

CLAIMS

WHAT IS CLAIMED IS:

1. An engineered oligonucleotide or salt thereof comprising a polynucleotide sequence, wherein the engineered oligonucleotide or salt thereof is at least partially complementary to at least a portion of at least a first and a second RNA originating from two genetic loci that are associated with a disease or condition, wherein when the engineered oligonucleotide or salt thereof at least partially binds to the first RNA, a first region of at least seven contiguous bases in the engineered oligonucleotide are complementary to contiguous nucleic acids contained within the first RNA, and a second region of at least five contiguous bases in the engineered oligonucleotide are complementary to contiguous nucleic acids contained within the first RNA, and wherein when the engineered oligonucleotide or salt thereof at least partially binds to the second RNA, a first region of at least seven contiguous bases in the engineered oligonucleotide are complementary to contiguous nucleotides contained within the second RNA, and a second region of at least five contiguous bases in the engineered oligonucleotide are complementary to contiguous nucleotides contained within the second RNA, and wherein a predicted Gibbs free energy (ΔG) of binding of the engineered oligonucleotide to the first and the second RNA ranges, individually, from about -17 to about -36 kcal mol⁻¹ at about 37 degrees Celsius and at a pH ranging from about 7.2 to about 7.6.
2. The engineered oligonucleotide or salt thereof of claim 1, wherein the engineered oligonucleotide or salt thereof is an antisense oligonucleotide, a synthetic microRNA (miRNA), or a small interfering RNA (siRNA).
3. The engineered oligonucleotide or salt thereof of claim 1, wherein the engineered oligonucleotide or salt thereof comprises one or more nucleotide insertions, nucleotide deletions, nucleotide substitutions, or any combination thereof, relative to one or more otherwise comparable non-coding RNAs (ncRNAs).
4. The engineered oligonucleotide or salt thereof of claim 3, wherein the engineered oligonucleotide or salt thereof, when at least partially bound to the first or the second RNA, has an at least about 10% lower Gibbs free energy (ΔG) of binding at about 37 degrees Celsius and at a pH ranging from about 7.2 to about 7.6, relative to a ΔG of binding of the otherwise comparable ncRNA binding to the first or the second RNA at about 37 degrees Celsius and at a pH ranging from about 7.2 to about 7.6.

5. The engineered oligonucleotide or salt thereof of any one of claims 1-4, wherein the engineered oligonucleotide or salt thereof is from about 5 to about 50 nucleotides in length.
6. The engineered oligonucleotide or salt thereof of any one of claims 1-5, wherein the engineered oligonucleotide or salt thereof comprises a ribose sugar.
7. The engineered oligonucleotide or salt thereof of any one of claims 1-6, wherein the engineered oligonucleotide or salt thereof comprises a deoxyribose sugar.
8. The engineered oligonucleotide or salt thereof of any one of claims 4-7, wherein the ncRNA is an miR-30 micro RNA (miRNA), an miR-29 miRNA, an miR-26 miRNA, an miR-27 miRNA, an miR-101 miRNA, an miR-145 miRNA, an miR-205 miRNA, an miR-338 miRNA, or an miR-375 miRNA.
9. The engineered oligonucleotide or salt thereof of any one of claims 1-8, wherein the engineered oligonucleotide or salt thereof has at least 90% sequence identity to any one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO: 105, SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 119, SEQ ID NO: 120, SEQ ID NO: 121, SEQ ID NO: 122, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 126, SEQ ID NO: 245, SEQ ID NO: 246, SEQ ID NO: 247, SEQ ID NO: 248, SEQ ID NO: 249, SEQ ID NO: 250, SEQ ID NO: 251, SEQ ID NO: 252, SEQ ID NO: 253, SEQ ID NO: 254, SEQ ID NO: 255, SEQ ID NO: 256, SEQ ID NO: 257, SEQ ID NO: 258, SEQ ID NO: 259, SEQ ID NO: 260, SEQ ID NO: 261, SEQ ID NO: 262, SEQ ID NO: 263, SEQ ID NO: 465, SEQ ID NO: 624, SEQ ID NO: 625, SEQ ID NO: 626, SEQ ID NO: 627, SEQ ID NO: 628, SEQ ID NO: 629, SEQ ID NO: 630, SEQ ID NO: 631, SEQ ID NO: 632, SEQ ID NO: 633, SEQ ID NO: 634, SEQ ID NO: 635, SEQ ID NO: 636, SEQ ID NO: 637, SEQ ID NO: 638, SEQ ID NO: 639, SEQ ID NO: 640, SEQ ID NO: 641, SEQ ID NO: 642, SEQ ID NO: 643, SEQ ID NO: 840, SEQ ID NO: 841, SEQ ID NO: 842, SEQ ID NO: 843, SEQ ID NO: 844, SEQ ID NO: 845, SEQ ID NO: 901, SEQ ID NO: 902, SEQ ID NO: 903, SEQ ID NO: 904, SEQ ID NO: 905, SEQ ID NO: 906, SEQ ID NO: 907, SEQ ID NO: 908, SEQ

ID NO: 909, SEQ ID NO: 910, SEQ ID NO: 911, SEQ ID NO: 912, SEQ ID NO: 913, SEQ ID NO: 914, SEQ ID NO: 915, SEQ ID NO: 916, SEQ ID NO: 917, SEQ ID NO: 918, SEQ ID NO: 919, SEQ ID NO: 920, SEQ ID NO: 921, SEQ ID NO: 922, SEQ ID NO: 923, SEQ ID NO: 924, SEQ ID NO: 925, SEQ ID NO: 926, SEQ ID NO: 927, SEQ ID NO: 928, SEQ ID NO: 929, SEQ ID NO: 930, SEQ ID NO: 931, SEQ ID NO: 932, SEQ ID NO: 933, SEQ ID NO: 934, SEQ ID NO: 935, SEQ ID NO: 936, SEQ ID NO: 937, SEQ ID NO: 938, SEQ ID NO: 939, SEQ ID NO: 940, SEQ ID NO: 941, SEQ ID NO: 942, SEQ ID NO: 943, SEQ ID NO: 944, SEQ ID NO: 945, SEQ ID NO: 946, SEQ ID NO: 947, SEQ ID NO: 948, or SEQ ID NO: 949, as determined by a BLAST pairwise sequence alignment algorithm.

10. The engineered oligonucleotide or salt thereof of any one of claims 1-9, wherein the engineered oligonucleotide forms a secondary structure comprising a stem-loop in an aqueous solution at a temperature ranging from about 15 degrees Celsius to about 37 Celsius at a pH ranging from about 6.5 to about 7.6.
11. The engineered oligonucleotide or salt thereof of any one of claims 1-10, wherein the engineered oligonucleotide or salt thereof comprises a chemically modified base, chemically modified sugar, chemically modified backbone or phosphate linkage, or any combination thereof relative to a naturally occurring base, sugar, backbone, or phosphate linkage.
12. The engineered oligonucleotide or salt thereof of claim 11, wherein the chemical modification is selected from the group consisting of: a methyl group, a fluoro group, a methoxyethyl group, an ethyl group, a hydroxymethyl group, a formyl group, bridged nucleic acid, locked nucleic acid, a carboxylic acid or salt thereof, a phosphothionate modified backbone, a methylphosphonate modified backbone, an amino-alkyl chain modification, and any combination thereof.
13. The engineered oligonucleotide or salt thereof of any one of claims 11 or 12, wherein the engineered oligonucleotide or salt thereof, when chemically modified, comprises the formula:

$$(N)_a(mN)_b(N)_cNN;$$

$$(N)_a(mN)_b(N)_c sfNsmN; \text{ or}$$

$$(fNmN)_h(mN)_i(fNmN)_j sfNsmN;$$
 wherein
 each N is independently uracil, guanine, adenine, cytosine, or other natural nucleotide;
 each mN is independently a 2'-O-methyl-modified uracil, guanine, adenine, or cytosine;

each s is independently a phosphothionate-modified backbone;

each fN is independently 2'-fluoro-modified uracil, guanine, adenine, or cytosine; and

each a is from 8-10, each b is from 7-10, each c is from 2-4, each h is from 5-7, each i is 0 or 1, and each j is from 3-4.

14. The engineered oligonucleotide or salt thereof of any one of claims 11-13, wherein the engineered oligonucleotide or salt thereof has at least 90% sequence identity to any one of SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, SEQ ID NO: 149, SEQ ID NO: 150, SEQ ID NO: 151, SEQ ID NO: 152, SEQ ID NO: 153, SEQ ID NO: 154, SEQ ID NO: 184, SEQ ID NO: 185, SEQ ID NO: 186, SEQ ID NO: 187, SEQ ID NO: 188, SEQ ID NO: 189, SEQ ID NO: 190, SEQ ID NO: 191, SEQ ID NO: 192, SEQ ID NO: 193, SEQ ID NO: 194, SEQ ID NO: 195, SEQ ID NO: 196, SEQ ID NO: 197, SEQ ID NO: 198, SEQ ID NO: 199, SEQ ID NO: 200, SEQ ID NO: 201, SEQ ID NO: 205, SEQ ID NO: 206, SEQ ID NO: 207, SEQ ID NO: 208, SEQ ID NO: 209, SEQ ID NO: 210, SEQ ID NO: 211, SEQ ID NO: 212, SEQ ID NO: 213, SEQ ID NO: 214, SEQ ID NO: 215, SEQ ID NO: 216, SEQ ID NO: 217, SEQ ID NO: 218, SEQ ID NO: 219, SEQ ID NO: 220, SEQ ID NO: 221, SEQ ID NO: 222, SEQ ID NO: 225, SEQ ID NO: 226, SEQ ID NO: 227, SEQ ID NO: 228, SEQ ID NO: 229, SEQ ID NO: 230, SEQ ID NO: 231, SEQ ID NO: 232, SEQ ID NO: 233, SEQ ID NO: 235, SEQ ID NO: 236, SEQ ID NO: 237, SEQ ID NO: 238, SEQ ID NO: 239, SEQ ID NO: 240, SEQ ID NO: 241, SEQ ID NO: 242, SEQ ID NO: 243, SEQ ID NO: 264, SEQ ID NO: 265, SEQ ID NO: 266, SEQ ID NO: 267, SEQ ID NO: 268, SEQ ID NO: 269, SEQ ID NO: 270, SEQ ID NO: 271, SEQ ID NO: 272, SEQ ID NO: 273, SEQ ID NO: 274, SEQ ID NO: 275, SEQ ID NO: 276, SEQ ID NO: 277, SEQ ID NO: 278, SEQ ID NO: 279, SEQ ID NO: 280, SEQ ID NO: 281, SEQ ID NO: 282, SEQ ID NO:

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ID NO: 797, SEQ ID NO: 798, SEQ ID NO: 799, SEQ ID NO: 800, SEQ ID NO: 801, SEQ ID NO: 802, SEQ ID NO: 803, SEQ ID NO: 804, SEQ ID NO: 805, SEQ ID NO: 806, SEQ ID NO: 807, SEQ ID NO: 808, SEQ ID NO: 809, SEQ ID NO: 810, SEQ ID NO: 811, SEQ ID NO: 812, SEQ ID NO: 813, SEQ ID NO: 814, SEQ ID NO: 815, SEQ ID NO: 816, SEQ ID NO: 817, SEQ ID NO: 818, SEQ ID NO: 819, SEQ ID NO: 820, SEQ ID NO: 821, SEQ ID NO: 822, SEQ ID NO: 823, SEQ ID NO: 824, SEQ ID NO: 825, SEQ ID NO: 835, SEQ ID NO: 836, SEQ ID NO: 837, SEQ ID NO: 846, SEQ ID NO: 847, SEQ ID NO: 848, SEQ ID NO: 849, SEQ ID NO: 850, SEQ ID NO: 851, SEQ ID NO: 852, SEQ ID NO: 853, SEQ ID NO: 854, SEQ ID NO: 855, SEQ ID NO: 856, SEQ ID NO: 857, SEQ ID NO: 858, SEQ ID NO: 859, SEQ ID NO: 860, SEQ ID NO: 861, SEQ ID NO: 862, SEQ ID NO: 863, SEQ ID NO: 864, SEQ ID NO: 865, SEQ ID NO: 866, SEQ ID NO: 867, SEQ ID NO: 868, SEQ ID NO: 869, SEQ ID NO: 870, SEQ ID NO: 871, SEQ ID NO: 872, SEQ ID NO: 873, SEQ ID NO: 874, SEQ ID NO: 875, SEQ ID NO: 876, SEQ ID NO: 877, SEQ ID NO: 878, SEQ ID NO: 879, SEQ ID NO: 880, SEQ ID NO: 881, SEQ ID NO: 882, SEQ ID NO: 883, SEQ ID NO: 884, SEQ ID NO: 885, SEQ ID NO: 886, SEQ ID NO: 887, SEQ ID NO: 888, SEQ ID NO: 889, SEQ ID NO: 890, SEQ ID NO: 891, SEQ ID NO: 892, SEQ ID NO: 893, SEQ ID NO: 894, SEQ ID NO: 895, SEQ ID NO: 896, SEQ ID NO: 897, SEQ ID NO: 898, or SEQ ID NO: 899, as determined by a BLAST pairwise sequence alignment algorithm.

15. The engineered oligonucleotide or salt thereof of claim 11, wherein the engineered oligonucleotide sequence comprises the sugar, base, or backbone modification.
16. The engineered oligonucleotide or salt thereof of claim 15, wherein the modification comprises a linker.
17. The engineered oligonucleotide or salt thereof of claim 16, wherein the linker is a covalent linker.
18. The engineered oligonucleotide or salt thereof of claim 16, wherein the linker is a cleavable linker.
19. The engineered oligonucleotide or salt thereof of claim 16-18, wherein the linker is further modified to comprises a conjugate.
20. The engineered oligonucleotide or salt thereof of claim 19, wherein the conjugate is an antibody, a naturally occurring ligand, a small molecule, or a peptide.
21. The engineered oligonucleotide or salt thereof of claim 19, wherein the conjugate is a drug or salt thereof.

22. The engineered oligonucleotide or salt thereof of any one of claims 1-21, wherein the engineered oligonucleotide comprises a base of a nucleotide that is glycosylated with a glycan.
23. The engineered oligonucleotide or salt thereof of any one of claims 1-22, wherein the first or the second RNA at least partially comprises an mRNA sequence.
24. The engineered oligonucleotide or salt thereof of claim 23, wherein the engineered oligonucleotide or salt thereof, when contacted with the mRNA sequence, produces at least about a 1.2-fold lower expression of a polypeptide encoded by the mRNA sequence, as compared to contacting an equivalent amount of the ncRNA with the mRNA sequence; as determined by:
- transfecting the engineered oligonucleotide or salt thereof into a first isolated mammalian cell comprising the mRNA sequence,
 - transfecting the ncRNA into a second isolated mammalian cell comprising the mRNA sequence, and
 - measuring an amount of the polypeptide expressed in the first isolated mammalian cell and the second isolated mammalian cell, wherein the first isolated mammalian cell and the second isolated mammalian cell are of the same type of mammalian cell.
25. The engineered oligonucleotide or salt thereof of claim 23, wherein the engineered oligonucleotide or salt thereof, when contacted with the mRNA sequence, produces at least about a 1.2-fold lower activity of a polypeptide encoded by the mRNA sequence, as compared to contacting an equivalent amount of the ncRNA with the mRNA sequence; as determined by:
- transfecting the engineered oligonucleotide or salt thereof into a first isolated mammalian cell comprising the mRNA sequence,
 - transfecting the ncRNA into a second isolated mammalian cell comprising the mRNA sequence, and
 - measuring an amount of activity from the polypeptide expressed in the first isolated mammalian cell and the second isolated mammalian cell, wherein the first isolated mammalian cell and the second isolated mammalian cell are of the same type of mammalian cell.
26. The engineered oligonucleotide or salt thereof of claim 24, wherein the engineered oligonucleotide or salt thereof when contacted with the mRNA sequence produces from about 1.2-fold to about 10-fold lower expression of the polypeptide encoded by the

mRNA sequence, as compared to contacting the equivalent amount of the ncRNA; as determined by:

- a. transfecting the engineered oligonucleotide or salt thereof into the first isolated mammalian cell comprising the mRNA sequence,
 - b. transfecting the ncRNA into the second isolated mammalian cell comprising the mRNA sequence, and
 - c. measuring the amount of the polypeptide expressed in the first isolated mammalian cell and the second isolated mammalian cell.
27. The engineered oligonucleotide or salt thereof of claim 25, wherein the engineered oligonucleotide or salt thereof when contacted with the mRNA sequence produces from about 1.2-fold to about 10-fold lower activity of the polypeptide encoded by the mRNA sequence, as compared to contacting the equivalent amount of the ncRNA; as determined by:
- a. transfecting the engineered oligonucleotide or salt thereof into the first isolated mammalian cell comprising the mRNA sequence,
 - b. transfecting the ncRNA into the second isolated mammalian cell comprising the mRNA sequence, and
 - c. measuring the amount of activity from the polypeptide expressed in the first isolated mammalian cell and the second isolated mammalian cell.
28. The engineered oligonucleotide or salt thereof of any one of claims 24-27, wherein the first isolated mammalian cell and second isolated mammalian cell is a human cell or a mouse cell.
29. The engineered oligonucleotide or salt thereof of claim 28, wherein the first isolated mammalian cell is the human cell, and wherein the human cell is a cancer cell, a fibroblast, a leukocyte, an epithelial cell, a squamous cell, a myoblast, a muscle cell
30. The engineered oligonucleotide or salt thereof of any one of claims 1-29, wherein at least about 80% of an initial amount of the engineered oligonucleotide or salt thereof remains when the engineered oligonucleotide or salt thereof is stored in a closed container stored for a time period of at least about 1 month at about 23 degrees Celsius with a relative atmospheric humidity of about 50%.
31. The engineered oligonucleotide or salt thereof of claim 30, wherein the time period is from about 1 month to about 1 year.
32. The engineered oligonucleotide or salt thereof of any one of claims 1-31, wherein the disease or condition comprises a cancer.

33. The engineered oligonucleotide or salt thereof of claim 32, wherein at least a portion of the first or the second RNA is encoded by an oncogene.
34. The engineered oligonucleotide or salt thereof of claim 33, wherein the oncogene comprises ABL1, ABL2, AKT1, AKT2, AKT3, ATF1, BCL11A, BCL2, BCL3, BCL6, BCR, BRAF, CARD11, CBLB, CBLC, CCND1, CCND2, CCND3, CDX2, CTNNB1, DDB2, BBT3, BBX6, DEK, EGFR, ELK4, ERBB2, ERBB3, E2F1, ZEB1, ETV4, ETV6, EVI1, EWSR1, FEV, FGFR1, FGFR1OP, FGR2, FUS, GOLGA5, GOPC, HMGA1, HMGA2, HRAS, IRF4, ITGA6, JUN, KIT, KRAS, LCK, LMO2, MAF, MAFB, MAML2, MDM2, MET, MITF, MLL, MPL, MYB, MYC, MYCL1, MYCN, NCOA4, NFKB2, NRAS, NTRK1, NUP214, PAX8, PDGFB, PIK3CA, PIM1, PLAG1, PPARG, PTPN11, RAF1, REL, RET, ROS1, SETDB1, SERPINE1, SMO, SS18, TCL1A, TET2, TFG, CDK6, ATG9A, TLX1, TPR, USP6, CSNK1G, KLF17, ARHGAP26, RAB11FIP1, RBJ, SERBP1, CTBP1, CRKL, ITGA3, ITGAV, LAMC1, G6PC2, PPP2R5E or any combination thereof.
35. The engineered oligonucleotide or salt thereof of claim 33, wherein the oncogene comprises ITGA6, BCL2, DEK, PLAG1, SERPINE1, MYCN, LMO2, PIM1, EGFR, IRS1, NT5E, GLDC, SOCS1, STAT1, LOX, PDGFRB, WNT5A, CD80, CCNA1, THBS2, IGF1R, AFAP1L2, CTHRC1, MET, FAP, IL1A, GJA1, MYBL2, or any combination thereof.
36. The engineered oligonucleotide or salt thereof of claim 33, wherein the engineered oligonucleotide or salt thereof is selective for an RNA sequence encoding ITGA6, SERPINE1, EGFR, MDTH or any combination thereof, among a plurality of RNA sequences.
37. The engineered oligonucleotide or salt thereof of any one of claims 1-31, wherein the disease or condition comprises fibrosis.
38. The engineered oligonucleotide or salt thereof of claim 37, wherein at least a portion of the first or the second RNA is encoded by a collagen super family gene, a platelet-derived growth factor gene, a TGF- β signaling gene, a collagen remodeling gene, an extracellular matrix remodeling gene, a Wnt signaling gene, a hepatoma-derived growth factor (HDGF) signaling gene, or any combination thereof.
39. The engineered oligonucleotide or salt thereof of claim 38, wherein at least a portion of the first or the second RNA is encoded by the collagen super family gene, wherein the collagen super family gene is selected from the group consisting of: COL1A1, COL11A1, COL2A1, COL5A3, COL5A2, COL4A4, COL21A1, COL7A1, COL9A1, COL19A1,

- COL5A1, COL22A1, COL8A1, COL4A2, COL6A2, COL24A1, COL4A3, COL4A6, COL25A1, COL16A1, COL15A1, and any combination thereof.
40. The engineered oligonucleotide or salt thereof of claim 38, wherein at least a portion of the first or the second RNA is encoded by the platelet-derived growth factor gene, wherein the platelet-derived growth factor gene is selected from the group consisting of: PDGFB, PDGFC, PDGFRB, and any combination thereof.
41. The engineered oligonucleotide or salt thereof of claim 38, wherein at least a portion of the first or the second RNA is encoded by the TGF- β signaling gene, wherein the TGF- β signaling gene is WISP1, TGFB2, or any combination thereof.
42. The engineered oligonucleotide or salt thereof of claim 38, wherein at least a portion of the first or the second RNA is encoded by the collagen remodeling gene, wherein the collagen remodeling gene is LOXL2.
43. The engineered oligonucleotide or salt thereof of claim 38, wherein at least a portion of the first or the second RNA is encoded by the extracellular matrix remodeling gene, wherein the extracellular matrix remodeling gene is selected from the group consisting of: COL1A1, COL11A1, COL2A1, COL5A3, COL5A2, COL4A4, COL21A1, COL7A1, COL9A1, COL19A1, COL5A1, COL22A1, COL8A1, COL4A2, COL6A2, COL24A1, COL4A3, COL4A6, COL25A1, COL16A1, COL15A1, LOXL2, Elastin, and any combination thereof.
44. The engineered oligonucleotide or salt thereof of claim 38, wherein at least a portion of the first or the second RNA is encoded by the Wnt signaling gene, wherein the Wnt signaling gene comprises WISP1.
45. The engineered oligonucleotide or salt thereof of claim 38, wherein at least a portion of the first or the second RNA is encoded by the HDGF signaling gene, wherein the HDGF signaling gene comprises HDGF.
46. The engineered oligonucleotide or salt thereof of any one of claims 1-31, wherein the disease or condition comprises a viral infection.
47. The engineered oligonucleotide or salt thereof of claim 46, wherein the viral infection is an HCV Genotype 1 infection.
48. The engineered oligonucleotide or salt thereof of claim 47, wherein at least a portion of the first or the second RNA is encoded in an HCV Genotype 1 genome.
49. The engineered oligonucleotide or salt thereof any one of claims 47-48, wherein the first or the second RNA comprises at least about 90% sequence identity to SEQ ID NO: 587, SEQ ID NO: 588, or SEQ ID NO: 589, as determined by a BLAST pairwise sequence alignment algorithm.

50. The engineered oligonucleotide or salt thereof of claim 46, wherein the viral infection is a coronavirus infection.
51. The engineered oligonucleotide or salt thereof of claim 50, wherein the coronavirus is SARS-CoV-2.
52. The engineered oligonucleotide or salt thereof of claim 50, wherein at least a portion of the first or the second RNA is encoded in a SARS-CoV-2 genome.
53. The engineered oligonucleotide or salt thereof of claims 51-52, wherein the first or the second RNA comprises at least about 90% sequence identity to any one of SEQ ID NO: 500 to SEQ ID NO: 531, SEQ ID NO: 829, SEQ ID NO: 830, or SEQ ID NO: 831.
54. The engineered oligonucleotide or salt thereof of claims 51-52, wherein the first or the second RNA comprises at least about 90% sequence identity to SEQ ID NO: 500, SEQ ID NO: 513, or SEQ ID NO: 518, as determined by a BLAST pairwise sequence alignment algorithm.
55. The engineered oligonucleotide or salt thereof of claim 50, wherein the coronavirus is SARS-CoV.
56. The engineered oligonucleotide or salt thereof of claim 50, wherein at least a portion of the first or the second RNA is encoded in a SARS-CoV genome.
57. The engineered oligonucleotide or salt thereof of claims 55-56, wherein the first or the second RNA comprises at least about 90% sequence identity to any one of SEQ ID NO: 474 to SEQ ID NO: 499, SEQ ID NO: 826, SEQ ID NO: 827, or SEQ ID NO: 828.
58. The engineered oligonucleotide or salt thereof of claims 55-56, wherein the first or the second RNA comprises at least about 90% sequence identity to SEQ ID NO: 476, SEQ ID NO: 481, or SEQ ID NO: 495, as determined by a BLAST pairwise sequence alignment algorithm.
59. The engineered oligonucleotide or salt thereof of claim 50, wherein the coronavirus is MERS-CoV.
60. The engineered oligonucleotide or salt thereof of claim 50, wherein at least a portion of the first or the second RNA is encoded in a MERS-CoV genome.
61. The engineered oligonucleotide or salt thereof of claims 59-60, wherein the first or the second RNA comprises at least about 90% sequence identity to any one of SEQ ID NO: 532 to SEQ ID NO: 554.
62. The engineered oligonucleotide or salt thereof of claim 50, wherein the coronavirus is CoV-HKU1.
63. The engineered oligonucleotide or salt thereof of claim 50, wherein at least a portion of the first or the second RNA is encoded in a CoV-HKU1 genome.

64. The engineered oligonucleotide or salt thereof of claims 62-63, wherein the first or the second RNA comprises at least about 90% sequence identity to any one of SEQ ID NO: 555 to SEQ ID NO: 586.
65. The engineered oligonucleotide or salt thereof of claim 46, wherein the viral infection is an HIV infection.
66. The engineered oligonucleotide or salt thereof of claim 46, wherein at least a portion of the first or the second RNA is encoded by an HIV genome.
67. The engineered oligonucleotide or salt thereof of claims 65-66, wherein the first or the second RNA comprises at least about 90% sequence identity to SEQ ID NO: 470, as determined by a BLAST pairwise sequence alignment algorithm.
68. The engineered oligonucleotide or salt thereof of claims 65-66, wherein the first or the second RNA comprises at least about 90% sequence identity to SEQ ID NO: 471, SEQ ID NO: 472, or SEQ ID NO: 473, as determined by a BLAST pairwise sequence alignment algorithm.
69. The engineered oligonucleotide or salt thereof of any one of claims 1-31, wherein the disease or condition comprises a neuromuscular disorder including a muscular dystrophy or a myopathy.
70. The engineered oligonucleotide or salt thereof of claim 69, wherein the disease or condition is a Duchenne's muscular dystrophy (DMD), Myotonic Dystrophy (MD), Facioscapulohumeral muscular dystrophy (FSHD), Limb-Girdle muscular dystrophy (LGMD), Becker muscular dystrophy, Oculopharyngeal muscular dystrophy, Emery-Dreifuss muscular dystrophy, or Distal muscular dystrophy.
71. The engineered oligonucleotide or salt thereof of claims 69-70 wherein the disease or condition is caused by an inherited or spontaneous autosomal dominant mutation.
72. The engineered oligonucleotide or salt thereof of any one of claims 69-71, wherein at least a portion of the first or the second RNA is encoded in the dystrophin, DMPK, CLCN1, CNBP, D4Z4 repeat, DUX4, SMCHD1, DBET, SVIL, GAL3ST2, FRG1, CAPN3, DYSF, LMNA, PABPN1, PYGM, MYOD1, MYH7, HNRNPC, HNRNPA2B1, ACVR1, ASIC2, ATG14, ATP1A1, B3GTNL1, BANF1, BPTF, CASP8AP2, CDX4, CELF2, CHMP7, CKMT1B, CLASP1, CNOT3, COL15A1, CYP3A4, DCAF15, DCN, DLX5, DUSP7, DUX1, DUX5, EMILIN1, EPG5, FAM13A, FBX03, FBXL22, FMNL3, FREM2, FRMPD2, GADD45A, GID4, GJD3, GMPR, GNAT1, GOSR1, GPRC6A, HERC1, HGF, HOOK3, HOXC9, HSP40, IRF9, IRX5, ITGA10, ITGA3, ITGA9, KCNC3, KLHL3, KLK6, LARP6, MALT1, MAP3K4, MAPK10, MIR4661, MIR8078,

MTSS1, NDUFAF6, NEBL, NKX2, NR2F1, PCID2, PDE10A, PKD1L2, PKHD1, PPP1R12B, PTPRN2, PYY, RABGAP1L, RBCK1, RFX3, RHBDF2, SCRIB, SEMA3B, SETD4, SHFL, SHH, SLC37A4, SLC9A8, SMAD1, SPEF1, SPRED3, ST3GAL6, STAG1, SUPV3L1, TBC1D26, TCEA2, TCF3, TM6SF1, TMEM108, TMEM259, TNFSF4, TNIP1, TRNP1, USH1G, WRNIP1, XIAP, ZNF574 gene or any combination thereof.

73. The engineered oligonucleotide or salt thereof of claims 69-72, wherein the first or the second RNA comprises at least about 90% sequence identity to any one of SEQ ID NO: 901 to SEQ ID NO: 949, as determined by a BLAST pairwise sequence alignment algorithm.
74. An engineered oligonucleotide or salt thereof comprising a polynucleotide sequence of from about 5 nucleotides to about 50 nucleotides, wherein the engineered oligonucleotide or salt thereof comprises:

a first region, a second region that is adjacent to the first region, and a third region that is adjacent to the second region, wherein the regions are arranged from 5' to 3' in the following order: the first region, the second region, and the third region;

wherein when the engineered oligonucleotide or salt thereof is bound to an mRNA sequence, the first region and the third region are complementary to the mRNA sequence and the second region comprises at least one base that is not complementary to the mRNA sequence, and

wherein the engineered oligonucleotide or salt thereof comprises an at least about 10% lower Gibbs free energy (ΔG) of binding, as determined for binding to the mRNA sequence at about 37 degrees Celsius and at about pH 7.2, relative to a ΔG of binding of an otherwise comparable oligonucleotide binding to the mRNA sequence at 37 degrees Celsius and at about pH 7.2, and wherein the otherwise comparable oligonucleotide lacks the at least one base in the engineered oligonucleotide that is not complementary to the mRNA sequence.
75. An engineered oligonucleotide or salt thereof comprising a polynucleotide sequence with at least about 90% sequence identity to any one of SEQ ID NOs: 1-5, 12-14, 19-20, 24-25, 28, 30, 32, 34, 36, 38-45, 52-89, 100-154, 184-201, 205-222, 225-233, 235-243, 245-443, 445-453, 455-463, 465, 620, 624-825, 835-837, 840-899, and 901-949, as determined by a BLAST pairwise sequence alignment algorithm, wherein the engineered oligonucleotide or salt thereof when contacted with an mRNA sequence produces at least about a 1.2-fold lower expression of a polypeptide encoded by the mRNA sequence, as

compared to contacting an equivalent amount of an miR-29 or miR-30 oligonucleotide or salt thereof naturally present in a human cell; as determined by:

- a. transfecting the engineered oligonucleotide or salt thereof into a first isolated human cell comprising the mRNA sequence,
- b. transfecting the miR-29 or miR-30 oligonucleotide into a second isolated human cell comprising the mRNA sequence, and
- c. measuring an amount of the polypeptide expressed in the first isolated human cell and the isolated second human cell.

76. The engineered oligonucleotide or salt thereof of any one of claims 1-75 where the structure and chemistry is optimized to impart greater than or equal to 100X stability to natural nucleases compared to an unmodified sequence or a comparable ncRNA.
77. An engineered passenger oligonucleotide or salt thereof comprising a polynucleotide sequence, wherein the engineered passenger oligonucleotide or salt thereof is at least partially complementary to at least a portion of the engineered oligonucleotide or salt thereof of any one of claims 1-76.
78. The engineered passenger oligonucleotide or salt thereof of claim 77, wherein the engineered passenger oligonucleotide or salt thereof is from about 5 to about 50 nucleotides in length.
79. The engineered passenger oligonucleotide or salt thereof of any one of claims 77-78, wherein the engineered passenger oligonucleotide or salt thereof comprises a ribose sugar.
80. The engineered passenger oligonucleotide or salt thereof of any one of claims 77-79, wherein the engineered passenger oligonucleotide or salt thereof comprises a deoxyribose sugar.
81. The engineered passenger oligonucleotide or salt thereof of any one of claims 77-80, wherein the engineered passenger oligonucleotide or salt thereof has at least 90% sequence identity to any one of SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 155, SEQ ID NO: 156, SEQ ID NO: 157, SEQ ID NO: 158, SEQ ID NO: 159, SEQ ID NO: 160, SEQ ID NO: 161, SEQ ID NO: 162, SEQ ID NO: 163, SEQ ID NO: 164, SEQ ID NO: 165, SEQ ID NO: 166, SEQ ID

- NO: 167, SEQ ID NO: 168, SEQ ID NO: 169, or SEQ ID NO: 466, as determined by a BLAST pairwise sequence alignment algorithm.
82. The engineered passenger oligonucleotide or salt thereof of any one of claims 77-81, wherein the engineered passenger oligonucleotide forms a secondary structure comprising a stem-loop.
83. The engineered passenger oligonucleotide or salt thereof of any one of claims 77-82, wherein the engineered passenger oligonucleotide or salt thereof comprises a chemically modified base, chemically modified sugar, chemically modified backbone or phosphate linkage, or any combination thereof relative to a naturally occurring base, sugar, backbone, or phosphate linkage.
84. The engineered passenger oligonucleotide or salt thereof of claim 83, wherein the chemical modification is selected from the group consisting of: a methyl group, a fluoro group, a methoxyethyl group, an ethyl group, a hydroxymethyl group, a formyl group, a carboxylic acid or salt thereof, a phosphothionate modified backbone, a methylphosphonate modified backbone, an amino-alkyl chain modification, and any combination thereof.
85. The engineered passenger oligonucleotide or salt thereof of any one of claims 83 or 84, wherein the engineered passenger oligonucleotide or salt thereof, when chemically modified, comprises the formula:
CAP-mNmNmN(N)_kmNmNmN; wherein
CAP is selected from a 5'-terminal methyl group (5'-OMethyl) or alkylamino group such as amino-carbon 6 chain (5'-Amino C6);
each N is independently uracil, guanine, adenine, or cytosine;
each mN is independently a 2'-O-methyl-modified uracil, guanine, adenine, or cytosine; and
each k is from 12-19.
86. The engineered passenger oligonucleotide or salt thereof of any one of claims 83-85, wherein the engineered passenger oligonucleotide or salt thereof has at least 90% sequence identity to any one of SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 170, SEQ ID NO: 171, SEQ ID NO: 172, SEQ ID NO: 173, SEQ ID NO: 174, SEQ ID NO: 175, SEQ ID NO: 176, SEQ ID NO: 177, SEQ ID NO: 178, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 181, SEQ ID NO: 182, SEQ ID NO: 183, SEQ ID NO: 202, SEQ ID NO: 203, SEQ ID NO: 204, SEQ ID NO: 223, SEQ ID NO: 224, SEQ ID NO: 234, SEQ ID NO: 244, SEQ ID NO: 444, SEQ ID

- NO: 454, SEQ ID NO: 464, SEQ ID NO: 838, SEQ ID NO: 839, or SEQ ID NO: 900, as determined by a BLAST pairwise sequence alignment algorithm.
87. The engineered passenger oligonucleotide or salt thereof any one of claims 77-86, wherein the engineered passenger oligonucleotide or salt thereof comprises a sugar modification.
88. The engineered passenger oligonucleotide or salt thereof of claim 87, wherein the sugar modification comprises a glycosylated base.
89. The engineered passenger oligonucleotide or salt thereof of any one of claims 77-88 where the structure and chemistry is optimized to impart greater than or equal to 100X stability to natural nucleases compared to an unmodified sequence or a comparable ncRNA.
90. A nucleic acid construct comprising: (a) a first strand comprising the engineered oligonucleotide or salt thereof of any one of claims 1-75 and (b) a second strand comprising an engineered passenger oligonucleotide or salt thereof of any one of claims 77-89 with a sequence complementary to at least a portion of the first strand.
91. A vector that comprises the engineered oligonucleotide or salt thereof of any one of claims 1-76 or the nucleic acid construct of claim 90.
92. The vector of claim 91, wherein the vector is present in a liposome, a nanoparticle, or any combination thereof.
93. The vector of claim 91, wherein the vector is a viral vector.
94. The vector of claim 93, wherein the viral vector is an adeno-associated viral (AAV) vector.
95. An isolated cell that comprises the engineered oligonucleotide or salt thereof of any one of claims 1-76, the nucleic acid construct of claim 90, or the vector of any one of claims 91-94.
96. A pharmaceutical composition comprising: (a) the engineered oligonucleotide or salt thereof of any one of claims 1-76, the nucleic acid construct of claim 90, or the vector of any one of claims 91-94; and (b) a pharmaceutically acceptable excipient, diluent, or carrier.
97. The pharmaceutical composition of claim 96, in unit dose form.
98. The pharmaceutical composition of claim 96 or 97, wherein the pharmaceutical composition is encapsulated.
99. The pharmaceutical composition of any one of claims 96-98, wherein the pharmaceutical composition is in the form of a liquid.

100. A method of treating a subject in need thereof comprising: administering to the subject a therapeutically effective amount of: the engineered oligonucleotide or salt thereof of any one of claims 1-76, the nucleic acid construct of claim 90, the vector of any one of claims 91-94, or the pharmaceutical composition of any one of claims 96-99.
101. The method of claim 100, wherein the administering is by an intravenous injection, an intramuscular injection, an intrathecal injection, an intraorbital injection, a subcutaneous injection, or any combination thereof.
102. The method of claim 100, wherein the administering is oral, otic, ocular, rectal, or any combination thereof.
103. The method of any one of claims 100-102, further comprising a second administering comprising a second therapy to the subject.
104. The method of claim 103, wherein the administering and the second administering are concurrent.
105. The method of claim 103, wherein the administering and the second administering are sequential.
106. The method of any one of claims 100-105, wherein the subject has or is at risk of developing a disease or condition.
107. The method of claim 106, wherein the disease or condition is a cancer.
108. The method of claim 107, wherein the cancer is a head cancer, a neck cancer, skin cancer, a cervical cancer, a prostate cancer, or any combination thereof.
109. The method of claim 106, wherein the disease or condition is a viral infection.
110. The method of claim 109, wherein the viral infection is a SARS-CoV infection, a SARS-COV-2 infection, a MERS-CoV infection, a CoV-HKU1 infection, an HIV infection, or an HCV infection.
111. The method of claim 106, wherein the disease or condition is a fibrosis.
112. The method of claim 106, wherein the disease or condition is muscular dystrophy.
113. The method of any one of claims 100-112, wherein the subject is a mammal.
114. The method of claim 113, wherein the mammal is a human.
115. The method of any one of claims 100-114, wherein the subject has been diagnosed with a disease or condition by a diagnostic test.
116. The method of claim 115, wherein the diagnostic test comprises an imaging procedure, a blood count analysis, a tissue pathology analysis, a biomarker analysis, or any combination thereof.

117. A method comprising: contacting the engineered oligonucleotide or salt thereof of any one of claims 1-76, the nucleic acid construct of claim 90, or the vector of any one of claims 91-94, with an isolated cell or an isolated tissue.
118. A kit that comprises the engineered oligonucleotide or salt thereof of any one of claims 1-76 in a container, the nucleic acid construct of claim 90 in a container, the vector of any one of claims 91-94 in a container, or the pharmaceutical composition of any one of claims 96-99 in a container.
119. The engineered oligonucleotide of any one of claims 1-76, wherein at least one base of a nucleotide in the engineered oligonucleotide is not complementary to the first or the second RNA.