What is Claimed

1. An antisense oligonucleotide (ASO) comprising a contiguous nucleotide sequence 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a angiopoietin like 2 (*ANGPTL2*) transcript, wherein the ASO is a gapmer comprising one or more sugar modified nucleosides, and wherein the contiguous nucleotide sequence comprises the sequence set forth in any one of SEQ ID NO: 4 to SEQ ID NO: 193 or the sequence set forth in any one of SEQ ID NO: 4 to SEQ ID NO: 193 with one or two mismatches.

2. The ASO of claim 1, which is at least 80%, at least 85%, at least 90%, at least 95%, or 100% complementary to the nucleic acid sequence within the *ANGPTL2* transcript.

3. The ASO of claim 1 or 2, wherein the *ANGPTL2* transcript is selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 196, SEQ ID NO: 197, SEQ ID NO: 198, SEQ ID NO: 199, and SEQ ID NO: 207.

4. The ASO of any one of claims 1 to 3, wherein the ASO is capable of reducing ANGPTL2 protein expression in a human cell (*e.g.*, SK-N-AS cell) which is expressing the ANGPTL2 protein.

5. The ASO of claim 4, wherein the ANGPTL2 protein expression is reduced by at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or 100% compared to ANGPTL2 protein expression in a human cell that is not exposed to the ASO.

6. The ASO of any one of claims 1 to 5, which is capable of reducing *ANGPTL2* transcript (*e.g.*, mRNA) expression in a human cell (*e.g.*, SK-N-AS cell), which is expressing the *ANGPTL2* transcript.

7. The ASO of claim 6, wherein the *ANGPTL2* transcript expression is reduced by at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or 100% compared to *ANGPTL2* transcript expression in a human cell that is not exposed to the ASO.

8. The ASO of claim 1, wherein one or more of the sugar modified nucleosides comprise a 2'-O-alkyl-RNA; 2'-O-methyl RNA (2'-OMe); 2'-alkoxy-RNA; 2'-O-methoxyethyl-RNA (2'-MOE); 2'-amino-DNA; 2'-fluro-RNA; 2'-fluoro-DNA; arabino nucleic acid (ANA); 2'-fluoro-ANA; bicyclic nucleoside analog; or combinations thereof.

9. The ASO of claim 1 or 8, wherein the one or more of the sugar modified nucleosides is an affinity enhancing 2' sugar modified nucleoside.

10. The ASO of claim 9, wherein the affinity enhancing 2' sugar modified nucleoside is a locked nucleic acid (LNA).

11. The ASO of claim 10, wherein the LNA is selected from the group consisting of constrained ethyl nucleoside (cEt), 2',4'-constrained 2′-O-methoxyethyl (cMOE), α-L-LNA, β-D-LNA, 2'-O,4'-C-ethylene-bridged nucleic acids (ENA), amino-LNA, oxy-LNA, thio-LNA, and any combination thereof.

12. The ASO of any one of claims 1 to 11, wherein the ASO comprises one or more 5'-methyl-cytosine nucleobases.

13. The ASO of any one of claims 1 to 12, wherein the ASO is capable of (i) reducing *ANGPTL2* mRNA level in SK-N-AS cells; (ii) reducing ANGPTL2 protein level in SK-N-AS cells; (iii) reducing, ameliorating, or treating one or more symptoms of a disease or disorder associated with abnormal ANGPTL2 expression and/or activity, wherein the disease or disorder associated with abnormal ANGPTL2 expression and/or activity comprises a cardiovascular disease, obesity, metabolic disease, type 2 diabetes, cancers, an atherosclerosis, coronary artery disease, stroke, heart failure, hypertensive heart disease, rheumatic heart disease, cardiomyopathy, heart arrhythmia, congenital heart disease, valvular heart disease carditis, aortic aneurysms, peripheral artery disease, thromboembolic disease, venous thrombosis, comprises a left-sided heart failure, a right-sided heart failure, a congestive heart failure, a heart failure with reduced ejection fraction (HFrEF), a heart failure with preserved ejection fraction (HFpEF), a heart failure with mid-range ejection fraction (HFmrEF), a hypertrophic cardiomyopathy (HCM), a hypertensive heart disease (HHD), hypertensive hypertrophic cardiomyopathy or combinations thereof; or (iv) any combination thereof.

14. The ASO of any one of claims 1 to 13, wherein the contiguous nucleotide sequence is complementary to a nucleic acid sequence comprising (i) nucleotides 1 – 211 of SEQ ID NO: 1; (ii) nucleotides 471 – 686 of SEQ ID NO: 1; (iii) nucleotides 1,069 – 1,376 of SEQ ID NO: 1; (iv) nucleotides 1,666 – 8,673 of SEQ ID NO: 1; (v) nucleotides 8,975 – 12,415 of SEQ ID NO: 1; (vi) nucleotides 12,739 – 18,116 of SEQ ID NO: 1; (vii) nucleotides 18,422 – 29,875 of SEQ ID NO: 1; or (viii) nucleotides 30,373 – 35,389 of SEQ ID NO: 1.

15. The ASO of any one of claims 1 to 14, wherein the contiguous nucleotide sequence is complementary to a nucleic acid sequence comprising (i) nucleotides 37 - 161 of SEQ ID NO: 1; (ii) nucleotides 521 - 636 of SEQ ID NO: 1; (iii) nucleotides 1,119 – 1,326 of SEQ ID NO: 1; (iv) nucleotides 1,716 – 8,623 of SEQ ID NO: 1; (v) nucleotides 9,025 – 12,365 of SEQ ID NO:

1; (vi) nucleotides 12,789 – 18,066 of SEQ ID NO: 1; (vii) nucleotides 18,472 – 29,825 of SEQ ID NO: 1; or (viii) nucleotides 30,423 – 35,339 of SEQ ID NO: 1.

16. The ASO of any one of claims 1 to 15, wherein the contiguous nucleotide sequence is complementary to a nucleic acid sequence comprising (i) nucleotides 87 – 111 of SEQ ID NO: 1; (ii) nucleotides 571 – 586 of SEQ ID NO: 1; (iii) nucleotides 1,169 – 1,276 of SEQ ID NO: 1; (iv) nucleotides 1,766 – 8,573 of SEQ ID NO: 1; (v) nucleotides 9,075 – 12,315 of SEQ ID NO: 1; (vi) nucleotides 12,839 – 18,016 of SEQ ID NO: 1; (vii) nucleotides 18,522 – 29,775 of SEQ ID NO: 1; or (viii) nucleotides 30,473 – 35,289 of SEQ ID NO: 1.

17. The ASO of any one of claims 1 to 16, wherein the contiguous nucleotide sequence is complementary to a nucleic acid comprising nucleotides 20,187 – 20,234 of SEQ ID NO: 1.

18. The ASO of any one of claims 1 to 17, wherein the contiguous nucleotide sequence is complementary to a nucleic acid comprising nucleotides 20,202 – 20,219 of SEQ ID NO: 1.

19. The ASO of any one of claims 1 to 18, wherein the contiguous nucleotide sequence comprises SEQ ID NO: 4 to SEQ ID NO: 193 with one or two mismatches.

20. The ASO of any one of claims 1 to 18, wherein the contiguous nucleotide sequence comprises the nucleotide sequence selected from the sequences in FIG. 2 (SEQ ID NO: 4 to SEQ ID NO: 193).

21. The ASO of any one of claims 1 to 20, wherein the contiguous nucleotide sequence comprises SEQ ID NO: 8, SEQ ID NO: 20, SEQ ID NO: 38, SEQ ID NO: 46, SEQ ID NO: 79, SEQ ID NO: 84, SEQ ID NO: 82, SEQ ID NO: 88, SEQ ID NO: 85, SEQ ID NO: 90, SEQ ID NO: 89, SEQ ID NO: 93, SEQ ID NO: 95, SEQ ID NO: 97, SEQ ID NO: 101, SEQ ID NO: 111, SEQ ID NO: 116, SEQ ID NO: 120, SEQ ID NO: 121, SEQ ID NO: 122, SEQ ID NO: 132, SEQ ID NO: 142, SEQ ID NO: 141, SEQ ID NO: 143, SEQ ID NO: 144, or SEQ ID NO: 146.

22. The ASO of any one of claims 1 to 20, wherein the contiguous nucleotide sequence comprises SEQ ID NO: 141, SEQ ID NO: 122, SEQ ID NO: 8, SEQ ID NO: 38, SEQ ID NO: 95, SEQ ID NO: 88, or SEQ ID NO: 120.

23. The ASO of any one of claims 1 to 20, wherein the contiguous nucleotide sequence comprises SEQ ID NO: 116, SEQ ID NO: 118, SEQ ID NO: 117, SEQ ID NO: 120, SEQ ID NO: 119, SEQ ID NO: 121, SEQ ID NO: 122, or combinations thereof.

24. The ASO of any one of claims 1 to 23, which has a design selected from the group consisting of the designs in FIG. 2, wherein the upper letter is a sugar modified nucleoside and the lower case letter is DNA.

25. The ASO of any one of claims 1 to 24, which has from 15 to 20 nucleotides in length.

26. The ASO of any one of claims 1 to 25, wherein the contiguous nucleotide sequence comprises one or more modified internucleoside linkage.

27. The ASO of claim 26, wherein the one or more modified internucleoside linkage is a phosphorothioate linkage.

28. The ASO of claim 26 or 27, wherein at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or 100% of internucleoside linkages are modified.

29. The ASO of claim 28, wherein each of the internucleoside linkages is a phosphorothioate linkage.

30. A conjugate comprising the ASO of any one of claims 1 to 29, wherein the ASO is covalently attached to at least one non-nucleotide or non-polynucleotide moiety.

31. The conjugate of claim 30, wherein the non-nucleotide or non-polynucleotide moiety comprises a protein, a fatty acid chain, a sugar residue, a glycoprotein, a polymer, or any combinations thereof.

32. A pharmaceutical composition comprising the ASO of any one of claims 1 to 29 or the conjugate of claim 30 or 31, and a pharmaceutically acceptable diluent, carrier, salt, or adjuvant.

33. The pharmaceutical composition of claim 32, wherein the pharmaceutically acceptable salt comprises a sodium salt, a potassium salt, an ammonium salt, or any combination thereof.

34. The pharmaceutical composition of claim 32 or 33, which further comprises at least one further therapeutic agent.

35. The pharmaceutical composition of claim 34, wherein the further therapeutic agent is a ANGPTL2 antagonist.

36. The pharmaceutical composition of claim 35, wherein the ANGPTL2 antagonist is an anti-ANGPTL2 antibody or fragment thereof.

37. A kit comprising the ASO of any one of claims 1 to 29, the conjugate of claim 30 or 31, or the pharmaceutical composition of any one of claims 32 to 36, and instructions for use.

38. A diagnostic kit comprising the ASO of any one of claims 1 to 29, the conjugate of claim 30 or 31, or the pharmaceutical composition of any one of claims 32 to 36, and instructions for use.

39. An *in vitro* method of inhibiting or reducing ANGPTL2 protein expression in a cell, comprising contacting the ASO of any one of claims 1 to 29, the conjugate of claim 30 or 31, or the pharmaceutical composition of any one of claims 32 to 36 to the cell expressing ANGPTL2

protein, wherein the ANGPTL2 protein expression in the cell is inhibited or reduced after the contacting.

40. The method of claim 39, wherein the ASO inhibits or reduces expression of *ANGPTL2* transcript (*e.g.*, mRNA) in the cell after the administration or after the contacting.

41. The method of claim 40, wherein the expression of *ANGPTL2* transcript (*e.g.*, mRNA) is reduced by at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100% after the administration compared to a cell not exposed to the ASO.

42. The method of any one of claims 39 to 41, wherein the expression of ANGPTL2 protein is reduced by at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% after the administration compared to a cell not exposed to the ASO.

43. The method of any one of claims 39 to 42, wherein the cell is a brain cell, *e.g.*, neuroblast (*e.g.*, SK-N-AS cell).

44. Use of the ASO of any one of claims 1 to 29, the conjugate of claim 30 or 31, or the pharmaceutical composition of any one of claims 32 to 36 in the manufacture of a medicament for reducing, ameliorating, or treating one or more symptoms of a disease or disorder associated with abnormal ANGPTL2 expression and/or activity in a subject in need thereof, wherein the medicament comprises an effective amount of the ASO, the conjugate, or the pharmaceutical composition, and wherein, the disease or disorder associated with abnormal ANGPTL2 expression and/or activity comprises a cardiovascular disease, obesity, metabolic disease, type 2 diabetes, cancers, an atherosclerosis, coronary artery disease, stroke, heart failure, hypertensive heart disease, rheumatic heart disease, cardiomyopathy, heart arrhythmia, congenital heart disease, valvular heart disease carditis, aortic aneurysms, peripheral artery disease, thromboembolic disease, venous thrombosis, comprises a left-sided heart failure, a right-sided heart failure, a congestive heart failure, a heart failure with reduced ejection fraction (HFrEF), a heart failure with preserved ejection fraction (HFpEF), a heart failure with mid-range ejection fraction (HFmrEF), a hypertrophic cardiomyopathy (HCM), a hypertensive heart disease (HHD), hypertensive hypertrophic cardiomyopathy or combinations thereof.

45. Use of the ASO of any one of claims 1 to 29, the conjugate of claim 30 or 31, or the pharmaceutical composition of any one of claims 32 to 36 in the manufacture of a medicament for reducing, ameliorating, or treating one or more symptoms of a disease or disorder associated with abnormal ANGPTL2 expression and/or activity in a subject in need thereof, wherein the disease

or disorder associated with abnormal ANGPTL2 expression and/or activity comprises a cardiovascular disease, obesity, metabolic disease, type 2 diabetes, cancers, an atherosclerosis, coronary artery disease, stroke, heart failure, hypertensive heart disease, rheumatic heart disease, cardiomyopathy, heart arrhythmia, congenital heart disease, valvular heart disease carditis, aortic aneurysms, peripheral artery disease, thromboembolic disease, venous thrombosis, comprises a left-sided heart failure, a right-sided heart failure, a congestive heart failure, a heart failure with reduced ejection fraction (HFrEF), a heart failure with preserved ejection fraction (HFpEF), a heart failure with mid-range ejection fraction (HFmrEF), a hypertrophic cardiomyopathy (HCM), a hypertensive heart disease (HHD), hypertensive hypertrophic cardiomyopathy or combinations thereof.

46. Use of the ASO of any one of claims 1 to 29, the conjugate of claim 30 or 31, or the pharmaceutical composition of any one of claims 32 to 36 in the manufacture of a medicament for the treatment of a disease or disorder associated with abnormal ANGPTL2 expression and/or activity in a subject in need thereof, wherein the disease or disorder associated with abnormal ANGPTL2 expression and/or activity comprises a cardiovascular disease, obesity, metabolic disease, type 2 diabetes, cancers, an atherosclerosis, coronary artery disease, stroke, heart failure, hypertensive heart disease, rheumatic heart disease, cardiomyopathy, heart arrhythmia, congenital heart disease, valvular heart disease carditis, aortic aneurysms, peripheral artery disease, thromboembolic disease, venous thrombosis, comprises a left-sided heart failure, a right-sided heart failure, a congestive heart failure, a heart failure with reduced ejection fraction (HFrEF), a heart failure with preserved ejection fraction (HFpEF), a heart failure with mid-range ejection fraction (HFmrEF), a hypertrophic cardiomyopathy (HCM), a hypertensive heart disease (HHD), hypertensive hypertrophic cardiomyopathy or combinations thereof.

47. The ASO of any one of claims 1 to 29, the conjugate of claim 30 or 31, or the pharmaceutical composition of any one of claims 32 to 36 for use in therapy.

48. The ASO of any one of claims 1 to 29, the conjugate of claim 30 or 31, or the pharmaceutical composition of any one of claims 32 to 36 for use in therapy of a disease or disorder associated with abnormal ANGPTL2 expression and/or activity in a subject in need thereof, wherein the disease or disorder associated with abnormal ANGPTL2 expression and/or activity comprises a cardiovascular disease, obesity, metabolic disease, type 2 diabetes, cancers, an atherosclerosis, coronary artery disease, stroke, heart failure, hypertensive heart disease, rheumatic heart disease, cardiomyopathy, heart arrhythmia, congenital heart disease, valvular heart disease carditis, aortic aneurysms, peripheral artery disease, thromboembolic disease, venous thrombosis,

comprises a left-sided heart failure, a right-sided heart failure, a congestive heart failure, a heart failure with reduced ejection fraction (HFrEF), a heart failure with preserved ejection fraction (HFpEF), a heart failure with mid-range ejection fraction (HFmrEF), a hypertrophic cardiomyopathy (HCM), a hypertensive heart disease (HHD), hypertensive hypertrophic cardiomyopathy or combinations thereof.

49. The use of any one of claims 44 to 46, or the ASO for use of claim 47 or 48, wherein the subject is a human.

50. The use of any one of claims 44 to 46, or the ASO for use of any one of claims 47 to 49, wherein the ASO, the conjugate, or the pharmaceutical composition is to be administered intracardially, orally, parenterally, intrathecally, intra-cerebroventricularly, pulmonarily, topically, or intraventricularly.