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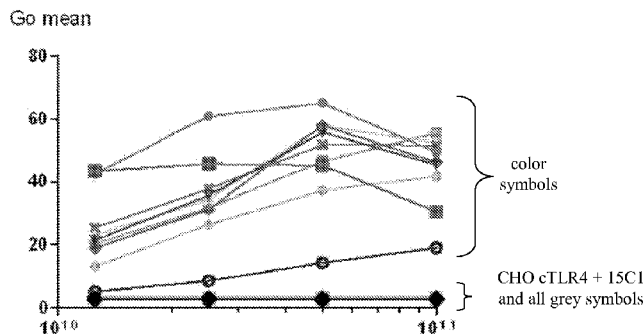
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AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,
BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
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KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
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NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU,
RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ,
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TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,

[Continued on next page]

(54) Title: ANTI-TLR4 ANTIBODIES AND USES THEREOF

FIGURE 1



- + CHO cTLR4 + 1A1
- + CHO + 1A1
- + CHO cTLR4 + 1A6
- + CHO + 1A6
- + CHO cTLR4 + 1B12
- + CHO + 1B12
- + CHO cTLR4 + 1C7
- + CHO + 1C7
- + CHO cTLR4 + 1C10
- + CHO + 1C10
- + CHO cTLR4 + 1C12
- + CHO + 1C12
- + CHO cTLR4 + 1D10
- + CHO + 1D10
- + CHO cTLR4 + 1E11
- + CHO + 1E11
- + CHO cTLR4 + 1G12
- + CHO + 1G12
- + CHO cTLR4 + 15C1
- + CHO + 15C1

(57) Abstract: Disclosed are antibodies that specifically bind Toll-like Receptor 4 (TLR-4), and to methods of using the anti-TLR4 antibodies as therapeutics and diagnostic agents.

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EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,
LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,
SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/28
ADD.

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)
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 practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/065015 A2 (NOVIMMUNE SA [CH]; ELSON GREG CHRISTOPHER ANDREW [FR]) 21 July 2005 (2005-07-21) cited in the application page 2, paragraph 3 - paragraph 4; claims 1-52; examples 5,13,19,27 -----	1-24
X	WO 2009/101479 A2 (NOVIMMUNE SA [CH]; ELSON GREG [FR]; LEGER OLIVIER [FR]) 20 August 2009 (2009-08-20) cited in the application paragraph [0180] - paragraph [0203]; examples 1,2,4 -----	1-24
X	WO 2009/138494 A2 (ABLYNX NV [BE]; VANLANDSCHOOT PETER [BE]; VERRIPS CORNELIS THEODORUS []) 19 November 2009 (2009-11-19) paragraph [0379]; examples 1,5 -----	1-21
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Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p>
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Date of the actual completion of the international search 6 November 2013	Date of mailing of the international search report 05/12/2013
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Siaterli, Maria
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/034543

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.:
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. 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.:

1-24(partially)

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.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/034543

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/110678 A2 (NOVIMMUNE SA [CH]; ELSON GREG [FR]; LEGER OLIVIER [FR]) 4 October 2007 (2007-10-04) cited in the application paragraph [0379]; claims 1-29; examples 35,38,39	1-24
X	----- DAUBEUF BRUNO ET AL: "TLR4/MD-2 monoclonal antibody therapy affords protection in experimental models of septic shock.", JOURNAL OF IMMUNOLOGY (BALTIMORE, MD. : 1950) 1 NOV 2007, vol. 179, no. 9, 1 November 2007 (2007-11-01), pages 6107-6114, XP002711709, ISSN: 0022-1767 page 6109, right-hand column - page 6110, right-hand column, paragraph 2; figure 5c	1-22
X	----- InvivoGen: "MAb-hTLR4", 1 May 2011 (2011-05-01), pages 1-1, XP002711710, Retrieved from the Internet: URL: http://www.invivogen.com/PDF/MAb_hTLR4 _TDS.pdf [retrieved on 2013-08-21] the whole document	1-21
X	----- S. SPILLER ET AL: "TLR4-induced IFN- production increases TLR2 sensitivity and drives Gram-negative sepsis in mice", JOURNAL OF EXPERIMENTAL MEDICINE, vol. 205, no. 8, 1 January 2008 (2008-01-01), pages 1747-1754, XP055028773, ISSN: 0022-1007, DOI: 10.1084/jem.20071990 page 1752, right-hand column paragraph [results&discussion]	1-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2013/034543

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005065015	A2	21-07-2005	AT 544783 T 15-02-2012
			AU 2004311541 A1 21-07-2005
			CA 2548990 A1 21-07-2005
			DK 1711531 T3 30-04-2012
			EP 1711531 A2 18-10-2006
			ES 2382039 T3 04-06-2012
			JP 4762152 B2 31-08-2011
			JP 2007517503 A 05-07-2007
			PL 1711531 T3 31-07-2012
			PT 1711531 E 18-04-2012
			WO 2005065015 A2 21-07-2005

WO 2009101479	A2	20-08-2009	AU 2008350535 A1 20-08-2009
			CA 2689680 A1 20-08-2009
			CN 101720232 A 02-06-2010
			EP 2173381 A2 14-04-2010
			JP 2010526868 A 05-08-2010
			US 2012142098 A1 07-06-2012
			WO 2009101479 A2 20-08-2009

WO 2009138494	A2	19-11-2009	NONE

WO 2007110678	A2	04-10-2007	AU 2005339476 A1 09-08-2007
			CA 2604334 A1 04-10-2007
			EP 1866336 A2 19-12-2007
			JP 2008527049 A 24-07-2008
			JP 2011190273 A 29-09-2011
			US 2005265998 A1 01-12-2005
			US 2008118514 A1 22-05-2008
			US 2010266619 A1 21-10-2010
			US 2012148606 A1 14-06-2012
			WO 2007110678 A2 04-10-2007

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-24(partially)

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 6 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 4, named 1A1;

2. claims: 1-24(partially)

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 8 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 4

3. claims: 1-24(partially)

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 10 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 4;

4. claims: 1-24(partially)

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 12 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 4;

5. claims: 1-24(partially)

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 14 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 4;

6. claims: 1-24(partially)

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 16 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 4;

7. claims: 1-24(partially)

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 18 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 4;

8. claims: 1-24(partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 2 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 4;

9. claims: 1-24(partially)

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 20 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 4;

10. claims: 1-24(partially)

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 22 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 4;

11. claims: 1-24(partially)

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 67 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 4;

12. claims: 1-24(partially)

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 69 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 4;

13. claims: 1-24(partially)

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 71 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 4;

14. claims: 1-24(partially)

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 73 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 4;

15. claims: 1-24(partially)

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 75 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 4;

16. claims: 1-24(partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 77 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 4;

17. claims: 1-24(partially)

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 2 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 79;

18. claims: 1-24(partially)

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 2 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 81;

19. claims: 1-24(partially)

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 2 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 83;

20. claims: 1-24(partially)

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 2 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 85;

21. claims: 1-24(partially)

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 2 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 87

22. claims: 1-24(partially)

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 69 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 79;

23. claims: 1-24(partially)

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 69 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 83;

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

24. claims: 1-24(partially)

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 69 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 85;

25. claims: 1-24(partially)

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 69 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 87.
