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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 November 2009 (19.11.2009)

PCT

(10) International Publication Number
WO 2009/140348 A4

(51) International Patent Classification:
C07K 16/24 (2006.01) *C12P 21/08* (2006.01)

(21) International Application Number:
PCT/US2009/043734

(22) International Filing Date:
13 May 2009 (13.05.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/127,403 13 May 2008 (13.05.2008) US
61/194,156 25 September 2008 (25.09.2008) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier applications:
US 61/127,403 (CIP)
Filed on 13 May 2008 (13.05.2008)
US 61/194,156 (CIP)
Filed on 25 September 2008 (25.09.2008)

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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, 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, ST, SV, SY, 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, 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, MK, 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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(54) Title: ANTI-IL-6/IL-6R ANTIBODIES AND METHODS OF USE THEREOF

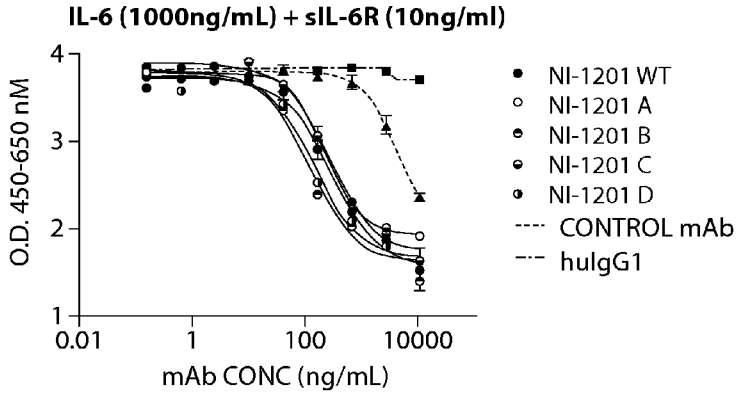

Fig. 1D

(57) Abstract: Fully human monoclonal antibodies that recognize the IL6/ IL-6R complex and methods of using such monoclonal antibodies as a therapeutic, diagnostic, and prophylactic are disclosed.

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Published:

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

— *with amended claims (Art. 19(1))*

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

(88) Date of publication of the international search report: 7 January 2010

Date of publication of the amended claims: 25 February 2010

AMENDED CLAIMS
received by the International Bureau on 4 December 2009 (04.12.2009)

1. An isolated fully human antibody that binds to IL-6/IL-6R complex (IL-6Rc) and prevents IL-6/IL-6 receptor complex (IL-6Rc) from binding to gp130 such that gp130-mediated intracellular signaling cascade is not activated in the presence of said antibody, wherein said antibody cross-blocks an antibody selected from the group comprising:

(i) an antibody comprising:

(a) the amino acid sequence QQSXSYPLT in the light chain complementarity determining region 3 (CDR3), where X is N or Q;

(b) the amino acid sequence GIIPX$_1$FX$_2$TTKYAQX$_3$FQG in the heavy chain complementarity determining region 2 (CDR2), where X$_1$ is L or A, X$_2$ is D or E, and X$_3$ is Q or K;

(c) the amino acid sequence DRDILTDYYPXGGMDV in the heavy chain complementarity determining region 3 (CDR3), where X is M or L; and

(d) the amino acid sequence TAVXYCAR in the framework region 3 (FRW3), where X is F or Y;

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

(iii) an antibody comprising the amino acid sequence QQSNSYPLT in the light chain CDR3 region, the amino acid sequence GIIPLFDTTKYAQKFQG in the heavy chain CDR2 region, the amino acid sequence DRDILTDYYPMGGMDV in the heavy chain CDR3 region, and the amino acid sequence TAVYYCAR in the FRW3 region;

(iv) an antibody comprising the amino acid sequence QQSNSYPLT in the light chain CDR3 region, the amino acid sequence GIIPLFDTTKYAQKFQG in the heavy chain CDR2 region, the amino acid sequence DRDILTDYYPLGGMDV in the heavy chain CDR3 region, and the amino acid sequence TAVYYCAR in the FRW3 region;

(v) an antibody comprising the amino acid sequence QQSNSYPLT in the light chain CDR3 region, the amino acid sequence GIIPAFETTKYAQKFQG in the heavy chain CDR2 region, the amino acid sequence

DRDILTDYYPLGGMDV in the heavy chain CDR3 region, and the amino acid sequence TAVYYCAR in the FRW3 region; and

(vi) an antibody comprising the amino acid sequence QQSQSYPLT in the light chain CDR3 region, the amino acid sequence GIIPAFETTKYAQKFQG in the heavy chain CDR2 region, the amino acid sequence DRDILTDYYPLGGMDV in the heavy chain CDR3 region, and the amino acid sequence TAVYYCAR in the FRW3 region.

2. The antibody of claim 1, wherein said antibody has an affinity of at least 1×10^{-8} for IL-6Rc.

3. The antibody of claim 1, wherein said antibody has an affinity of at least 1×10^{-9} for IL-6Rc.

4. The antibody of claim 1, wherein said antibody binds to an epitope in domain 3 of IL-6 receptor (IL-6R), wherein said epitope comprises at least the amino acid sequence AERSKT.

5. The antibody of claim 1, wherein said antibody does not modulate the interaction between IL-6 and IL-6R.

6. The antibody of claim 1, wherein said antibody also binds the IL-6R.

7. The antibody of claim 1, wherein said antibody comprises a V_H CDR1 region comprising the amino acid sequence of SEQ ID NO: 15, a V_H CDR2 region comprising the amino acid sequence of SEQ ID NO: 16, a V_H CDR3 region comprising the amino acid sequence of SEQ ID NO: 17, a V_L CDR1 region comprising the amino acid sequence of SEQ ID NO: 24, a V_L CDR2 region comprising the amino acid sequence of SEQ ID NO: 25, and a V_L CDR3 region comprising the amino acid sequence of SEQ ID NO: 26.

8. The isolated antibody of claim 1, wherein said antibody comprises:

(a) a V_H CDR1 region comprising the amino acid sequence of SEQ ID NO: 15, 18 or 21;

(b) a V_H CDR2 region comprising the amino acid sequence of SEQ ID NO: 16, 19, 22, 33, 34 or 35;

(c) a V_H CDR3 region comprising the amino acid sequence of SEQ ID NO: 17, 20, 23, 36 or 37;

(d) a V_L CDR1 region comprising the amino acid sequence of SEQ ID NO: 24, 27, 28, or 30;

(e) a V_L CDR2 region comprising the amino acid sequence of SEQ ID NO: 25; and

(f) a V_L CDR3 region comprising the amino acid sequence of SEQ ID NO: 26, 29, 31 or 32.

9. The antibody of claim 1, wherein said antibody comprises a heavy chain variable sequence comprising the amino acid sequence selected from SEQ ID NO: 2 and a light chain variable sequence comprising the amino acid sequence of SEQ ID NO: 4.

10. The antibody of claim 1, wherein said antibody is an IgG isotype.

11. The antibody of claim 1, wherein said antibody is an IgG1 isotype.

12. The antibody of claim 1, wherein said antibody comprises a heavy chain variable sequence comprising an amino acid sequence selected from SEQ ID NO: 2, 8, or 12 and a light chain variable sequence comprising the amino acid sequence of SEQ ID NO: 4, 6, 10 or 14.

13. An isolated fully human monoclonal anti-IL-6Rc antibody, or fragment thereof, wherein said antibody comprises:

(a) a V_H CDR1 region comprising the amino acid sequence of SEQ ID NO: 15, 18 or 21;

(b) a V_H CDR2 region comprising the amino acid sequence of SEQ ID NO: 16, 19, 22, 33, 34 or 35;

(c) a V_H CDR3 region comprising the amino acid sequence of SEQ ID NO: 17, 20, 23, 36 or 37;

(d) a V_L CDR1 region comprising the amino acid sequence of SEQ ID NO: 24, 27, 28, or 30;

(e) a V_L CDR2 region comprising the amino acid sequence of SEQ ID NO: 25; and

(f) a V_L CDR3 region comprising the amino acid sequence of SEQ ID NO: 26, 29, 31 or 32,

wherein said antibody binds the IL-6/IL-6R complex.

14. The antibody of claim 13, wherein said antibody also binds the IL-6R.

15. The antibody of claim 13, wherein said antibody is an IgG isotype.

16. The antibody of claim 13, wherein said antibody is an IgG1 isotype.

17. The antibody of claim 13, wherein said antibody comprises a heavy chain variable sequence comprising an amino acid sequence selected from SEQ ID NO: 2, 8, or 12 and a light chain variable sequence comprising the amino acid sequence of SEQ ID NO: 4, 6, 10 or 14.

18. The antibody of claim 13, wherein said antibody comprises a heavy chain variable sequence comprising the amino acid sequence selected from SEQ ID NO: 2 and a light chain variable sequence comprising the amino acid sequence of SEQ ID NO: 4.

19. A pharmaceutical composition comprising an antibody of any one of the preceding claims and a carrier.

20. A method of alleviating a symptom of a clinical indication associated with rheumatoid arthritis, Crohn's disease, psoriasis, multiple sclerosis or asthma in a subject, the method comprising administering the antibody any one of claims 1 to 18 to a subject in need thereof in an amount sufficient to alleviate the symptom of the clinical indication associated with rheumatoid arthritis, Crohn's disease, psoriasis, multiple sclerosis or asthma.

21. The method of claim 20, wherein said subject is a human.

22. A method of alleviating a symptom of a cancer, autoimmune disease or inflammatory disorder, the method comprising administering an antibody according to any one of claims 1 to 18 to a subject in need thereof in an amount sufficient to alleviate the symptom of the cancer, autoimmune disease or inflammatory disorder in the subject.

23. The method of claim 22, wherein said subject is a human.

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