What is Claimed

1. An antisense oligonucleotide (ASO) comprising a contiguous nucleotide sequence up 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 locked nucleic acids (LNAs), wherein the contiguous nucleotide sequence comprises a sequence as set forth in SEQ ID NO: 4 or SEQ ID NO: 5, optionally with one or two mismatches and wherein the contiguous nucleotide sequence is at least 85% complementary to a nucleic acid sequence within nucleotides 1-211 of SEQ ID NO: 1.

2. The ASO of claims 1, 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.

3. The ASO of claim 2, 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.

4. The ASO of any one of claims 1 to 3, 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.

5. The ASO of claim 4, 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.

6. The ASO of claim 1, 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.

7. The ASO of any one of claims 1 to 6, wherein the ASO comprises one or more 5'-methyl-cytosine nucleobases.

8. The ASO of any one of claims 1 to 7, 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.

9. The ASO of any one of claims 1 to 8, which has a design selected from the group consisting of the designs in FIG. 2, wherein the upper letter is a locked nucleic acid (LNA) and the lower case letter is DNA.

10. The ASO of any one of claims 1 to 9, wherein the contiguous nucleotide sequence comprises one or more modified internucleoside linkage.

11. The ASO of claim 10, wherein the one or more modified internucleoside linkage is a phosphorothioate linkage.

12. The ASO of claim 10 or 11, wherein at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or 100% of internucleoside linkages are modified.

13. The ASO of claim 12, wherein each of the internucleoside linkages is a phosphorothioate linkage.

14. A conjugate comprising the ASO of any one of claims 1 to 13, wherein the ASO is covalently attached to at least one non-nucleotide or non-polynucleotide moiety.

15. The conjugate of claim 14, 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.

16. A pharmaceutical composition comprising the ASO of any one of claims 1 to 13 or the conjugate of claim 14 or 15, and a pharmaceutically acceptable diluent, carrier, salt, or adjuvant.

17. The pharmaceutical composition of claim 16, wherein the pharmaceutically acceptable salt comprises a sodium salt, a potassium salt, an ammonium salt, or any combination thereof.

18. The pharmaceutical composition of claim 16 or 17, which further comprises at least one further therapeutic agent.

19. The pharmaceutical composition of claim 18, wherein the further therapeutic agent is a ANGPTL2 antagonist.

20. The pharmaceutical composition of claim 19, wherein the ANGPTL2 antagonist is an anti-ANGPTL2 antibody or fragment thereof.

21. A kit comprising the ASO of any one of claims 1 to 13, the conjugate of claim 14 or 15, or the pharmaceutical composition of any one of claims 16 to 20, and instructions for use.

22. A diagnostic kit comprising the ASO of any one of claims 1 to 13, the conjugate of claim 14 or 15, or the pharmaceutical composition of any one of claims 16 to 20, and instructions for use.

23. 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 13, the conjugate of claim 14 or 15, or the pharmaceutical composition of any one of claims 16 to 20 to the cell expressing ANGPTL2 protein, wherein the ANGPTL2 protein expression in the cell is inhibited or reduced after the contacting.

24. The method of claim 23, wherein the ASO inhibits or reduces expression of *ANGPTL2* transcript (*e.g.*, mRNA) in the cell after the administration or after the contacting.

25. The method of claim 24, 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.

26. The method of any one of claims 23 to 25, 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.

27. The method of any one of claims 23 to 26, wherein the cell is a brain cell, *e.g.*, neuroblast (*e.g.*, SK-N-AS cell).

28. Use of the ASO of any one of claims 1 to 13, the conjugate of claim 14 or 15, or the pharmaceutical composition of any one of claims 16 to 20 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.

29. Use of the ASO of any one of claims 1 to 13, the conjugate of claim 14 or 15, or the pharmaceutical composition of any one of claims 16 to 20 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.

30. Use of the ASO of any one of claims 1 to 13, the conjugate of claim 14 or 15, or the pharmaceutical composition of any one of claims 16 to 20 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.

31. The ASO of any one of claims 1 to 13, the conjugate of claim 14 or 15, or the pharmaceutical composition of any one of claims 16 to 20 for use in therapy.

32. The ASO of any one of claims 1 to 13, the conjugate of claim 14 or 15, or the pharmaceutical composition of any one of claims 16 to 20 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.

33. The use of any one of claims 28 to 30, or the ASO for use of claim 31 or 32, wherein the subject is a human.

34. The use of any one of claims 28 to 30, or the ASO for use of any one of claims 31 to 33, wherein the ASO, the conjugate, or the pharmaceutical composition is to be administered intracardially, orally, parenterally, intrathecally, intra-cerebroventricularly, pulmonarily, topically, or intraventricularly.