located in helices A and C (Deller et al. *Structure* **8**(8): 863-874, 2000; Liu et al. *Int. J. Mol. Med.* **23**: 161-172, 2009). Site III, the epitope responsible for OSM interaction with OSMRβ and LIFRα, is believed to be largely defined by residues located in helix D (Deller et al. *Structure* **8**(8): 863-874, 2000).

Crystallization

Crystallization of the complex was performed by the sitting-drop vapor-diffusion method at 20°C using the Oryx4 protein crystallization robot (Douglas Instruments), dispensing equal volumes of 0.2 µL protein complex (10.95 mg/mL) and 0.2 µL reservoir solution. Multiple crystallization screens were performed. The majority of droplets remained clear, reflecting the high solubility of the complex. Crystals were obtained from 0.1 M MES pH 6.5, 2.4 M ammonium sulfate and 0.1 M Tris pH 8.5, 3.5 M sodium formate.

Result of Crystal Structure Solution

The OSM residues in contact with H14/L180 Fab constitute the binding epitope. The antibody residues in contact with OSM constitute the binding paratope. All six CDRs of the two variable domains are involved in OSM binding. Residues in contact are given in Table 13 and shown in Figure 5. The long CDR-L1, together with the CDRs of the heavy chain variable region H1, form a valley-like antigen binding site with a small ridge at the bottom (Figure 4C, left panel). Upon binding, the two sides of the valley embrace the OSM four-helix bundle along helices A and C with the bottom ridge binding in between the two helices (Figure 4C, right panel). The antibody and antigen binding interface buries 2,514 Å2 of solvent accessible surface (1225 Å2 for Ab and 1298 Å2 for Ag). Although there are a number of charges residues at the interface, there is no charge-charge pairing, suggesting vdw and H-bonding play the most important roles in antibody and antigen interactions.

WHAT IS CLAIMED:

1. An isolated antibody that specifically binds to human OSM protein and modulates the interaction between human OSM protein and gp130 protein, comprising a heavy chain complementarity determining region 3 (H-CDR3) selected from the amino acid sequence of SEQ ID NOS: 20 and 21.

2. The antibody of claim 1, further comprising a heavy chain framework 1 sequence, H-CDR1 sequence, framework 2 sequence, H-CDR2 sequence, and framework 3 sequence having the amino acid sequence of SEQ ID NO: 48.

3. The antibody of claim 2, wherein the heavy chain residue S31 contacts the OSM protein having the amino acid sequence of SEQ ID NO: 11 at position Q20 and heavy chain residues T30 and Y52 contact the OSM protein having the amino acid sequence of SEQ ID NO: 11 at position G120.

4. The antibody of claim 2, wherein residues of the human variable light chain framework are derived from a human Vkappa germline gene.

5. The antibody of claim 4, wherein the Vkappa germline gene is an IGKV4 germline gene sequence.

6. The antibody of claim 2, further comprising a light chain variable region comprising SEQ ID NO: 8, wherein X_1 is Y, S, or A; X_2 is K, E, or N; X_3 is Y, W or F; and X_4 is W.

7. The antibody of claim 6, wherein the L-CDR3 sequence comprises an amino acid sequence of SEQ ID NO: 29.

8. The antibody of claim 7, wherein the L-CDR3 sequence comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 27, 28, 45, and 46.

9. The antibody of claim 6, wherein the L-CDR1 sequence comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 23-25 and 30-41.

10. The antibody of claim 9, wherein the L-CDR2 sequence comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 26 and

42-44.

11. An isolated antibody that specifically binds to human OSM and modulates the interaction between human OSM and human gp130 protein, comprising a light chain variable region amino acid sequence selected from the group consisting of SEQ ID NOS: 49-53 and/or a heavy chain variable region amino acid sequence selected from the group consisting of SEQ ID NOS: 54 and 55.

12. The isolated antibody of claim 11, wherein the antibody comprises a light chain variable region amino acid sequence of SEQ ID NO: 51 and a heavy chain variable region amino acid sequence SEQ ID NO: 55.

13. The isolated antibody of claim 11, wherein the antibody comprises a light chain variable region amino acid sequence of SEQ ID NO: 53 and a heavy chain variable region amino acid sequence SEQ ID NO: 54.

14. The isolated antibody of claim 11, wherein an antibody paratope contacts epitope residues of human OSM having the amino acid sequence of SEQ ID NO: 11 at positions Q16, Q20, and G120.

15. An isolated antibody according to any of claims 1-14, further comprising a human heavy chain constant region selected from the group consisting of IgA1, IgA2, IgD, IgE, IgG1, IgG2, IgG3, IgG4, and IgM.

16. The isolated antibody of claim 15, wherein the constant region comprises a human IgG isotype.

17. The isolated antibody of claim 16, wherein the isotype is IgG1.

18. The isolated antibody of claim 17, wherein the constant region is mutated to render the antibody non-lytic.

19. The isolated antibody of claim 16, wherein the constant region is mutated to enhance the affinity of the antibody to the neonatal receptor (FcRn) as compared to an antibody with the wild-type IgG1 constant domain sequence.

20. The isolated antibody of claim 19, wherein the constant region is mutated at positions 428 and 434, wherein the numbering is according to the Kabat EU

numbering.

21. The isolated antibody of claim 20, wherein the mutations are M428L and N434S, wherein the numbering is according to the Kabat EU numbering.

22. An antigen binding fragment of any of the antibodies of claims 1-21.

23. The antigen binding fragment of claim 22, wherein said fragment is selected from the group consisting of a Fab, Fab', Fd, F(ab)2, and ScFv.

24. A pharmaceutical composition comprising an isolated antibody or antigen binding fragment of the antibody according to any of claims 1-23 and a pharmaceutically acceptable excipient or carrier.

25. The composition of claim 24 for use in the treatment of a human patient afflicted with a disease or disorder responsive to modulation of the interaction between human OSM protein and human gp130 protein.

26. The composition of claim 25, wherein the disease or disorder is an arthropathy selected from the group consisting of osteoarthritis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, neuropathic arthropathy, reactive arthritis, and rotator cuff tear arthropathy.

27. The composition of claim 24 for use in the treatment of a human patient afflicted with a disease or disorder characterized by the release of pro-inflammatory cytokines and chemokines by macrophages and monocytes.

28. The composition of claim 25, wherein the disease or disorder is selected from the group consisting of rheumatoid arthritis, juvenile onset arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis, chronic plaque disease, lupus erythematosus, inflammatory lung disease, idiopathic pulmonary fibrosis, sepsis, pre-eclampsia, COPD, asthma, and multiple sclerosis.

29. The composition of claim 25, wherein the disease is fibrotic disease selected from the group consisting of atherosclerosis, diabetic nephropathy, pulmonary fibrosis, idiopathic pulmonary fibrosis, systemic sclerosis, and cirrhosis.

30. An isolated polynucleotide encoding the heavy chain and/or light chain of the therapeutic antibody or antigen binding fragment thereof of any of claims 1-21.

31. A stably transformed or transfected recombinant host cell comprising the isolated polynucleotide of claim 30.

32. The stably transformed or transfected recombinant host cell of claim 31, comprising a vector comprising a polynucleotide encoding the light chain variable amino acid sequence of SEQ ID NO: 53 and a second polynucleotide encoding the heavy chain variable amino acid sequence of SEQ ID NO: 54.

33. The stably transformed or transfected recombinant host cell of claim 31, comprising a vector comprising a polynucleotide encoding the light chain variable amino acid sequence of SEQ ID NO: 51 and a second polynucleotide encoding the heavy chain variable amino acid sequence of SEQ ID NO: 55.

34. The host cell of either of claims 32 or 33, wherein said cell is mammalian.

35. The host cell of claim 34, wherein said cell is CHO.

36. A process for the manufacture of an antibody, comprising the steps of culturing a host cell of claim 34 and recovering the antibody from the cell.

37. A kit comprising a sterile preparation of an isolated antibody or fragment according to any of claims 1-21 and instructions for the administration of the antibody to a subject in need thereof.

38. An isolated antibody that specifically binds to human OSM protein, comprising:

a. a light chain complementarity determining region 1 (L-CDR1) amino acid sequence selected from the group consisting of SEQ ID NOS: 23-25, and 30-41;

b. a light chain complementarity determining region 2 (L-CDR2)

amino acid sequence selected from the group consisting of SEQ ID NOS: 26, 42-44; and

c. a light chain complementarity determining region 3 (L-CDR3) amino acid sequence selected from the group consisting of SEQ ID NOS: 10, 27-29, 45, 47.

39. An isolated antibody that specifically binds to OSM, comprising:

a. a heavy chain complementarity determining region 1 (H-CDR1) amino acid sequence selected from the group consisting of SEQ ID NOS: 14 and 15;

b. a heavy chain complementarity determining region 2 (H-CDR2) amino acid sequence selected from the group consisting of SEQ ID NOS: 16-18; and

c. a heavy chain complementarity determining region 3 (H-CDR3) amino acid sequence selected from the group consisting of SEQ ID NOS: 19-22.

40. An isolated antibody comprising the light chain L-CDR1, 2, and 3 of claim 38 and the heavy chain H-CDR1, 2, and 3 of claim 39.

41. An isolated antibody that specifically binds to OSM, comprising:

an H-CDR1 having an amino acid sequence of SEQ ID NO: 14;

an H-CDR2 having an amino acid sequence of SEQ ID NO: 17;

an H-CDR3 having an amino acid sequence of SEQ ID NO: 21;

an L-CDR1 having an amino acid sequence of SEQ ID NO: 38;

an L-CDR2 having an amino acid sequence of SEQ ID NO: 43; and

an L-CDR3 having an amino acid sequence of SEQ ID NO: 46.

42. Any invention described herein.

located in helices A and C (Deller et al. *Structure* **8**(8): 863-874, 2000; Liu et al. *Int. J. Mol. Med.* **23**: 161-172, 2009). Site III, the epitope responsible for OSM interaction with OSMRβ and LIFRα, is believed to be largely defined by residues located in helix D (Deller et al. *Structure* **8**(8): 863-874, 2000).

Crystallization

Crystallization of the complex was performed by the sitting-drop vapor-diffusion method at 20°C using the Oryx4 protein crystallization robot (Douglas Instruments), dispensing equal volumes of 0.2 µL protein complex (10.95 mg/mL) and 0.2 µL reservoir solution. Multiple crystallization screens were performed. The majority of droplets remained clear, reflecting the high solubility of the complex. Crystals were obtained from 0.1 M MES pH 6.5, 2.4 M ammonium sulfate and 0.1 M Tris pH 8.5, 3.5 M sodium formate.

Result of Crystal Structure Solution

The OSM residues in contact with H17/L180 Fab constitute the binding epitope. The antibody residues in contact with OSM constitute the binding paratope. All six CDRs of the two variable domains are involved in OSM binding. Residues in contact are given in Table 13 and shown in Figure 5. The long CDR-L1, together with the CDRs of the heavy chain variable region H1, form a valley-like antigen binding site with a small ridge at the bottom (Figure 4C, left panel). Upon binding, the two sides of the valley embrace the OSM four-helix bundle along helices A and C with the bottom ridge binding in between the two helices (Figure 4C, right panel). The antibody and antigen binding interface buries 2,514 Å2 of solvent accessible surface (1225 Å2 for Ab and 1298 Å2 for Ag). Although there are a number of charged residues at the interface, there is no charge-charge pairing, suggesting vdw and H-bonding play the most important roles in antibody and antigen interactions.

WHAT IS CLAIMED:

1. An isolated antibody that specifically binds to human OSM protein and modulates the interaction between human OSM and human gp130 protein, comprising a light chain variable region amino acid sequence selected from the group consisting of SEQ ID NOS: 49, 50, 52 and 53 and a heavy chain variable region amino acid sequence of SEQ ID NO: 54.

2. The isolated antibody of claim 1, wherein the antibody comprises a light chain variable region amino acid sequence of SEQ ID NO: 53 and a heavy chain variable region amino acid sequence SEQ ID NO: 54.

3. The isolated antibody of claim 1, wherein an antibody paratope contacts epitope residues of human OSM protein having the amino acid sequence of SEQ ID NO: 11 at positions Q16, Q20, and G120.

4. An isolated antibody comprising a light chain variable region amino acid sequence of SEQ ID NO: 51 and a heavy chain variable region amino acid sequence SEQ ID NO: 55.

5. The isolated antibody of claim 4, further comprising a human heavy chain constant region selected from the group consisting of IgA1, IgA2, IgD, IgE, IgG1, IgG2, IgG3, IgG4, and IgM.

6. The isolated antibody of claim 5, wherein the constant region comprises a human IgG isotype.

7. The isolated antibody of claim 6, wherein the isotype is IgG1.

8. The isolated antibody of claim 7, wherein the constant region is mutated to render the antibody non-lytic.

9. The isolated antibody of claim 6, wherein the constant region is mutated to enhance the affinity of the antibody to the neonatal receptor (FcRn) as compared to an antibody with the wild-type IgG1 constant domain sequence.

10. The isolated antibody of claim 9, wherein the constant region is mutated at positions 428 and 434, wherein the numbering is according to the Kabat EU numbering.

11. The isolated antibody of claim 10, wherein the mutations are M428L and N434S, wherein the numbering is according to the Kabat EU numbering.

12. An antigen binding fragment of the antibody of claim 4.

13. The antigen binding fragment of claim 12, wherein said fragment is selected from the group consisting of a Fab, Fab', Fd, F(ab)2, and ScFv.

14. A pharmaceutical composition comprising the isolated antibody of claim 4 and a pharmaceutically acceptable excipient or carrier.

15. A kit comprising a sterile preparation of the isolated antibody of claim 4 and instructions for the administration of the antibody to a subject in need thereof.

16. An isolated antibody that specifically binds to human OSM protein comprising a light chain variable region and a heavy chain variable region, the light chain variable region comprising:

a light chain complementarity determining region 1 (L-CDR1) amino acid sequence selected from the group consisting of SEQ ID NOS: 23-25, 30-37 and 39-41;

a light chain complementarity determining region 2 (L-CDR2) amino acid sequence selected from the group consisting of SEQ ID NOS: 26, 42 and 44; and

a light chain complementarity determining region 3 (L-CDR3) amino acid sequence selected from the group consisting of SEQ ID NOS: 10, 27-29, 45 and 47
the heavy chain variable region comprising:

a heavy chain complementarity determining region 1 (H-CDR1) amino acid sequence selected from the group consisting of SEQ ID NOS: 14 and 15;

a heavy chain complementarity determining region 2 (H-CDR2) amino acid sequence selected from the group consisting of SEQ ID NOS: 16-18; and

a heavy chain complementarity determining region 3 (H-CDR3) amino acid sequence selected from the group consisting of SEQ ID NOS: 19-22.

17. An isolated antibody that specifically binds to OSM, comprising:

an H-CDR1 having an amino acid sequence of SEQ ID NO: 14;

an H-CDR2 having an amino acid sequence of SEQ ID NO: 17;

an H-CDR3 having an amino acid sequence of SEQ ID NO: 21;

an L-CDR1 having an amino acid sequence of SEQ ID NO: 38;

an L-CDR2 having an amino acid sequence of SEQ ID NO: 43; and

an L-CDR3 having an amino acid sequence of SEQ ID NO: 46.

18. The isolated antibody of claim 17, further comprising a human heavy chain constant region selected from the group consisting of IgA1, IgA2, IgD, IgE, IgG1, IgG2, IgG3, IgG4, and IgM.

19. The isolated antibody of claim 18, wherein the constant region comprises a human IgG isotype.

20. The isolated antibody of claim 19, wherein the isotype is IgG1.

21. The isolated antibody of claim 20, wherein the constant region is mutated to render the antibody non-lytic.

22. The isolated antibody of claim 19, wherein the constant region is mutated to enhance the affinity of the antibody to the neonatal receptor (FcRn) as compared to an antibody with the wild-type IgG1 constant domain sequence.

23. The isolated antibody of claim 22, wherein the constant region is mutated at positions 428 and 434, wherein the numbering is according to the Kabat EU numbering.

24. The isolated antibody of claim 23, wherein the mutations are M428L and N434S, wherein the numbering is according to the Kabat EU numbering.

25. An antigen binding fragment of the antibody of claim 17.

26. The antigen binding fragment of claim 25, wherein said fragment is selected from the group consisting of a Fab, Fab', Fd, F(ab)2, and ScFv.

27. A pharmaceutical composition comprising the isolated antibody of claim 17 and a pharmaceutically acceptable excipient or carrier.

28. An isolated antibody that specifically binds to OSM, comprising:

an H-CDR1 having an amino acid sequence of SEQ ID NO: 14;

an H-CDR2 having an amino acid sequence of SEQ ID NO: 17;

an H-CDR3 having an amino acid sequence of SEQ ID NO: 21;

an L-CDR1 having an amino acid sequence of SEQ ID NO: 38;
an L-CDR2 having an amino acid sequence of SEQ ID NO: 43; and
an L-CDR3 having an amino acid sequence of SEQ ID NO: 46, wherein the antibody comprises an IgG1 constant region mutated to enhance the affinity of the antibody to the neonatal receptor (FcRn) as compared to an antibody with a wild-type IgG1 constant domain sequence and the mutations are M428L and N434S according to the Kabat EU numbering.