CLAIMS

What is claimed is:

1. An oligonucleotide for reducing ANGPTL3 expression, the oligonucleotide comprising an antisense strand comprising a sequence as set forth in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, and 116.

2. The oligonucleotide of claim 1, comprising a sense strand comprising a sequence as set forth in any one of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, and 115.

3. The oligonucleotide of claim 1 or 2, wherein the antisense strand comprises a sequence as set forth in any one of SEQ ID NOs: 100, 102, 104, 20, 26, 50, 72, 74, 76, 80, and 114.

4. The oligonucleotide of claim 2 or 3, wherein the sense strand comprises a sequence as set forth in any one of SEQ ID NOs: 99, 101, 103, 19, 25, 49, 71, 73, 75, 79, and 113.

5. An oligonucleotide for reducing ANGPTL3 expression, the oligonucleotide comprising an antisense strand of 15 to 30 nucleotides in length and a sense strand of 15 to 40 nucleotides in length, wherein the antisense strand has a region of complementarity to a target sequence of ANGPTL3 as set forth in any one of SEQ ID NOs: 125, 126, 127, 118, 119, 120, 121, 122, 123, 124, and 117, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

6. The oligonucleotide of claim 5, wherein the region of complementarity is fully complementary to the target sequence of ANGPTL3.

7. The oligonucleotide of any one of claims 1 to 6, wherein the antisense strand is 19 to 27 nucleotides in length.

8. The oligonucleotide of any one of claims 1 to 7, wherein the antisense strand is 21 to 27 nucleotides in length, optionally wherein the antisense strand is 22 nucleotides in length.

9. The oligonucleotide of any one of claims 2 to 8, wherein the sense strand forms a duplex region with the antisense strand.

10. The oligonucleotide of claim 9, wherein the sense strand is 19 to 40 nucleotides in length, optionally wherein the sense strand is 36 nucleotides in length.

11. The oligonucleotide of claim 9 or 10, wherein the duplex region is at least 19 nucleotides in length.

12. The oligonucleotide of any one of claims 9 to 11, wherein the duplex region is at least 21 nucleotides in length, optionally wherein the duplex region is 20 nucleotides in length.

13. The oligonucleotide of any one of claims 5 to 12, wherein the region of complementarity to ANGPTL3 is at least 19 contiguous nucleotides in length.

14. The oligonucleotide of any one of claims 5 to 13, wherein the region of complementarity to ANGPTL3 is at least 21 contiguous nucleotides in length.

15. The oligonucleotide of any one of claims 5 to 14, wherein the antisense strand comprises a sequence as set forth in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, and 116.

16. The oligonucleotide of any one of claims 5 to 15, wherein the sense strand comprises a sequence as set forth in any one of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, and 115.

17. The oligonucleotide of any one of claims 5 to 16, wherein the antisense strand comprises a sequence as set forth in any one of SEQ ID NOs: 100, 102, 104, 20, 26, 50, 72, 74, 76, 80, and 114.

18. The oligonucleotide of any one of claims 5 to 17, wherein the sense strand comprises a sequence as set forth in any one of SEQ ID NOs: 99, 101, 103, 19, 25, 49, 71, 73, 75, 79, and 113.

19. The oligonucleotide of any one of claims 2 to 18, wherein the sense strand comprises at its 3′ end a stem-loop set forth as: S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length.

20. An oligonucleotide for reducing ANGPTL3 expression, the oligonucleotide comprising an antisense strand and a sense strand,

wherein the antisense strand is 21 to 27 nucleotides in length and has a region of complementarity to ANGPTL3, wherein the sense strand comprises at its 3′ end a stem-loop set forth as: S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, and

wherein the antisense strand and the sense strand form a duplex structure of at least 19 nucleotides in length but are not covalently linked.

21. The oligonucleotide of claim 20, wherein the region of complementarity is fully complementary to at least 19 contiguous nucleotides of ANGPTL3 mRNA.

22. The oligonucleotide of any one of claims 19 to 21, wherein L is a tetraloop.

23. The oligonucleotide of any one of claims 19 to 22, wherein L is 4 nucleotides in length.

24. The oligonucleotide of any one of claims 19 to 23, wherein L comprises a sequence set forth as GAAA.

25. The oligonucleotide of any one of claims 5 to 24, wherein the antisense strand is 27 nucleotides in length and the sense strand is 25 nucleotides in length, optionally wherein the antisense strand is 22 nucleotides in length and the sense strand is 36 nucleotides in length.

26. The oligonucleotide of claim 25, wherein the antisense strand and sense strand form a duplex region of 25 nucleotides in length, optionally wherein the duplex is 20 nucleotides in length.

27. The oligonucleotide of any one of claims 20 to 24, comprising a 3′-overhang sequence on the antisense strand of 2 nucleotides in length.

28. The oligonucleotide of any one of claims 9 to 18, wherein the oligonucleotide comprises an antisense strand and a sense strand that are each in a range of 21 to 23 nucleotides in length.

29. The oligonucleotide of claim 28, wherein the oligonucleotide comprises a duplex structure in a range of 19 to 21 nucleotides in length.

30. The oligonucleotide of claim 28 or 29, wherein the oligonucleotide comprises a 3′-overhang sequence of one or more nucleotides in length, wherein the 3′-overhang sequence is present on the antisense strand, the sense strand, or the antisense strand and sense strand.

31. The oligonucleotide of claim 28 or 29, wherein the oligonucleotide comprises a 3′-overhang sequence of 2 nucleotides in length, wherein the 3′-overhang sequence is on the antisense strand, and wherein the sense strand is 21 nucleotides in length and the antisense strand is 23 nucleotides in length, such that the sense strand and antisense strand form a duplex of 21 nucleotides in length.

32. The oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified nucleotide.

33. The oligonucleotide of claim 32, wherein the modified nucleotide comprises a 2′-modification.

34. The oligonucleotide of claim 33, wherein the 2′-modification is a modification selected from 2′-aminoethyl, 2′-fluoro, 2′-O-methyl, 2′-O-methoxyethyl, and 2′-deoxy-2′-fluoro-β-d-arabinonucleic acid.

35. The oligonucleotide of any one of claims 32 to 34, wherein all of the nucleotides of the oligonucleotide are modified.

36. The oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified internucleotide linkage.

37. The oligonucleotide of claim 36, wherein the at least one modified internucleotide linkage is a phosphorothioate linkage.

38. The oligonucleotide of any one of the preceding claims, wherein the 4′-carbon of the sugar of the 5′-nucleotide of the antisense strand comprises a phosphate analog.

39. The oligonucleotide of claim 38, wherein the phosphate analog is oxymethylphosphonate, vinylphosphonate or malonylphosphonate.

40. The oligonucleotide of any one of the preceding claims, wherein at least one nucleotide of the oligonucleotide is conjugated to one or more targeting ligands.

41. The oligonucleotide of claim 40, wherein each targeting ligand comprises a carbohydrate, amino sugar, cholesterol, polypeptide or lipid.

42. The oligonucleotide of claim 40, wherein each targeting ligand comprises a N-acetylgalactosamine (GalNAc) moiety.

43. The oligonucleotide of claim 42, wherein the GalNac moiety is a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety or a tetravalent GalNAc moiety.

44. The oligonucleotide of any one of claims 19 to 24, wherein up to 4 nucleotides of L of the stem-loop are each conjugated to a monovalent GalNAc moiety.

45. The oligonucleotide of any one of the preceding claims, wherein the oligonucleotide is an RNAi oligonucleotide.

46. A pharmaceutical composition comprising the oligonucleotide of any one of the preceding claims and a pharmaceutically acceptable carrier, delivery agent or excipient.

47. A method of delivering an oligonucleotide to a subject, the method comprising administering pharmaceutical composition of claim 46 to the subject.

48. A method for reducing ANGPTL3 expression in a cell, a population of cells or a subject, the method comprising the step of:

i. contacting the cell or the population of cells with the oligonucleotide of any one of claims 1 to 45, or the pharmaceutical composition of claim 46; or

ii. administering to the subject the oligonucleotide of any one of claims 1 to 45, or the pharmaceutical composition of claim 46.

49. The method of claim 48, wherein reducing ANGPTL3 expression comprises reducing an amount or a level of ANGPTL3 mRNA, an amount or a level of ANGPTL3 protein, or both.

50. A method for reducing an amount or level of triglyceride (TG) in a subject, the method comprising administering to the subject the oligonucleotide of any one of claims 1 to 45, or the pharmaceutical composition of claim 46.

51. A method for reducing an amount or level of cholesterol in a subject, the method comprising administering to the subject the oligonucleotide of any one of claims 1 to 45, or the pharmaceutical composition of claim 46.

52. The method of any one of claims 48 to 51, wherein the subject has a disease, disorder or condition associated with ANGPTL3 expression.

53. A method for treating a subject having a disease, disorder or condition associated with ANGPTL3 expression, the method comprising administering to the subject a therapeutically effective amount of the oligonucleotide of any one of claims 1 to 45, or the pharmaceutical composition of claim 46, thereby treating the subject.

54. A method for treating a subject having a disease, disorder or condition associated with ANGPTL3 expression, the method comprising administering to the subject a therapeutically

effective amount of an oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand of 15 to 30 nucleotides in length, wherein the sense strand forms a duplex region with the antisense strand, wherein the sense strand comprises a sequence as set forth in any one of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, and 115, and wherein the antisense strand comprises a complementary sequence selected from SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, and 116, or pharmaceutical composition thereof, thereby treating the subject.

55. A method for treating a subject having a disease, disorder or condition associated with ANGPTL3 expression, the method comprising administering to the subject a therapeutically effective amount of an oligonucleotide comprising a pair of sense and antisense strands selected from a row set forth in **Table 5**, or pharmaceutical composition thereof, thereby treating the subject.

56. The method of any one of claims 52-55, wherein the disease, disorder or condition associated with ANGPTL3 expression is selected from the group consisting of hypertriglyceridemia, obesity, hyperlipidemia, abnormal lipid and/or cholesterol metabolism, atherosclerosis, type II diabetes mellitus, cardiovascular disease, coronary artery disease, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease, homozygous and heterozygous familial hypercholesterolemia, and statin-resistant hypercholesterolemia.

57. The method of claim 56, wherein the disease, disorder or condition associated with ANGPTL3 expression is cardiovascular disease, type II diabetes mellitus, hypertriglyceridemia, NASH, obesity, or a combination thereof.

58. The method of any one of claims 53-57, wherein the oligonucleotide, or pharmaceutical composition, is administered in combination with a second composition or therapeutic agent.

59. Use of the oligonucleotide of any one of claims 1-45, or the pharmaceutical composition of claim 46, in the manufacture of a medicament for the treatment of a disease, disorder or condition associated with ANGPTL3 expression.

60. The oligonucleotide of any one of claims 1-45, or the pharmaceutical composition of claim 46, for use, or adaptable for use, in the treatment of a disease, disorder or condition associated with ANGPTL3 expression.

61. A kit comprising the oligonucleotide of any one of claims 1-45, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration to a subject having a disease, disorder or condition associated with ANGPTL3 expression.

62. The use of claim 59, the oligonucleotide or pharmaceutical composition for use of claim 60, or the kit of claim 61, wherein the disease, disorder or condition associated with ANGPTL3 expression is selected from the group consisting of hypertriglyceridemia, obesity, hyperlipidemia, abnormal lipid and/or cholesterol metabolism, atherosclerosis, type II diabetes mellitus, cardiovascular disease, coronary artery disease, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease, homozygous and heterozygous familial hypercholesterolemia, and statin-resistant hypercholesterolemia.

63. The use of claim 59, the oligonucleotide or pharmaceutical composition for use of claim 60, or the kit of claim 61, wherein the disease, disorder or condition associated with ANGPTL3 expression is cardiovascular disease, type II diabetes mellitus, hypertriglyceridemia, NASH, obesity, or a combination thereof.