTINUED FROM PCT/1SA/ £10

16. claims: 1-324 (all in part and only as far as and if relating to antiCCL2 (= MCPl) VHH according to SeqID 141)

antiCCL2 VHH according to SeqID 141

17. claims: 1-324 (all in part and only as far as and if relating to antiCCL2 (= MCPl) VHH according to SeqID 142)

antiCCL2 VHH according to SeqID 142

18. claims: 1-324 (all in part and only as far as and if relating to antiCCL2 (= MCPl) VHH according to SeqID 143)

antiCCL2 VHH according to SeqID 143

19. claims: 1-324 (all 1n part and only as far as and if relating to antiCCL2 (= MCPl) VHH according to SeqID 144)

ant1CCL2 VHH according to SeqID 144

20. claims: 1-324 (all in part and only as far as and if relating to antiCCL2 (= MCPl) VHH according to SeqID 145)

antiCCL2 VHH according to SeqID 145

21. claims: 1-324 (all in part and only as far as and if relating to antiCCL2 (= MCPl) VHH according to SeqID 146)

antiCCL2 VHH according to SeqID 146

22. claims: 1-324 (all in part and only as far as and if relating to antiCCL2 (= MCPl) VHH according to SeqID 147)

antiCCL2 VHH according to SeqID 147

23. claims: 1-324 (all in part and only as far as and if relating to antiCCL2 (= MCPl) VHH according to SeqID 148)

antiCCL2 VHH according to SeqID 148

FURTHERINFORMATION CONTINUED FROM PCT∧SA/ 210

24. claims: 1-324 (all in part and only as far as and if relating to ant-CCL2 (= MCPl) VHH according to SeqID 149)

antiCCL2 VHH according to SeqID 149
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25. claims: 1-324 (all in part and only as far as and if relating to antiCCL2 (= MCPl) VHH according to SeqID 150)

antiCCL2 VHH according to SeqID 150
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26. claims: 1-324 (all in part and only as far as and if relating to antiCCL2 (= MCPl) VHH according to SeqID 151)

antiCCL2 VHH according to SeqID 151
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27. claims: 1-324 (all in part and only as far as and if relating to antiCCL2 (= MCPl) VHH according to SeqID 152)

antiCCL2 VHH according to SeqID 152
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28. claims: 1-324 (all in part and only as far as and if relating to CCL3)

amino acids directed to and /or binding specifically to CCL3 (= scya3; Id78alpha; mipla; Id78 alpha beta; chemokine cc motif ligand 3; small inducible cytokine a3 homologous to mouse m; gθsl91; mipi alpha)
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29. claims: 1-324 (all in part and only as far as and if relating to CCL5)

amino acids directed to and /or binding specifically to CCL5 (= small inducible cytokine a5; sis delta; mgcl7164; small inducible cytokine subfamily a cys cys member 5; rantes; beta chemokine rantes precursor; small Inducible cytokine subfamily a cys cys me; tcp228; small inducible cytokine a5 rantes; sisd; chemokine cc motif ligand 5; scya5; regulated upon activation normally texpressed a; tcell specific rantes; beta chemokine rantes; regulated upon activation normally texpressed and presumably secreted; tcell specific protein p288; dl7sl36e; chemokine (C C motif) ligand 5)
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30. claims: 1-324 (all 1n part and only as far as and if relating to CXCLIl)

FURTHER INFORWIATION CONTINUED FROM PCT/ISA/ 210

amino acids directed to and /or binding specifically to CXCLIl (= scyb9b; small .inducible cytokine subfamily b cysx cys member 9b; itac; scybll; mgcl02770; hl74; brl; small inducible cytokine subfamily b cysx cys member 11; small inducible cytokine bll; chemokine cxc motif ligand 11; ip9; small inducible cytokine subfamily b cysx cys; chemokine (C X C motif) ligand 11)

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31. claims: 1-324 (all in part and only as far as and if relating to CXCL12)

amino acids directed to and /or binding specifically to CXCL12 (= tlsfb; stromal cell derived factor Ia; sdflb; tlsfa; chemokine cxc motif ligand 12 stromal cell derived factor 1; chemokine; stromal cell derived factor 1; sdfla; stromal cell derived factor 1 delta; tparl; scybl2; pbsf; stromal cell derived factor 1 gamma; sdfl; chemokine (C X C motif) ligand 12 (stromal cell-derived factor I))

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2007/064466

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