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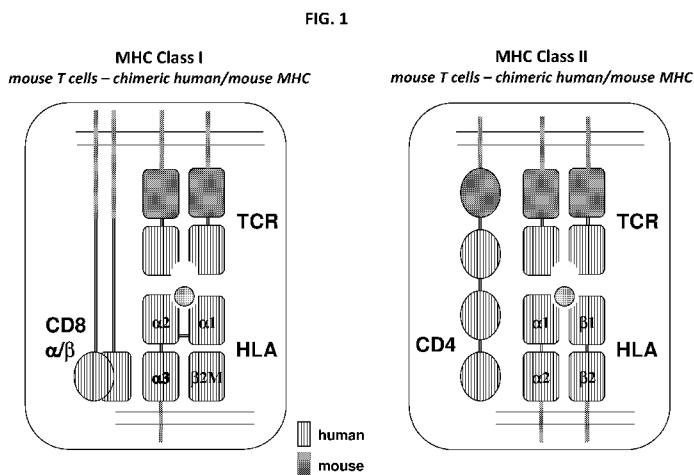
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— of inventorship (Rule 4.17(iv))

[Continued on next page]

(54) Title: HUMANIZED T CELL MEDIATED IMMUNE RESPONSES IN NON-HUMAN ANIMALS



(57) Abstract: Disclosed herein are non-human animals (e.g., rodents, e.g., mice or rats) genetically engineered to express a humanized T cell co-receptor (e.g., humanized CD4 and/or CD8 (e.g., CD8 α and/or CD8 β)), a human or humanized T cell receptor (TCR) comprising a variable domain encoded by at least one human TCR variable region gene segment and/or a human or humanized major histocompatibility complex that binds the humanized T cell co-receptor (e.g., human or humanized MHC II (e.g., MHC II α and/or MHC II β chains) and/or MHC I (e.g., MHC I α) respectively, and optionally human or humanized β 2 microglobulin). Also provided are embryos, tissues, and cells expressing the same. Methods for making a genetically engineered animal that expresses at least one humanized T cell co-receptor (e.g., humanized CD4 and/or CD8), at least one humanized MHC that associates with the humanized T cell co-receptor (e.g., humanized MHC II and/or MHC I, respectively) and/or the humanized TCR are also provided. Methods for using the genetically engineered animals that mount a substantially humanized T cell immune response for developing human therapeutics are also provided.





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INTERNATIONAL SEARCH REPORT

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B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
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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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/059263 A2 (SUNOL MOLECULAR CORP [US]) 1 August 2002 (2002-08-01)	1-3,5,7,8,14-18,20-23,30,31,34-37,41-70
Y	page 6, paragraph 1 - page 11, paragraph 3 page 17, paragraph 2 - page 22, paragraph 1 page 31, paragraph 6 - page 32, paragraph 3; claims; examples	1-31,33-70
Y	WO 2013/063361 A1 (REGENERON PHARMA [US]) 2 May 2013 (2013-05-02) claims; examples	1-31,33-70
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Further documents are listed in the continuation of Box C.

See patent family annex.

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Date of the actual completion of the international search 25 October 2016	Date of mailing of the international search report 08/11/2016
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 Sommer, Birgit

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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	WO 2014/164640 A1 (REGENERON PHARMA [US]) 9 October 2014 (2014-10-09) paragraph [[00181]]; claims; examples -----	1-31, 33-70
Y	WO 2014/130667 A1 (REGENERON PHARMA [US]) 28 August 2014 (2014-08-28) claims; examples -----	1-31, 33-70
Y	WO 2014/130671 A1 (REGENERON PHARMA [US]) 28 August 2014 (2014-08-28) claims; examples -----	1-31, 33-70

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2016/026260

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
WO 02059263	A2	01-08-2002	CA 2432133 A1	01-08-2002
			DK 1409646 T3	06-08-2012
			EP 1409646 A2	21-04-2004
			ES 2389251 T3	24-10-2012
			JP 2005505236 A	24-02-2005
			JP 2009034106 A	19-02-2009
			US 2003093818 A1	15-05-2003
			WO 02059263 A2	01-08-2002

WO 2013063361	A1	02-05-2013	AU 2012327204 A1	23-05-2013
			AU 2016202512 A1	12-05-2016
			CA 2853707 A1	02-05-2013
			CN 104011071 A	27-08-2014
			EP 2771357 A1	03-09-2014
			HK 1198171 A1	13-03-2015
			JP 2014532413 A	08-12-2014
			KR 20140077219 A	23-06-2014
			NZ 623147 A	31-03-2016
			RU 2014121160 A	10-12-2015
			SG 11201401030W A	28-04-2014
			US 2013109053 A1	02-05-2013
			US 2016021856 A1	28-01-2016
			WO 2013063361 A1	02-05-2013

WO 2014164640	A1	09-10-2014	AU 2014249150 A1	24-09-2015
			CA 2902543 A1	09-10-2014
			CN 105188358 A	23-12-2015
			EP 2967014 A1	20-01-2016
			HK 1212859 A1	24-06-2016
			JP 2016510998 A	14-04-2016
			KR 20150131150 A	24-11-2015
			WO 2014164640 A1	09-10-2014

WO 2014130667	A1	28-08-2014	AU 2014218893 A1	10-09-2015
			CA 2900824 A1	28-08-2014
			CN 105164154 A	16-12-2015
			EP 2958937 A1	30-12-2015
			HK 1214613 A1	29-07-2016
			JP 2016507247 A	10-03-2016
			KR 20150122710 A	02-11-2015
			US 2014245467 A1	28-08-2014
			WO 2014130667 A1	28-08-2014

WO 2014130671	A1	28-08-2014	AU 2014218897 A1	10-09-2015
			CA 2900832 A1	28-08-2014
			CN 105164153 A	16-12-2015
			EP 2958938 A1	30-12-2015
			HK 1213908 A1	15-07-2016
			JP 2016506761 A	07-03-2016
			KR 20150119409 A	23-10-2015
			US 2014245466 A1	28-08-2014
			WO 2014130671 A1	28-08-2014
