What is Claimed

1. An antisense oligonucleotide (ASO) comprising a contiguous nucleotide sequence up ~~of 10~~ to 30 nucleotides in length, wherein the contiguous nucleotide sequence comprises at least one non-naturally occurring nucleoside, wherein the ASO is capable of reducing calcium/calmodulin-dependent protein kinase type II delta (CAMK2D) protein and/or CAMK2D transcript expression in a human cell, and wherein the contiguous nucleotide sequence comprises the sequence set forth in SEQ ID NO: 657, SEQ ID NO: 659, SEQ ID NO: 822, SEQ ID NO: 827, SEQ ID NO: 981, SEQ ID NO: 982, SEQ ID NO: 983, SEQ ID NO: 984, SEQ ID NO: 986, SEQ ID NO: 989, SEQ ID NO: 1247, SEQ ID NO: 1249, SEQ ID NO: 1326, SEQ ID NO: 1359, SEQ ID NO: 1363, SEQ ID NO: 1371, SEQ ID NO: 1387, SEQ ID NO: 1389, SEQ ID NO: 1390, SEQ ID NO: 1409, SEQ ID NO: 1415, SEQ ID NO: 1420, or SEQ ID NO: 1429~~that is complementary, such as fully complementary, to a nucleic acid sequence within a calcium/calmodulin-dependent protein kinase type II delta (*CAMK2D*) transcript~~.

2. The ASO of claim 1, wherein the ASO is a gapmer~~or contiguous nucleotide sequence thereof, which is at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100% complementary to the nucleic acid sequence within the *CAMK2D* transcript~~.

3. The ASO of claim 1 ~~or 2~~, wherein the non-naturally occurring nucleoside is a sugar modified nucleoside~~*CAMK2D* transcript is selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 2~~.

~~4. The ASO of any one of claims 1 to 3, wherein the ASO is capable of reducing CAMK2D protein expression in a human cell (*e.g.*, HEK293 cell) which is expressing the CAMK2D protein.~~

~~5. The ASO of claim 4, wherein the CAMK2D protein expression is reduced by at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100% compared to CAMK2D 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 *CAMK2D* transcript (*e.g.*, mRNA) expression in a human cell (*e.g.*, HEK293 cell), which is expressing the CAMK2D transcript.~~

~~7. The ASO of claim 6, wherein the *CAMK2D* transcript expression is reduced by at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at~~

~~least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100% compared to *CAMK2D* transcript expression in a human cell that is not exposed to the ASO.~~

~~8. The ASO of any one of claims 1 to 7, wherein the ASO is a gapmer.~~

~~9. The ASO of any one of claims 1 to 8, wherein the ASO has a design of $LLLD_nLLL$, $LLLLD_nLLLL$, or $LLLLLD_nLLLLL$, wherein the L is a nucleoside analog, the D is DNA, and n can be any integer between 4 and 24.~~

~~10. The ASO of claim 9, wherein the n can be any integer between 6 and 14.~~

~~11. The ASO of claim 9, wherein the n can be any integer between 8 and 12.~~

~~12~~4. The ASO of ~~any one of claims 9 to 11~~claim 3, wherein the non-naturally occurring nucleoside ~~nucleoside analog~~ comprises a 2'-O-alkyl-RNA; 2'-O-methyl RNA (2'-OMe); 2'-alkoxy-RNA; 2'-O-methoxyethyl-RNA (2'-MOE); 2'-amino-DNA; 2'-fluoro-RNA; 2'-fluoro-DNA; arabino nucleic acid (ANA); 2'-fluoro-ANA; or bicyclic nucleoside analog (LNA).

~~13. The ASO of any one of claims 9 to 12, wherein one or more of the nucleoside analog is a sugar modified nucleoside.~~

~~14~~5. The ASO of claim ~~13~~3, wherein the sugar modified nucleoside is an affinity enhancing 2' sugar modified nucleoside.

~~15. The ASO of any one of claims 9 to 12, wherein one or more of the nucleoside analog comprises a nucleoside comprising a bicyclic sugar.~~

~~16~~6. The ASO of claim ~~14~~5, wherein the affinity enhancing 2' sugar modified nucleoside is an LNA.

~~17. The ASO of claim 16, 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, or any combination thereof.~~

~~18~~7. The ASO of ~~any one of~~ claim~~s~~ 1~~ to 17~~, wherein the ASO comprises one or more 5'-methyl-cytosine nucleobases.

8. The ASO of claim 1, wherein the contiguous nucleotide sequence comprises one or more modified internucleoside linkages.

9. The ASO of claim 8, wherein the one or more modified internucleoside linkages is a phosphorothioate linkage.

10. A conjugate comprising the ASO of claim 1, wherein the ASO is covalently attached to at least one non-nucleotide or non-polynucleotide moiety.

11. A pharmaceutical composition comprising the ASO of claim 1 and a pharmaceutically acceptable diluent, carrier, salt, or adjuvant.

12. A kit comprising the ASO of claim 1 and instructions for use.

13. The ASO of claim 6, wherein the LNA is constrained ethyl nucleoside (cEt), 2′,4′-constrained 2′-O-methoxyethyl (cMOE), α-L-LNA, β-D-LNA, 2′-0,4′-C-ethylene-bridged nucleic acids (ENA), amino-LNA, oxy-LNA, thio-LNA, or any combination thereof.

14. The ASO of claim 6, wherein the LNA is β-D-LNA or oxy-LNA.

15. The ASO of claim 1, wherein the contiguous nucleotide sequence comprises the sequence set forth in SEQ ID NO: 1390.

16. The ASO of claim 1, wherein the contiguous nucleotide sequence comprises the sequence set forth in SEQ ID NO: 657 or SEQ ID NO: 659.

17. The ASO of claim 1, wherein the ASO is capable of reducing CAMK2D protein and/or CAMK2D transcript expression in the human cell by at least about 20% compared to a corresponding cell not exposed to the ASO.

~~19. The ASO of any one of claims 1 to 18, wherein the ASO is capable of (i) reducing an mRNA level encoding CAMK2D in Inducible Pluripotent Stem Cell-Derived Cardiomyocytes (hiPSC-CM); (ii) reducing a protein level of CAMK2D in hiPSC-CM; (iii) reducing, ameliorating, or treating one or more symptoms of a cardiovascular disease or disorder, and (iv) any combination thereof.~~

~~20. The ASO of any one of claims 1 to 19, wherein the contiguous nucleotide sequence is complementary to a nucleic acid sequence comprising (i) nucleotides 625 – 842 of SEQ ID NO: 1; (ii) nucleotides 1,398 – 59,755 of SEQ ID NO: 1; (iii) nucleotides 61,817 – 104,725 of SEQ ID NO: 1; (iv) nucleotides 112,162 – 118,021 of SEQ ID NO: 1; (v) nucleotides 119,440 – 135,219 of SEQ ID NO: 1; (vi) nucleotides 137,587 – 157,856 of SEQ ID NO: 1; (vii) nucleotides 159,191 – 266,174 of SEQ ID NO: 1; or (viii) nucleotides 272,788 – 310,949 of SEQ ID NO: 1.~~

~~21. The ASO of any one of claims 1 to 19, wherein the contiguous nucleotide sequence is complementary to a nucleic acid sequence comprising (i) nucleotides 675 – 792 of SEQ ID NO: 1; (ii) nucleotides 1,448 – 59,705 of SEQ ID NO: 1; (iii) nucleotides 61,867 – 104,675 of SEQ ID NO: 1; (iv) nucleotides 112,212 – 117,971 of SEQ ID NO: 1; (v) nucleotides 119,490 – 135,169~~

~~of SEQ ID NO: 1; (vi) nucleotides 137,637 – 157,806 of SEQ ID NO: 1; (vii) nucleotides 159,241 – 266,124 of SEQ ID NO: 1; or (viii) nucleotides 272,838 – 310,899 of SEQ ID NO: 1.~~

~~22. The ASO of any one of claims 1 to 19, wherein the contiguous nucleotide sequence is complementary to a nucleic acid sequence comprising (i) nucleotides 725 – 742 of SEQ ID NO: 1; (ii) nucleotides 1,498 – 59,655 of SEQ ID NO: 1; (iii) nucleotides 61,917 – 104,625 of SEQ ID NO: 1; (iv) nucleotides 112,262 – 117,921 of SEQ ID NO: 1; (v) nucleotides 119,540 – 135,119 of SEQ ID NO: 1; (vi) nucleotides 137,687 – 157,756 of SEQ ID NO: 1; (vii) 159,291 – 266,074 of SEQ ID NO: 1; or (viii) nucleotides 272,888 – 310,849 of SEQ ID NO: 1.~~

~~23. The ASO of any one of claims 1 to 22, wherein the contiguous nucleotide sequence comprises SEQ ID NO: 4 to SEQ ID NO: 1713 with one or two mismatches.~~

~~24. The ASO of any one of claims 1 to 23, wherein the contiguous nucleotide sequence comprises the nucleotide sequence selected from the sequences in FIGs. 1A and 1B (SEQ ID NO: 4 to SEQ ID NO: 1713).~~

~~25. The ASO of any one of claims 1 to 24, wherein the contiguous nucleotide sequence comprises SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 114, SEQ ID NO: 158, SEQ ID NO: 190, SEQ ID NO: 327, SEQ ID NO: 463, SEQ ID NO: 513, SEQ ID NO: 516, SEQ ID NO: 519, SEQ ID NO: 657, SEQ ID NO: 659, SEQ ID NO: 827, SEQ ID NO: 1249, SEQ ID NO: 1326, SEQ ID NO: 1409, SEQ ID NO: 1524, SEQ ID NO: 1530, SEQ ID NO: 1662, or SEQ ID NO: 1676.~~

~~26. The ASO of any one of claims 1 to 24, wherein the contiguous nucleotide comprises SEQ ID NO: 55, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 79, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 92, SEQ ID NO: 102, SEQ ID NO: 105, SEQ ID NO: 128, SEQ ID NO: 130, SEQ ID NO: 133, SEQ ID NO: 138, SEQ ID NO: 161, SEQ ID NO: 178, SEQ ID NO: 180, SEQ ID NO: 186, SEQ ID NO: 195, SEQ ID NO: 200, SEQ ID NO: 202, SEQ ID NO: 234, SEQ ID NO: 264, SEQ ID NO: 387, SEQ ID NO: 390, SEQ ID NO: 396, SEQ ID NO: 441, SEQ ID NO: 446, SEQ ID NO: 457, SEQ ID NO: 467, SEQ ID NO: 523, SEQ ID NO: 524, SEQ ID NO: 636, SEQ ID NO: 640, SEQ ID NO: 700, SEQ ID NO: 740, SEQ ID NO: 832, SEQ ID NO: 965, SEQ ID NO: 1015, SEQ ID NO: 1065, SEQ ID NO: 1071, SEQ ID NO: 1155, SEQ ID NO: 1475, SEQ ID NO: 1508, SEQ ID NO: 1685, SEQ ID NO: 1686, SEQ ID NO: 1687, SEQ ID NO: 1688, or SEQ ID NO: 1690.~~

~~27. The ASO of claim 1 or 26, which has a design selected from the group consisting of the designs in Fig. 3, wherein the upper letter is a sugar modified nucleoside and the lower case letter is DNA.~~

28. The ASO of any one of claims 1 to 27, which is capable of reducing expression of CAMK2D protein in a hiPSC-CM cell which is expressing the CAMK2D protein.

29. The ASO of claim 28, wherein the expression of CAMK2D protein is reduced by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% compared to a cell not exposed to the ASO.

30. The ASO of any one of claims 1 to 29, which is capable of reducing expression of *CAMK2D* transcript (*e.g.*, mRNA) in a hiPSC-CM cell which is expressing the *CAMK2D* transcript.

31. The ASO of claim 30, wherein the expression of *CAMK2D* transcript is reduced by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% compared to a cell not exposed to the ASO.

32. The ASO of any one of claims 1 to 31, which has from 14 to 20 nucleotides in length.

33. The ASO of any one of claims 1 to 32, wherein the nucleotide sequence comprises one or more modified internucleoside linkages.

34. The ASO of any one of claims 1 to 33, wherein the one or more modified internucleoside linkages is a phosphorothioate linkage.

35. The ASO of claim 33 or 34, wherein at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or 100% of internucleoside linkages are modified.

36. The ASO of claim 35, wherein each of the internucleoside linkages in the ASO is a phosphorothioate linkage.

37. A conjugate comprising the ASO of any one of claims 1 to 36, wherein the ASO is covalently attached to at least one non-nucleotide or non-polynucleotide moiety.

38. The conjugate of claim 37, 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.

39. A pharmaceutical composition comprising the ASO of any one of claims 1 to 36 or the conjugate of claim 37 or 38, and a pharmaceutically acceptable diluent, carrier, salt, or adjuvant.

40. The pharmaceutical composition of claim 39, wherein the pharmaceutically acceptable salt comprises a sodium salt, a potassium salt, an ammonium salt, or any combination thereof.

41. The pharmaceutical composition of claim 39 or 40, which further comprises at least one further therapeutic agent.

42. The pharmaceutical composition of claim 41, wherein the further therapeutic agent is a CAMK2D antagonist.

43. The pharmaceutical composition of claim 42, wherein the CAMK2D antagonist is an anti-CAMK2d antibody or fragment thereof.

44. A kit comprising the ASO of any one of claims 1 to 36, the conjugate of claim 37 or 38, or the pharmaceutical composition of any one of claims 39 to 43, and instructions for use.

45. A diagnostic kit comprising the ASO of any one of claims 1 to 36, the conjugate of claim 37 or 38, or the pharmaceutical composition of any one of claims 39 to 43, and instructions for use.

46. A method of inhibiting or reducing CAMK2D protein expression in a cell, comprising administering the ASO of any one of claims 1 to 36, the conjugate of claim 37 or 38, or the pharmaceutical composition of any one of claims 39 to 43 to the cell expressing CAMK2D protein, wherein the CAMK2D protein expression in the cell is inhibited or reduced after the administration.

47. An *in vitro* method of inhibiting or reducing CAMK2D protein expression in a cell, comprising contacting the ASO of any one of claims 1 to 36, the conjugate of claim 37 or 38, or the pharmaceutical composition of any one of claims 39 to 43 to the cell expressing CAMK2D protein, wherein the CAMK2D protein expression in the cell is inhibited or reduced after the contacting.

48. The method of claim 46 or 47, wherein the ASO inhibits or reduces expression of *CAMK2D* transcript (*e.g.*, mRNA) in the cell after the administration.

49. The method of claim 48, wherein the expression of *CAMK2D* transcript (*e.g.*, mRNA) is reduced by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% after the administration compared to a cell not exposed to the ASO.

50. The method of any one of claims 46 to 49, wherein the expression of CAMK2D protein is reduced by at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% after the administration compared to a cell not exposed to the ASO.

51. The method of any one of claims 46 to 50, wherein the cell is a cardiac cell, *e.g.*, hiPSC-CM.

52. A method of reducing, ameliorating, or treating one or more symptoms of a cardiovascular disease or disorder in a subject in need thereof, comprising administering an

effective amount of the ASO of any one of claims 1 to 36, the conjugate of claim 37 or 38, or the pharmaceutical composition of any one of claims 39 to 43 to the subject.

53. Use of the ASO of any one of claims 1 to 36, the conjugate of claim 37 or 38, or the pharmaceutical composition of any one of claims 39 to 43 for the manufacture of a medicament.

54. Use of the ASO of any one of claims 1 to 36, the conjugate of claim 37 or 38, or the pharmaceutical composition of any one of claims 39 to 43 for the manufacture of a medicament for the treatment of a cardiovascular disease or disorder in a subject in need thereof.

55. The ASO of any one of claims 1 to 36, the conjugate of claim 37 or 38, or the pharmaceutical composition of any one of claims 39 to 43 for use in therapy.

56. The ASO of any one of claims 1 to 36, the conjugate of claim 37 or 38, or the pharmaceutical composition of any one of claims 39 to 43 for use in therapy of a cardiovascular disease or disorder in a subject in need thereof.

57. The ASO of claim 19, the method of claim 52, the use of claim 54, or the ASO for use of claim 56, wherein the cardiovascular disease or disorder comprises a 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, or any combination thereof.

58. The method, use, or ASO of claim 57, wherein the cardiovascular disease or disorder is heart failure.

59. The method, use, or ASO of claim 58, wherein the heart failure 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), or hypertensive hypertrophic cardiomyopathy.

60. The method of any one of claims 52 and 57 to 59, , the use of any one of claims 54 and 57 to 59, or the ASO for use of any one of claims 56 to 59, wherein the subject is a human.

61. The method of any one of claims 52 and 57 to 60, the use of any one of claims 54 and 57 to 60, or the ASO for use of any one of claims 56 to 60, wherein the ASO, the conjugate, or the pharmaceutical composition is administered intracardially, orally, parenterally, intrathecally, intra-cerebroventricularly, pulmorarily, topically, or intraventricularly.