SUMMARY OF VARIOUS EMBODIMENTS

[0006a] In one aspect, disclosed herein is a monoclonal antibody that binds to human PCSK9, said antibody comprising: a heavy chain polypeptide comprising: a CDRH1 comprising SEQ ID NO: 308, a CDRH2 comprising SEQ ID NO: 175, and a CDRH3 comprising SEQ ID NO: 180; and a heavy chain constant domain having the amino acid sequence as set forth in SEQ ID NO: 154; and a light chain polypeptide comprising: a CDRL1 comprising SEQ ID NO: 158, a CDRL2 comprising SEQ ID NO: 162, and a CDRL3 comprising SEQ ID NO: 395; and a light chain constant domain having the amino acid sequence as set forth in SEQ ID NO: 156.

[0006b] In another aspect, disclosed herein is a monoclonal antibody that binds to human PCSK9, said antibody comprising: a heavy chain polypeptide comprising: a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 49, wherein the first residue is a glutamic acid instead of a glutamine; and a heavy chain constant domain having the amino acid sequence as set forth in SEQ ID NO: 154; and a light chain polypeptide comprising: a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 23, wherein the first residue is a glutamic acid instead of a glutamine, and a light chain constant domain having the amino acid sequence as set forth in SEQ ID NO: 156.

[0006c] In another aspect, disclosed herein is a monoclonal antibody that binds to human PCSK9, said antibody comprising: a heavy chain polypeptide comprising: a heavy chain variable domain comprising residue 1 to residue 115 of SEQ ID NO: 298; and a heavy chain constant domain having the amino acid sequence as set forth in SEQ ID NO: 154; and a light chain polypeptide comprising: a light chain variable domain comprising residue 1 to residue 110 of SEQ ID NO: 297, and a light chain constant domain having the amino acid sequence as set forth in SEQ ID NO: 156.

[0006d] In another aspect, disclosed herein is an isolated nucleic acid encoding the monoclonal antibody of the disclosure.

[0006e] In another aspect, disclosed herein is a recombinant expression vector comprising the nucleic acid of the disclosure.

[0006f] In another aspect, disclosed herein is host cell comprising the vector of the disclosure.

[0006g] In another aspect, disclosed herein is hybridoma capable of producing the monoclonal antibody of the disclosure.

[0006h] In another aspect, disclosed herein is a method of making the monoclonal antibody of the disclosure, comprising the step of preparing said antibody from a host cell that secretes said antibody.

[0006i] In another aspect, disclosed herein is a monoclonal antibody produced by the expression of recombinant DNA in the host cell of the disclosure or the hybridoma of the disclosure.

[0006j] In another aspect, disclosed herein is a pharmaceutical composition comprising the monoclonal antibody of the disclosure, and a pharmaceutically acceptable excipient.

[0006k] In another aspect, disclosed herein is a use of the monoclonal antibody of the disclosure in the manufacture of a medicament for the treatment or prevention of a condition associated with elevated serum cholesterol levels in a subject in need thereof.

[0006l] In another aspect, disclosed herein is monoclonal antibody of the disclosure for use in therapy.

[0007] In some embodiments, the invention comprises an antigen binding protein to PCSK9.

[0008] In some aspects, the invention comprises an isolated antigen binding protein that binds PCSK9 comprising: A) one or more heavy chain complementary determining regions (CDRHs) selected from the group consisting of: (i) a CDRH1 from a CDRH1 in a sequence selected from the group consisting of SEQ ID NO: 74, 85, 71, 72, 67, 87, 58, 52, 51, 53, 48, 54, 55, 56, 49, 57, 50, 91, 64, 62, 89, 65, 79, 80, 76, 77, 78, 83, 69, 81, and 60; (ii) a CDRH2 from a CDRH2 in a sequence selected from the group consisting of SEQ ID NO: 74, 85, 71, 72, 67, 87, 58, 52, 51, 53, 48, 54, 55, 56, 49, 57, 50, 91, 64, 62, 89, 65, 79, 80, 76, 77, 78, 83, 69, 81, and 60; (iii) a CDRH3 from a CDRH3 in a sequence selected from the group consisting of SEQ ID NO: 74, 85, 71, 72, 67, 87, 58, 52, 51, 53, 48, 54, 55, 56, 49, 57, 50, 91, 64, 62, 89, 65, 79, 80, 76, 77, 78, 83, 69, 81, and 60; and (iv) a CDRH of (i), (ii), and (iii) that contains one or more amino acid substitutions, deletions or insertions of no more than 4 amino acids; B) one or more light chain complementary determining regions (CDRLs) selected from the group consisting of: (i) a CDRL1 from a CDRL1 in a sequence selected from the group consisting of SEQ ID NO: 5, 7, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 31, 32, 33, 35, 36, 37, 38, 39, 40, 42, 44, and 46; (ii) a CDRL2 from a CDRL2 in a sequence selected from the group consisting of

SEQ ID NO: 5, 7, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 31, 32, 33, 35, 36, 37, 38, 39, 40, 42, 44, and 46; (iii) a CDRL3 from a CDRL3 in a sequence selected from the group consisting of SEQ ID NO: 5, 7, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 31, 32, 33, 35, 36, 37, 38, 39, 40, 42, 44, and 46; and (iv) a CDRL of (i), (ii) and (iii) that contains one or more amino acid substitutions, deletions or insertions of no more than 4 amino acids; or C) one or more heavy chain CDRHs of A) and one or more light chain CDRLs of B). In some embodiments, the isolated antigen binding protein comprises at least one CDRH of A) and at least one CDRL of B). In some embodiments, the isolated antigen binding protein comprises at least two CDRH of A) and at least two CDRL of B). In some embodiments, the isolated antigen binding protein comprises said CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3. In some embodiments, the CDRH of A) is selected from at least one of the group consisting of: (i) a CDRH1 amino acid sequence selected from the CDRH1 in a sequence selected from the group consisting of SEQ ID NO: 67, 79, 89, and 49; (ii) a CDRH2 amino acid

WHAT IS CLAIMED IS:

1. A monoclonal antibody that binds to human PCSK9, said antibody comprising:

a heavy chain polypeptide comprising:

a CDRH1 comprising SEQ ID NO: 308, a CDRH2 comprising SEQ ID NO: 175, and a CDRH3 comprising SEQ ID NO: 180; and

a heavy chain constant domain having the amino acid sequence as set forth in SEQ ID NO: 154; and

a light chain polypeptide comprising:

a CDRL1 comprising SEQ ID NO: 158, a CDRL2 comprising SEQ ID NO: 162, and a CDRL3 comprising SEQ ID NO: 395; and

a light chain constant domain having the amino acid sequence as set forth in SEQ ID NO: 156.

2. A monoclonal antibody that binds to human PCSK9, said antibody comprising:

a heavy chain polypeptide comprising:

a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 49, wherein the first residue is a glutamic acid instead of a glutamine; and

a heavy chain constant domain having the amino acid sequence as set forth in SEQ ID NO: 154; and

a light chain polypeptide comprising:

a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 23, wherein the first residue is a glutamic acid instead of a glutamine, and

a light chain constant domain having the amino acid sequence as set forth in SEQ ID NO: 156.

3. A monoclonal antibody that binds to human PCSK9, said antibody comprising:

a heavy chain polypeptide comprising:

a heavy chain variable domain comprising residue 1 to residue 115 of SEQ ID NO: 298; and

a heavy chain constant domain having the amino acid sequence as set forth in SEQ ID NO: 154; and

a light chain polypeptide comprising:

a light chain variable domain comprising residue 1 to residue 110 of SEQ ID NO: 297, and

a light chain constant domain having the amino acid sequence as set forth in SEQ ID NO: 156.

4. The monoclonal antibody of any one of the preceding claims, wherein the monoclonal antibody is neutralizing in that an excess of said antibody is capable of reducing the quantity of PCSK9 bound to LDLR in an in vitro competitive binding assay.

5. The monoclonal antibody of any one of the preceding claims, wherein the monoclonal antibody binds to PCSK9 with a K_d that is smaller than 1 nM.

6. The monoclonal antibody of any one of the preceding claims, wherein the human PCSK9 comprises the amino acid sequence of SEQ ID NO: 1.

7. The monoclonal antibody of any one of the preceding claims, wherein the monoclonal antibody blocks the binding of D374Y PCSK9 to LDLR with an IC_{50} of less than 200 pM.

8. An isolated nucleic acid encoding the monoclonal antibody of any one of the preceding claims.

9. A recombinant expression vector comprising the nucleic acid according to Claim 8.

10. A host cell comprising the vector of Claim 9.

11. A hybridoma capable of producing the monoclonal antibody of any one of Claims 1-7.

12. A method of making the monoclonal antibody of any one of Claims 1-7, comprising the step of preparing said antibody from a host cell that secretes said antibody.

13. A monoclonal antibody produced by the expression of recombinant DNA in the host cell of Claim 10 or the hybridoma of Claim 11.

14. The method of Claim 12 or the monoclonal antibody of Claim 13, wherein the host cell is selected from the group consisting of Chinese hamster ovary (CHO) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells, and human epithelial kidney 293 cells.

15. A pharmaceutical composition comprising the monoclonal antibody according to any one of Claims 1 to 7, or 13, or as defined in claim 12, and a pharmaceutically acceptable excipient.

16. The pharmaceutical composition of Claim 15, wherein the pharmaceutical composition is formulated for administration prior to, concurrent with, or subsequent to, the administration of at least one other therapeutic agent.

17. The pharmaceutical composition of Claim 16, wherein the other therapeutic agent is a statin.

18. Use of the monoclonal antibody of any one of claims 1 to 7 or 13 in the manufacture of a medicament for the treatment or prevention of a condition associated with elevated serum cholesterol levels in a subject in need thereof.

19. The use according to claim 18, wherein the condition is selected from hypercholesterolemia, cardiovascular disease, metabolic syndrome, diabetes, stroke, and dyslipidemia.

20. The use of Claim 18 or 19, wherein the pharmaceutical composition is formulated to be administered prior to, concurrent with, or subsequent to, the administration of at least one other therapeutic agent.

21. The use of Claim 20, wherein the other therapeutic agent is a statin.

22. A monoclonal antibody of any one of claims 1 to 7 or 13 for use in therapy.