(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 May 2016 (12.05.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/071376 A3

(51) **International Patent Classification**:
C07K 16/22 (2006.01) *C07K 16/46* (2006.01)
C07K 16/28 (2006.01)

(21) **International Application Number**:
PCT/EP2015/075656

(22) **International Filing Date**:
4 November 2015 (04.11.2015)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
14192052.0 6 November 2014 (06.11.2014) EP

(71) **Applicant** *(for all designated States except US)*: **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, CH-4070 Basel (CH).

(71) **Applicant** *(for US only)*: **HOFFMANN-LA ROCHE INC.** [US/US]; Great Notch, 150 Clove Road, 8th Floor, Little Falls, New Jersey 07424 (US).

(72) **Inventors**: **MOESSNER, Ekkehard**; Felsenburgweg 5, CH-8280 Kreuzlingen (CH). **SCHLOTHAUER, Tilman**; Sonnenstrasse 3a, 82377 Penzberg (DE).

(74) **Agents**: **SKOLAUT, Alexander** et al.; Roche Diagnostics GmbH, Patent Department (LPP.....6164), P.O.Box 11 52, 82372 Penzberg (DE).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, 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, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, 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, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

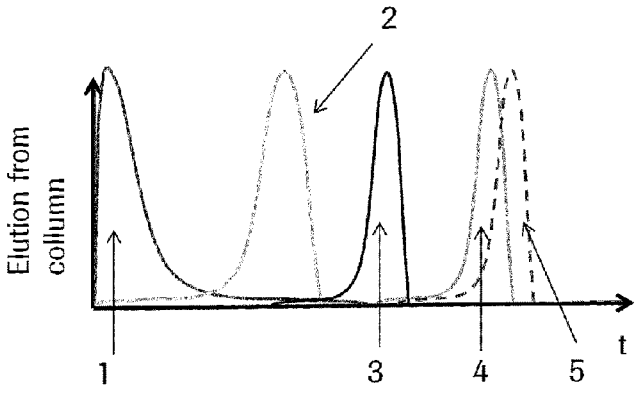
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

[Continued on next page]

(54) **Title**: FC-REGION VARIANTS WITH MODIFIED FCRN-BINDING AND METHODS OF USE

Figure 1



(57) **Abstract**: Herein is reported an IgG class Fc-region comprising a first variant Fc-region polypeptide and a second variant Fc-region polypeptide, wherein a) the first variant Fc-region polypeptide is derived from a first parent IgG class Fc-region polypeptide and the second variant Fc-region polypeptide is derived from a second parent IgG class Fc-region polypeptide, whereby the first parent IgG class Fc-region polypeptide is identical to or different from the second parent IgG class Fc-region polypeptide, and b) the first variant Fc-region polypeptide differs from the second variant Fc-region polypeptide in one or more amino acid residues other than those amino acid residues in which the first parent IgG class Fc-region polypeptide differs from the second parent IgG class Fc-region polypeptide, and c) the IgG class Fc-region comprising the first variant Fc-region polypeptide and the second variant Fc-region polypeptide has an affinity to a human Fc-receptor that is different than that of an IgG class Fc-region comprising the first parent IgG class Fc-region polypeptide of a) and the second parent IgG class Fc-region polypeptide of a), wherein either the first Fc-region polypeptide or the second Fc-region polypeptide or both Fc-region polypeptides comprise independently of each other mutations or combination of mutations as specified in the application.

WO 2016/071376 A3

(88) Date of publication of the international search report:
30 June 2016

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2015/075656

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed:

      [X] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

      [ ] in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      [ ] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2015/075656

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.:

1-15(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/EP2015/075656

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/22 C07K16/28 C07K16/46
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, Sequence Search, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YEUNG YIK ANDY ET AL: "A Therapeutic Anti-VEGF Antibody with Increased Potency Independent of Pharmacokinetic Half-life", CANCER RESEARCH, vol. 70, no. 8, April 2010 (2010-04), pages 3269-3277, XP002738426, ISSN: 0008-5472 the whole document ----- -/--	1-15

[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 application or patent 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

"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 documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 December 2015	11/05/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Kania, Thomas

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YEUNG YIK ANDY ET AL: "Engineering Human IgG1 Affinity to Human Neonatal Fc Receptor: Impact of Affinity Improvement on Pharmacokinetics in Primates", THE JOURNAL OF IMMUNOLOGY, THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS, US, vol. 182, no. 12, 1 June 2009 (2009-06-01) , pages 7663-7671, XP002566420, ISSN: 0022-1767, DOI: 10.4049/JIMMUNOL.0804182 the whole document	1-15
X	SHIELDS R L ET AL: "High resolution mapping of the binding site on human IgG1 for FcgammaRI, FcgammaRII, FcgammaRIII, and FcRn and design of IgG1 variants with improved binding to the FcgammaR", JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY, US, vol. 276, no. 9, 2 March 2001 (2001-03-02) , pages 6591-6604, XP002271092, ISSN: 0021-9258, DOI: 10.1074/JBC.M009483200 the whole document	1-15
A	MONNET CELINE ET AL: "Combined glyco- and protein-Fc engineering simultaneously enhance cytotoxicity and half-life of a therapeutic antibody", MABS, vol. 6, no. 2, March 2014 (2014-03), pages 422-436, XP002738427,	1-15
A	MEDESAN C ET AL: "Delineation of the amino acid residues involved in transcytosis and catabolism of mouse IgG1", THE JOURNAL OF IMMUNOLOGY, THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS, US, vol. 158, no. 5, 1 March 1997 (1997-03-01) , pages 2211-2217, XP002532767, ISSN: 0022-1767	1-15
A	KIM J-K ET AL: "Mapping the site on human IgG for binding of the MHC class I-related receptor, FcRn", EUROPEAN JOURNAL OF IMMUNOLOGY, WILEY - V C H VERLAG GMBH & CO. KGAA, DE, vol. 29, no. 9, 1 September 1999 (1999-09-01), pages 2819-2825, XP002300286, ISSN: 0014-2980, DOI: 10.1002/(SICI)1521-4141(199909)29:09<2819: :AID-IMMU2819>3.0.CO;2-6	1-15

1 -/--

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KIM H ET AL: "FcRn receptor-mediated pharmacokinetics of therapeutic IgG in the eye", MOLECULAR VISION, MOLECULAR VISION, SN, ATLANTA , vol. 15 16 December 2009 (2009-12-16), pages 2803-2812, XP002688851, ISSN: 1090-0535 Retrieved from the Internet: URL:http://www.molvis.org/molvis/v15/a296 -----	1-15
A	TIMOTHY T KUO ET AL: "Neonatal Fc Receptor: From Immunity to Therapeutics", JOURNAL OF CLINICAL IMMUNOLOGY, KLUWER ACADEMIC PUBLISHERS-PLENUM PUBLISHERS, NE, vol. 30, no. 6, 1 October 2010 (2010-10-01), pages 777-789, XP019858481, ISSN: 1573-2592, DOI: 10.1007/S10875-010-9468-4 -----	1-15
A	KUO TIMOTHY T ET AL: "Neonatal Fc receptor and IgG-based therapeutics", MABS, vol. 3, no. 5, September 2011 (2011-09), pages 422-430, XP002738428, -----	1-15
A	SPASSOV VELIN Z ET AL: "pH-selective mutagenesis of protein-protein interfaces: In silico design of therapeutic antibodies with prolonged half-life", PROTEINS STRUCTURE FUNCTION AND BIOINFORMATICS, vol. 81, no. 4, April 2013 (2013-04), pages 704-714, XP002738429, -----	1-15
A	WO 2012/125850 A1 (AMGEN INC [US]; LIU ZHI [US]; KANNAN GUNASEKARAN [US]; YAN WEI [US]) 20 September 2012 (2012-09-20) -----	1-15
A	WO 2014/006217 A1 (GENMAB B V [NL]) 9 January 2014 (2014-01-09) -----	1-15
A	WO 2011/028952 A1 (XENCOR INC [US]; LAZAR GREGORY A; MOORE GREGORY L) 10 March 2011 (2011-03-10) -----	1-15
A	WO 2010/151792 A1 (REGENERON PHARMA [US]; DAVIS SAMUEL [US]; SMITH ERIC [US]; MACDONALD D) 29 December 2010 (2010-12-29) -----	1-15

-/--

1

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/075656

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	WO 2014/177459 A2 (HOFFMANN LA ROCHE [CH]; HOFFMANN LA ROCHE [US]) 6 November 2014 (2014-11-06)	
T	WO 2014/177460 A1 (HOFFMANN LA ROCHE [CH]; HOFFMANN LA ROCHE [US]) 6 November 2014 (2014-11-06)	

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2015/075656

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012125850 A1	20-09-2012	AU 2012229048 A1	19-09-2013
		CA 2830254 A1	20-09-2012
		EP 2686345 A1	22-01-2014
		JP 2014509857 A	24-04-2014
		US 2014112926 A1	24-04-2014
		WO 2012125850 A1	20-09-2012
WO 2014006217 A1	09-01-2014	AU 2013285355 A1	29-01-2015
		CN 104736174 A	24-06-2015
		JP 2015524387 A	24-08-2015
		JP 2016508153 A	17-03-2016
		SG 11201408646V A	29-01-2015
		US 2015175707 A1	25-06-2015
		US 2015337049 A1	26-11-2015
		WO 2014006217 A1	09-01-2014
		WO 2014108483 A1	17-07-2014
WO 2011028952 A1	10-03-2011	US 2011054151 A1	03-03-2011
		WO 2011028952 A1	10-03-2011
WO 2010151792 A1	29-12-2010	AU 2010265933 A1	19-01-2012
		AU 2015207952 A1	20-08-2015
		CA 2766220 A1	29-12-2010
		CN 102471378 A	23-05-2012
		CN 103833855 A	04-06-2014
		EP 2445936 A1	02-05-2012
		EP 2975051 A1	20-01-2016
		JP 5816170 B2	18-11-2015
		JP 2012531439 A	10-12-2012
		JP 2015227386 A	17-12-2015
		KR 20120027055 A	20-03-2012
		KR 20140112569 A	23-09-2014
		MY 152963 A	15-12-2014
		RU 2012102602 A	10-08-2013
		RU 2014114172 A	20-10-2015
		SG 176868 A1	28-02-2012
		TW 201116625 A	16-05-2011
		US 2010331527 A1	30-12-2010
		US 2014248664 A1	04-09-2014
		WO 2010151792 A1	29-12-2010
WO 2014177459 A2	06-11-2014	CA 2904805 A1	06-11-2014
		CN 105164157 A	16-12-2015
		EP 2992010 A2	09-03-2016
		KR 20160003818 A	11-01-2016
		US 2016068613 A1	10-03-2016
		WO 2014177459 A2	06-11-2014
WO 2014177460 A1	06-11-2014	AU 2014261630 A1	17-09-2015
		CA 2904806 A1	06-11-2014
		CN 105143262 A	09-12-2015
		CR 20150512 A	19-11-2015
		EP 2992012 A1	09-03-2016
		KR 20160002858 A	08-01-2016
		PE 18072015 A1	02-12-2015
		PH 12015502470 A1	22-02-2016
		SG 11201508911P A	27-11-2015
		TW 201446799 A	16-12-2014

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2015/075656

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		WO 2014177460 A1	06-11-2014

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-15(partially)

An IgG class Fc-region comprising a first variant Fc-region polypeptide and a second variant Fc-region polypeptide, wherein a) the first variant Fc-region polypeptide is derived from a first parent IgG class Fc-region polypeptide and the second variant Fc-region polypeptide is derived from a second parent IgG class Fc-region polypeptide, whereby the first parent IgG class Fc-region polypeptide is identical to or different from the second parent IgG class Fc-region polypeptide, and b) the first variant Fc-region polypeptide differs from the second variant Fc-region polypeptide in one or more amino acid residues other than those amino acid residues in which the first parent IgG class Fc-region polypeptide differs from the second parent IgG class Fc-region polypeptide, and c) the IgG class Fc-region comprising the first variant Fc-region polypeptide and the second variant Fc-region polypeptide has an affinity to a human Fc-receptor that is different than that of an IgG class Fc-region comprising the first parent IgG class Fc-region polypeptide of a) and the second parent IgG class Fc-region polypeptide of a). Related products and medical uses, in particular wherein either the first Fc-region or the second Fc-region or both Fc-region polypeptides comprise independently of each other one of the following mutations or combinations of mutations:
- T307H
- T307H and (Q311H or E430H or N434A or N434H)
- T307H and Q311H and E430H and N434A
- T307H and Q311H and E430H and N434H
- T307H and Q311H and E430H and N434Y
- T307H and M252Y and S254T and T256E
- T307H and Q311H and M252Y and S254T and T256E
- T307H and E430H and M252Y and S254T and T256E
- T307H and N434A and M252Y and S254T and T256E
- T307H and N434H and M252Y and S254T and T256E
- T307H and Q311H and E430H and N434A and M252Y and S254T and T256E
- T307H and Q311H and E430H and N434H and M252Y and S254T and T256E
- T307H and Q311H and E430H and N434Y and M252Y and S254T and T256E.

---

2. claims: 1-15(partially)

idem for the following mutations or combinations of mutations:
- Q311H, as far as not covered by the previous subject
- T307Q and Q311H
- T307Q and Q311H and E430h and N434A
- T307Q and Q311H and E430h and N434H

- T307Q and Q311H and E430h and N434Y
- Q311H and M252Y and S254T and T256E
- T307Q and Q311H and M252Y and S254T and T256E
- T307Q and Q311H and E430H and N434A and M252Y and S254T and T256E
- T307Q and Q311H and E430H and N434H and M252Y and S254T and T256E
- T307Q and Q311H and E430H and N434Y and M252Y and S254T and T256E

---

3. claims: 1-15(partially)

idem for the following mutations or combinations of mutations:
- E430H as far as not covered by any of the previous subjects
- T307Q and E430H as far as not covered by any of the previous subjects
- E430H and M252Y and S254T and T256E
- T307Q and E430H and M252Y and S254T and T256E

---

4. claims: 1-15(partially)

idem for the following mutations or combinations of mutations:
- N434H as far as not covered by any of the previous subjects
- T307Q and N434H as far as not covered by any of the previous subjects
- N434H and M252Y and S254T and T256E as far as not covered by any of the previous subjects
- T307Q and N434H and M252Y and S254T and T256E

---

5. claims: 1-15(partially)

idem for the following mutations or combinations of mutations:
- T307Q and V308P and N434Y and Y436H
- T307Q and M252Y and S254T and T256E as far as not covered by any of the previous subjects
- T307Q and V308P and N434Y and Y436H and M252Y and S254T and T256E
