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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 February 2016 (04.02.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/016278 A3

(51) International Patent Classification:
C07K 16/18 (2006.01) *G01N 33/68* (2006.01)
C07K 14/47 (2006.01) *A61K 39/00* (2006.01)

(21) International Application Number:
PCT/EP2015/067327

(22) International Filing Date:
29 July 2015 (29.07.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
14179004.8 29 July 2014 (29.07.2014) EP

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(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))*

(88) Date of publication of the international search report:
24 March 2016

WO 2016/016278 A3

(54) Title: HUMAN-DERIVED ANTI-HUNTINGTIN (HTT) ANTIBODIES AND USES THEREOF

(57) Abstract: Provided are novel human-derived anti-huntingtin (HTT) antibodies and biotechnological derivatives thereof, preferably capable of binding mutated and/or aggregated HTT species and or fragments thereof, as well as methods related thereto. The human-derived anti-HTT antibodies and biotechnological derivatives can be used in pharmaceutical and diagnostic compositions for HTT targeted immunotherapy of Huntington Disease and diagnosis thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/067327

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/18 C07K14/47 G01N33/68 A61K39/00
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 G01N 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 practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DAVID C. BUTLER ET AL: "Bifunctional Anti-Huntingtin Proteasome-Directed Intrabodies Mediate Efficient Degradation of Mutant Huntingtin Exon 1 Protein Fragments", PLOS ONE, vol. 6, no. 12, 22 December 2011 (2011-12-22), page e29199, XP055160792, DOI: 10.1371/journal.pone.0029199 abstract page e29199, right-hand column ----- -/--	1-23

[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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 January 2016	26/01/2016

Name and mailing address of the ISA/	Authorized officer
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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.
A	LECERF J-M ET AL: "Human single-chain Fv intrabodies counteract in situ huntingtin aggregation in cellular models of Huntington's disease", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, NATIONAL ACADEMY OF SCIENCES, US, vol. 98, no. 8, 10 April 2001 (2001-04-10) , pages 4764-4769, XP002323805, ISSN: 0027-8424, DOI: 10.1073/PNAS.071058398 abstract page 4764, right-hand column, paragraphs 1,3 page 4765, left-hand column, paragraph 4 - right-hand column, paragraph 3 -----	1-23
X	US 2003/232052 A1 (KHOSHNAN ALI [US] ET AL) 18 December 2003 (2003-12-18) paragraphs [0178], [0183], [0191]; example 2 paragraphs [0141] - [0177]; example 1 paragraphs [0085] - [0088] paragraph [0092] paragraph [0093] paragraphs [0103] - [0108] -----	1-23
Y	JAN KO ET AL: "New anti-huntingtin monoclonal antibodies: implications for huntingtin conformation and its binding proteins", BRAIN RESEARCH BULLETIN, ELSEVIER SCIENCE LTD, OXFORD, GB, vol. 56, no. 3-4, 1 October 2001 (2001-10-01), pages 319-329, XP002509144, ISSN: 0361-9230, DOI: 10.1016/S0361-9230(01)00599-8 abstract; figure 2 ----- -/--	1-23

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KHOSHNAN ALI ET AL: "Effects of intracellular expression of anti-huntingtin antibodies of various specificities on mutant huntingtin aggregation and toxicity", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, NATIONAL ACADEMY OF SCIENCES, US, vol. 99, no. 2, 22 January 2002 (2002-01-22), pages 1002-1007, XP002401586, ISSN: 0027-8424, DOI: 10.1073/PNAS.022631799 abstract page 1003, right-hand column, paragraph 1 - page 1004, right-hand column, paragraph 3 -----	1-23
Y	J. LEGLEITER ET AL: "Monoclonal Antibodies Recognize Distinct Conformational Epitopes Formed by Polyglutamine in a Mutant Huntingtin Fragment", JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 284, no. 32, 7 August 2009 (2009-08-07), pages 21647-21658, XP055161156, ISSN: 0021-9258, DOI: 10.1074/jbc.M109.016923 abstract page 21651, right-hand column, paragraph 3 - page 21654, right-hand column, paragraph 1 -----	1-23
A	COLBY D W ET AL: "Development of a Human Light Chain Variable Domain (VL) Intracellular Antibody Specific for the Amino Terminus of Huntingtin via Yeast Surface Display", JOURNAL OF MOLECULAR BIOLOGY, ACADEMIC PRESS, UNITED KINGDOM, vol. 342, no. 3, 17 September 2004 (2004-09-17), pages 901-912, XP004536915, ISSN: 0022-2836, DOI: 10.1016/J.JMB.2004.07.054 abstract page 905, left-hand column, paragraph 4 - page 907, right-hand column, paragraph 3 ----- -/--	1-23

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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.
A	WO 2005/052002 A2 (MASSACHUSETTS INST TECHNOLOGY [US]; COLBY DAVID W [US]; WITTRUP DANE K) 9 June 2005 (2005-06-09) page 70, line 6 - page 73, line 6; example 3 page 21, lines 4-18; sequences 3,4	1-23
A	C. LANDLES ET AL: "Proteolysis of Mutant Huntingtin Produces an Exon 1 Fragment That Accumulates as an Aggregated Protein in Neuronal Nuclei in Huntington Disease", JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 285, no. 12, 19 March 2010 (2010-03-19), pages 8808-8823, XP055160798, ISSN: 0021-9258, DOI: 10.1074/jbc.M109.075028 Supplemental data: Table of Primary Antibodies; figure 1	1-23
A	WO 2008/081008 A1 (UNIV ZUERICH [CH]; NITSCH ROGER [CH]; HOCK CHRISTOPH [CH]; ESSLINGER C) 10 July 2008 (2008-07-10) paragraphs [0004] - [0006] paragraphs [0019], [0246], [0247], [0262]	1-23
Y	SOUTHWELL AMBER L ET AL: "Intrabody Gene Therapy Ameliorates Motor, Cognitive, and Neuropathological Symptoms in Multiple Mouse Models of Huntington's Disease", JOURNAL OF NEUROSCIENCE, vol. 29, no. 43, October 2009 (2009-10), pages 13589-13602, XP002752702, ISSN: 0270-6474 abstract page 13598, left-hand column, paragraph 4 - page 13600, right-hand column, paragraph 4	1-23
Y	SOUTHWELL AMBER L ET AL: "Intrabodies binding the proline-rich domains of mutant huntingtin increase its turnover and reduce neurotoxicity", JOURNAL OF NEUROSCIENCE, vol. 28, no. 36, September 2008 (2008-09), pages 9013-9020, XP002752703, ISSN: 0270-6474 abstract page 9018, left-hand column, paragraph 2 - page 9019, right-hand column, paragraph 1 page 9016, left-hand column, paragraph 1	1-23

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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.
Y	DEHAY BENJAMIN ET AL: "Mapping of the epitope of monoclonal antibody 2B4 to the proline-rich region of human Huntingtin, a region critical for aggregation and toxicity", BIOTECHNOLOGY JOURNAL, vol. 2, no. 5, May 2007 (2007-05), pages 559-564, XP002752704, ISSN: 1860-6768 abstract page 560, left-hand column, paragraph 3 -----	1-23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2015/067327

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.:

1-23(partially)

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 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.

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(partially)

   An antibody recognizing a polyP-region of HTT and a peptide having an epitope of HTT, i.e. an epitope of polyP-region

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2. claims: 1-23(partially)

   An antibody recognizing the P-rich-region and a peptide having an epitope of HTT, i.e. an epitope of the P-rich-region

   ---

3. claims: 1-23(partially)

   An antibody recognizing the C-term-region of exon1 of HTT and a peptide having an epitope of HTT, i.e. an epitope of the C-term region of exon 1 comprising e.g. the sequence referred to as SEQ ID NO. 145 or 202

   ---

4. claims: 1-23(partially)

   An antibody recognizing the N-terminal region of HTT exon 1 and a peptide having an epitope of HTT, i.e. an epitope of the N-terminal region of exon1, comprising e.g. the sequence referred to as SEQ ID NO. 144

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5. claims: 1-23(partially)

   An antibody recognizing the Q/P-rich-region comprising e.g. the amino acid sequence referred to as SEQ ID NO. 201.

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6. claims: 1-23(partially)

   An antibody recognizing a conformational epitope of HTT exon1 (e.g. which is not present on a linear peptide derived from HTT exon1 but on aggregated recombinant HTT exon1 proteins HttExon1Q21 (HD21) and HttExon1Q49 (HD49))

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2015/067327

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2003232052 A1	18-12-2003	US 2003232052 A1	18-12-2003
		US 2008107657 A1	08-05-2008
		US 2010233180 A1	16-09-2010
WO 2005052002 A2	09-06-2005	US 2005226863 A1	13-10-2005
		WO 2005052002 A2	09-06-2005
WO 2008081008 A1	10-07-2008	AU 2008203703 A1	10-07-2008
		BR PI0806328 A2	06-09-2011
		CA 2674140 A1	10-07-2008
		CA 2764852 A1	10-07-2008
		CN 101622275 A	06-01-2010
		CN 102603893 A	25-07-2012
		CN 103408661 A	27-11-2013
		DK 2099826 T3	20-01-2014
		EA 200900954 A1	26-02-2010
		EA 201201067 A1	30-10-2013
		EP 2099826 A1	16-09-2009
		EP 2426143 A2	07-03-2012
		EP 2436696 A1	04-04-2012
		ES 2439490 T3	23-01-2014
		JP 5398545 B2	29-01-2014
		JP 2010514454 A	06-05-2010
		KR 20090114388 A	03-11-2009
		KR 20120017469 A	28-02-2012
		PT 2099826 E	09-01-2014
		SG 177954 A1	28-02-2012
		SI 2099826 T1	28-02-2014
		US 2010202968 A1	12-08-2010
		WO 2008081008 A1	10-07-2008