

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
4 December 2008 (04.12.2008)

PCT

(10) International Publication Number
WO 2008/145140 A3

(51) International Patent Classification:
C12N 15/85 (2006.01) C07K 16/28 (2006.01)

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(21) International Application Number:
PCT/DK2008/050127

(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, BR, BW, BY, BZ, CA, CH, 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, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(22) International Filing Date: 30 May 2008 (30.05.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PA 2007 00795 31 May 2007 (31.05.2007) DK

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(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- with sequence listing part of description published separately in electronic form and available upon request from the International Bureau

(88) Date of publication of the international search report:
29 January 2009

(54) Title: TRANSGENIC ANIMALS PRODUCING MONOVALENT HUMAN ANTIBODIES AND ANTIBODIES OBTAINABLE FROM THESE ANIMALS

(57) Abstract: The invention relates to novel non-human transgenic animals, which upon antigenic stimulation are capable of producing monovalent antibodies binding to a selected antigen, modified heavy chain transgenes, methods for producing the non-human transgenic animals, methods for immunizing the non-human transgenic animals for as well as monovalent antibodies obtainable by such immunization methods.



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INTERNATIONAL SEARCH REPORT

International application No

PCT/DK2008/050127

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C12N15/85 C07K16/28

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)
 C12N 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-Internal, WPI Data, BIOSIS, EMBASE, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/026427 A (GTC BIOTHERAPEUTICS INC [US]; BIRCK-WILSON ESZTER [US]; DAY MARIA [US]) 1 April 2004 (2004-04-01) page 17, paragraph 77 - page 21, paragraph 91	1, 37-39, 67
Y	page 25, paragraph 103 - page 29, paragraph 116; examples	1, 3-5, 13-16, 28-39, 41-46, 67-73
P, X	----- WO 2007/059782 A (GENMAB AS [DK]; PARREN PAUL [NL]; SCHUURMAN JANINE [NL]; VINK TOM [NL]) 31 May 2007 (2007-05-31) claims; examples ----- -/--	1, 3-5, 13-16, 28-39, 41-46, 67-73

Further documents are listed in the continuation of Box C.

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 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.
- *G* document member of the same patent family

Date of the actual completion of the international search

14 August 2008

Date of mailing of the international search report

25/11/2008

Name and mailing address of the ISA/
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 Sommer, Birgit

INTERNATIONAL SEARCH REPORT

International application No

PCT/DK2008/050127

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 2007/068255 A (GENMAB AS [DK]; LOSEN MARIO [NL]; MARTINEZ-MARTINEZ PILAR [NL]; DE BAE) 21 June 2007 (2007-06-21) page 44, line 7 - page 48, line 33; claims	1, 3-5, 13-16, 28-39, 41-46, 67-73
Y	WO 2004/056847 A (GENMAB AS [DK]; MEDAREX INC [US]; VAN DE WINKEL JAN G J [NL]; VAN DIJK) 8 July 2004 (2004-07-08) page 28, line 3 - line 25 page 44, line 4 - line 28; claims page 7, line 11 - line 22	1, 3-5, 13-16, 28-39, 41-46, 67-73
Y	WO 2004/045512 A (GENMAB AS [DK]; SCHUURMAN JANINE [NL]; HAVENITH CATHARINA EMANUELE GE) 3 June 2004 (2004-06-03) page 18, line 11 - line 33; claims	1, 3-5, 13-16, 28-39, 41-46, 67-73
Y	WO 02/12437 A (SCHOOTEN WIM VAN [US]; BUELOW ROLAND [US]; PLATZER JOSEF [DE]; BUELOW) 14 February 2002 (2002-02-14) claims	1, 3-5, 13-16, 28-39, 41-46, 67-73

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK2008/050127

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 allsearchable 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.:

see annex

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: 1-5 (all completely), 13-16, 28-39, 41-46, 67-73 (all partially)

a transgenic animal according to claim 1, i.e. a transgenic animal producing a monovalent antibody in general comprising a human VH region and a human CH region with a modified hinge region forming no inter-heavy chain bonds, as well as subject-matter related thereto;

2. claims: 6, 7 (all completely), 13-16, 28-39, 41-46, 67-73 (all partially)

a transgenic animal according to claim 6, i.e. a transgenic animal producing a monovalent IgG4 antibody comprising a human VH region, a human CH region with a modified hinge region forming no inter-heavy chain disulfide bonds, a human VL region and a human CL region, as well as subject-matter related thereto;

3. claims: 8, 9, 47-66 (all completely), 13-16, 28-39, 41-46, 67-73 (all partially)

a transgenic animal according to claim 8, i.e. a transgenic animal producing a monovalent IgG4 antibody comprising a human VH region, a human CH region with a modified hinge region forming no inter-heavy chain disulfide bonds and with additional specific amino acid substitutions in the CH3 region, a human VL chain and a human CL region, as well as subject-matter related thereto;

4. claims: 10, 11 (all completely), 13-16, 21-23, 28-39, 41-46, 67-73 (all partially)

a transgenic animal according to claim 10, i.e. a transgenic animal producing a monovalent IgG1 antibody comprising a human VH region, a human CH region with a modified hinge region and a modified CH3 region forming no inter-heavy chain bonds, a human VL region and a modified human CL region forming no inter-light chain bonds, as well as subject-matter related thereto;

5. claims: 12 (completely), 13-16, 28-39, 41-46, 67-73 (all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

a transgenic animal according to claim 12, i.e. a transgenic animal producing simultaneously a monovalent IgG1 antibody as defined in claims 10 or 11 and a monovalent IgG4 antibody as defined in any of claims 6-9, as well as subject-matter related thereto;

6. claims: 17-20 (all completely), 21-23, 28-39, 41-46, 67-73 (all partially)

a transgenic animal according to claim 17, i.e. a transgenic animal producing a monovalent IgG1 antibody comprising a human VH region, a human CH region with a modified hinge region and a modified CH3 region forming no inter-heavy chain bonds, wherein the CH3 region comprises the IgG1 CH3 region with SEQ ID No. 19 carrying additional specific amino acid substitutions, a human VL region and a modified human CL region forming no inter-light chain bonds, as well as subject-matter related thereto;

7. claims: 24, 25 (all completely), 28-39, 41-46, 67-73 (all partially)

a transgenic animal according to claim 24, i.e. a transgenic animal producing a monovalent antibody comprising a human VH region, a human CH region with a modified hinge region forming no inter-heavy chain bonds, wherein the CH3 region comprises the IgG2 CH3 region with SEQ ID No. 20 carrying additional specific amino acid substitutions; as well as subject-matter related thereto;

8. claims: 26, 27 (all completely), 28-39, 41-46, 67-73 (all partially)

a transgenic animal according to claim 26, i.e. a transgenic animal producing a monovalent antibody comprising a human VH region, a human CH region with a modified hinge region forming no inter-heavy chain bonds, wherein the CH3 region comprises the IgG3 CH3 region with SEQ ID No. 21 carrying additional specific amino acid substitutions, as well as subject-matter related thereto;

9. claims: 40 (completely), 68, 69 (all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

a heavy chain transgene comprising
(i) a plurality of human V genes, a plurality of human D genes, a plurality of human J genes and
(ii) a plurality of human CH genes and associated isotype switch sequences, comprising a human m CH gene and at least one modified y CH gene, wherein the human y CH gene is in closer proximity to the human m CH gene than in a naturally occurring human immunoglobulin heavy chain gene locus as well as subject-matter related thereto;

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/DK2008/050127

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2004026427	A	01-04-2004	AU 2003267135	A1 08-04-2004
			CA 2499269	A1 01-04-2004
			CN 1856324	A 01-11-2006
			EP 1549342	A2 06-07-2005
			JP 2006508062	T 09-03-2006
WO 2007059782	A	31-05-2007	AU 2006317242	A1 31-05-2007
			CA 2631184	A1 31-05-2007
			EP 1973576	A1 01-10-2008
WO 2007068255	A	21-06-2007	EP 1960431	A1 27-08-2008
WO 2004056847	A	08-07-2004	AU 2003303237	A1 14-07-2004
			EP 1572746	A2 14-09-2005
			JP 2006509828	T 23-03-2006
WO 2004045512	A	03-06-2004	AU 2003295471	A1 15-06-2004
			BR 0316282	A 11-10-2005
			CA 2505991	A1 03-06-2004
			CN 101124244	A 13-02-2008
			EP 1578397	A2 28-09-2005
			JP 2006523433	T 19-10-2006
			KR 20050086628	A 30-08-2005
			MX PA05005160	A 22-07-2005
NZ 540555	A 30-04-2008			
WO 0212437	A	14-02-2002	AU 8470301	A 18-02-2002
			CA 2422155	A1 14-02-2002
			CA 2634294	A1 14-02-2002
			CN 1468250	A 14-01-2004
			EP 1311530	A2 21-05-2003
			MX PA03001915	A 10-09-2004
			NO 20031054	A 02-04-2003
			NZ 524523	A 24-02-2006