CLAIMS

We claim:

1. An isolated human antibody or antigen-binding fragment thereof that specifically binds human angiopoietin-like protein 3 (hANGPTL3) of SEQ ID NO:161 and neutralizes, reduces, or interferes with, at least one activity of hANGPTL3.

2. The antibody or fragment of claim 1, wherein the antibody or fragment thereof binds to an epitope situated within the N-terminal coiled-coil region at residues 17 to 209 of SEQ ID NO:161.

3. The antibody or fragment of claim 1 or 2, wherein the antibody or fragment thereof does not bind to the ANGPTL3 peptide of SEQ ID NO:170.

4. The antibody or fragment of any one of claims 1 to 3, wherein the epitope is situated within residues 17 to 200, 17 to 100, 17 to 70, 17 to 65, 17 to 60, 17 to 57, 17 to 50, 40 to 200, 40 to 100, 40 to 70, 50 to 200, 50 to 100, 50 to 70, 58 to 200, 58 to 100, 58 to 70, 58 to 68, or 61 to 66, of SEQ ID NO:161.

5. The antibody or fragment of any one of claims 1 to 4, wherein the antibody or fragment is a chimeric or fully human antibody or antibody fragment.

6. The antibody or fragment of any one of claims 1 to 5, comprising a heavy chain variable region (HCVR) selected from the group consisting of SEQ ID NO:2, 18, 34, 50, 66, 82, 98, 114, 130, 146 and 180; and/or a light chain variable region (LCVR) selected from the group consisting of SEQ ID NO:10, 26, 42, 58, 74, 90, 106, 122, 138, 154 and 188.

7. The antibody or fragment of claim 6, wherein the antibody or fragment thereof comprises a HCVR and LCVR sequence pair (HCVR/LCVR) selected from the group consisting of SEQ ID NO:2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154 and 180/188.

8. The antibody or fragment of any one of claims 1 to 5, wherein the antibody or fragment comprises heavy chain complementarity determining region (CDR) sequences, HCDR1, HCDR2 and HCDR3, and light chain CDR sequences, LCDR1, LCDR2 and LCDR3, contained within a heavy chain variable region (HCVR) and light chain variable region (LCVR) sequence pair (HCVR/LCVR) selected from the group consisting of SEQ ID NO:2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154 and 180/188.

9. The antibody or fragment of claim 8, wherein the HCDR1/HCDR2/HCDR3 sequence combination is selected from the group consisting of SEQ ID NO:4/6/8, 20/22/24, 36/38/40, 52/54/56, 68/70/72, 84/86/88, 100/102/104, 116/118/120, 132/134/136, 148/150/152 and 182/184/186; and/or the LCDR1/LCDR2/LCDR3 sequence combination selected from the group consisting of SEQ ID NO:12/14/16, 28/30/32, 44/46/48, 60/62/64, 76/78/80, 92/94/96,

108/110/112, 124/126/128, 140/142/144, 156/158/160 and 190/192/194.

10. The antibody or fragment of claim 8 or 9, wherein the antibody or fragment comprises a HCDR1/HCDR2/HCDR3/LCDR1/LCDR2/LCDR3 sequence combination selected from the group consisting of 4/6/8/12/14/16, 20/22/24/28/30/32, 36/38/40/44/46/48, 52/54/56/60/62/64, 68/70/72/76/78/80, 84/86/88/92/94/96, 100/102/104/108/110/112, 116/118/120/124/126/128, 132/134/136/140/142/144, 148/150/152/156/158/160 and 182/184/186/190/192/194.

11. An antibody or antigen-binding fragment thereof which competes for binding to hANGPTL3 with, or which binds the same epitope on hANGPTL3 as, an antibody or antigen-binding fragment comprising a heavy chain and light chain complementarity determining region (CDR) sequence combination selected from the group consisting of 4/6/8/12/14/16, 20/22/24/28/30/32, 36/38/40/44/46/48, 52/54/56/60/62/64, 68/70/72/76/78/80, 84/86/88/92/94/96, 100/102/104/108/110/112, 116/118/120/124/126/128, 132/134/136/140/142/144, 148/150/152/156/158/160 and 182/184/186/190/192/194.

12. The antibody or antigen-binding fragment according to any one of claims 1 to 11, wherein the antibody or antigen-binding fragment cross-reacts with cynomolgus monkey ANGPTL3.

13. The antibody or antigen-binding fragment according to any one of claims 1 to 12, wherein the antibody or antigen-binding fragment cross-reacts with mouse or rat ANGPTL3.

14. The antibody or antigen-binding fragment according to any one of claims 1 to 13, wherein the antibody or fragment cross-reacts with any of cynomolgus monkey ANGPTL3, mouse ANGPTL3, and rat ANGPTL3.

15. The antibody or fragment of any one of claims 1 to 14, wherein the antibody fragment is a single chain antibody, an Fab, or an $F(ab')_2$.

16. An isolated nucleic acid molecule encoding the antibody or fragment thereof according to any one of claims 1 to 15.

17. An expression vector comprising the nucleic acid molecule of claim 16.

18. An isolated host cell comprising the expression vector of claim 17.

19. A method of producing an anti-hANGPTL3 antibody or antigen-binding fragment thereof, comprising growing the host cell of claim 18 under conditions permitting production of the antibody or fragment thereof, and recovering the antibody or fragment thereof so produced.

20. A pharmaceutical composition comprising one or more antibodies or fragments thereof of any one of claims 1 to 15, and a pharmaceutically acceptable carrier.

21. The pharmaceutical composition of claim 20, wherein the antibody or fragment

thereof comprises a heavy chain and light chain complementarity determining region (CDR) sequence combination of SEQ ID NO:68/70/72/76/78/80, or a heavy chain variable region and a light chain variable region HCVR/LCVR pair comprising SEQ ID NO:66/74.

22. The pharmaceutical composition of claim 20, comprising a combination of antibodies or fragments thereof selected from the group consisting of heavy chain variable region (HCVR) and light chain variable region (LCVR) sequence pairs (HCVR/LCVR) of:

(i) SEQ ID NO:82/90 and 180/188;

(ii) SEQ ID NO:114/122 and 180/188;

(iii) SEQ ID NO:82/90 and 18/26; and

(iv) SEQ ID NO:114/122 and 18/26.

23. The pharmaceutical composition of any one of claims 20 to 22, further comprising one or more additional therapeutic agents selected from the group consisting of an inhibitor of HMG-CoA reductase; an inhibitor of cholesterol uptake or bile acid re-absorption, or both; an agent which increases lipoprotein catabolism; an agent which reduces the number of non-fatal heart attacks; and an activator of the LXR transcription factor.

24. The pharmaceutical composition of claim any one of claims 20 to 22, further comprising one or more additional therapeutic agents selected from the group consisting of statin, niacin, fibrate, anti-hANGPTL4 antibody and anti-PCSK9 antibody.

25. A method for preventing or treating a disease or disorder which is prevented, ameliorated, improved or inhibited by reduction or inhibition of ANGPTL3 activity, comprising administering to a subject in need thereof a therapeutically effective amount of the pharmaceutical composition of any one of claims 20 to 24.

26. A method for preventing or treating a disease or disorder which is prevented, ameliorated, improved or inhibited by reduction or inhibition of ANGPTL3 activity, comprising administering to a subject in need thereof a therapeutically effective amount of one or more antibodies or fragments thereof of any one of claims 1 to 15.

27. The method of claim 26, further comprising administering to the subject one or more additional therapeutic agents selected from the group consisting of an inhibitor of HMG-CoA reductase; an inhibitor of cholesterol uptake or bile acid re-absorption, or both; an agent which increases lipoprotein catabolism; an agent which reduces the number of non-fatal heart attacks; and an activator of the LXR transcription factor.

28. The method of claim 26, further comprising administering to the subject one or more additional therapeutic agents selected from the group consisting of statin, niacin, fibrate, anti-hANGPTL4 antibody and anti-PCSK9 antibody.

29. The method of claim 27 or 28, wherein one or more antibodies or fragments thereof

and one or more additional therapeutic agents are administered concurrently or sequentially.

30. The method of any one of claims 25 to 29, wherein said disease or disorder is selected from the group consisting of hypertriglyceridemia, hypercholesterolemia, chylomicronemia, atherogenic dyslipidemia, a cardiovascular disease or disorder, acute pancreatitis, nonalcoholic steatohepatitis (NASH), diabetes and obesity.

31. A method of enhancing the clearance of hANGPTL3 from the circulation of a subject in need thereof, comprising administering to the subject at least two antibodies or antigen-binding fragments thereof that do not compete with one another for binding to hANGPTL3 and do not block at least one activity of hANGPTL3.

32. The method of claim 31, wherein the one activity of hANGPTL3 is the inhibition of lipoprotein lipase (LPL) activity.

33. The method of claim 31 or 32, wherein the two antibodies are selected from the group consisting of heavy chain variable region (HCVR) and light chain variable region (LCVR) sequence pairs (HCVR/LCVR) of:

(i) SEQ ID NO:82/90 and 180/188;

(ii) SEQ ID NO:82/90 and 18/26;

(Iii) SEQ ID NO:114/122 and 180/188; and

(iv) SEQ ID NO:114/122 and 18/26.

34. The pharmaceutical composition of any one of claims 20 to 24, for use in treating a disease or disorder which is prevented, ameliorated, improved or inhibited by reduction or inhibition of ANGPTL3 activity.

35. The pharmaceutical composition of claim 34, wherein the disease or disorder is selected from the group consisting of hypertriglyceridemia, hypercholesterolemia, chylomicronemia, atherogenic dyslipidemia, a cardiovascular disease or disorder, acute pancreatitis, nonalcoholic steatohepatitis (NASH), diabetes and obesity.

CLAIMS

1. An isolated human antibody or antigen-binding fragment thereof that specifically binds human angiopoietin-like protein 3 (hANGPTL3) of SEQ ID NO:161 and neutralizes, reduces, or interferes with, at least one activity of hANGPTL3, wherein the antibody binds amino acids 36-68 of AngPTL3, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region (HCVR) selected from the group consisting of SEQ ID NO:2, 18, 34, 50, 66, 82, 98, 114, 130, 146 and 180; and/or a light chain variable region (LCVR) selected from the group consisting of SEQ ID NO:10, 26, 42, 58, 74, 90, 106, 122, 138, 154 and 188.

2. The antibody or fragment of claim 1, wherein the antibody or fragment thereof comprises a HCVR and LCVR sequence pair (HCVR/LCVR) selected from the group consisting of SEQ ID NO:2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154 and 180/188.

3. The antibody or fragment of claim 1, wherein the antibody or fragment comprises heavy chain complementarity determining region (CDR) sequences, HCDR1, HCDR2 and HCDR3, and light chain CDR sequences, LCDR1, LCDR2 and LCDR3, contained within a heavy chain variable region (HCVR) and light chain variable region (LCVR) sequence pair (HCVR/LCVR) selected from the group consisting of SEQ ID NO:2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154 and 180/188.

4. The antibody or fragment of claim 3, wherein the HCDR1/HCDR2/HCDR3 sequence combination is selected from the group consisting of SEQ ID NO:4/6/8, 20/22/24, 36/38/40, 52/54/56, 68/70/72, 84/86/88, 100/102/104, 116/118/120, 132/134/136, 148/150/152 and 182/184/186, respectively; and the LCDR1/LCDR2/LCDR3 sequence combination is selected from the group consisting of SEQ ID NO:12/14/16, 28/30/32, 44/46/48, 60/62/64, 76/78/80, 92/94/96, 108/110/112, 124/126/128, 140/142/144, 156/158/160 and 190/192/194, respectively.

5. The antibody or fragment of claim 4, wherein the antibody or fragment comprises a HCDR1/HCDR2/HCDR3/LCDR1/LCDR2/LCDR3 sequence combination selected from the group consisting of 4/6/8/12/14/16, 20/22/24/28/30/32, 36/38/40/44/46/48, 52/54/56/60/62/64, 68/70/72/76/78/80, 84/86/88/92/94/96, 100/102/104/108/110/112, 116/118/120/124/126/128, 132/134/136/140/142/144, 148/150/152/156/158/160 and 182/184/186/190/192/194.

6. The antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen-binding fragment cross-reacts with cynomolgus monkey ANGPTL3.

7. The antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen-binding fragment cross-reacts with mouse or rat ANGPTL3.

8. The antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen-binding fragment cross-reacts with any of cynomolgus monkey ANGPTL3, mouse ANGPTL3, and rat ANGPTL3.

9. The antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen-binding fragment is a single chain antibody, an Fab, or an F(ab').sub.2.

10. A pharmaceutical composition comprising the antibody or antigen-binding fragment of claim 1 and a pharmaceutically acceptable carrier.

11. The pharmaceutical composition of claim 10, wherein the antibody or fragment thereof comprises a heavy chain and light chain complementarity determining region (CDR) sequence combination of SEQ ID NO:68/70/72/76/78/80, or a heavy chain variable region and a light chain variable region HCVR/LCVR pair comprising SEQ ID NO:66/74.

12. The antibody or fragment of claim 1, wherein the antibody or fragment is a chimeric or fully human antibody or antibody fragment.