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 each of a first and a second RNA originating from two different 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 -17 to -36 kcal mol^{-1} at 37 degrees Celsius and at a pH ranging from 7.2 to 7.6,

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.

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 a ribose sugar.

4. The engineered oligonucleotide or salt thereof of claim 1, wherein the engineered oligonucleotide or salt thereof comprises a deoxyribose sugar.

5. The engineered oligonucleotide or salt thereof of claim 1, 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.

6. The engineered oligonucleotide or salt thereof of claim 1, wherein the engineered oligonucleotide or salt thereof, when chemically modified, comprises the formula:

(N)a(mN)b(N)cNN;

(N)a(mN)b(N)csfNsmN; or

(fNmN)h(mN)i(fNmN)jsfNsmN; 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.

7. The engineered oligonucleotide or salt thereof of claim 1, wherein the engineered oligonucleotide sequence comprises the sugar, base, or backbone modification.

8. The engineered oligonucleotide or salt thereof of claim 7, wherein the modification comprises a linker.

9. The engineered oligonucleotide or salt thereof of claim 8, wherein the linker is a covalent linker.

10. The engineered oligonucleotide or salt thereof of claim 8, wherein the linker is a cleavable linker.

11. The engineered oligonucleotide or salt thereof of claim 8, wherein the linker is further modified to comprise a conjugate.

12. The engineered oligonucleotide or salt thereof of claim 11, wherein the conjugate is an antibody, a naturally occurring ligand, a small molecule, or a peptide.

13. The engineered oligonucleotide or salt thereof of claim 1, wherein the first or the second RNA at least

partially comprises an mRNA sequence.

14. The engineered oligonucleotide or salt thereof of claim 1, wherein the disease or condition comprises a neuromuscular disorder including a muscular dystrophy or a myopathy.

15. The engineered oligonucleotide or salt thereof of claim 14, 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.

16. The engineered oligonucleotide or salt there of claim 14, wherein the disease or condition is caused by an inherited or spontaneous autosomal dominant mutation.

17. The engineered oligonucleotide or salt thereof of claim 14, 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.

18. 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 claim 1.

19. A nucleic acid construct comprising:

(a) a first strand comprising the engineered oligonucleotide or salt thereof of claim 1; and

(b) a second strand comprising 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 claim 1.

20. A vector that comprises the engineered oligonucleotide or salt thereof of claim 1.

21. The vector of claim 20, wherein the vector is present in a liposome, a nanoparticle, or any combination thereof.

22. A pharmaceutical composition comprising: (a) the engineered oligonucleotide or salt thereof of any one of claims 1-18, the nucleic acid construct of claim 19, or the vector of any one of claims 20-21; and (b) a pharmaceutically acceptable excipient, diluent, or carrier.

23. Use of the engineered oligonucleotide or salt thereof of any one of claims 1-18, the nucleic acid construct of claim 19, the vector of any one of claims 20-21, or the pharmaceutical composition of claim 22 in the manufacture of a medicament for the treatment of a disease.

24. The use of claim 23, wherein the disease is muscular dystrophy.

25. A method comprising: contacting the engineered oligonucleotide or salt thereof of any one of claims 1-18, the nucleic acid construct of claim 19, or the vector of any one of claims 20-21, with an isolated cell or an isolated tissue.

26. A kit that comprises a container and the engineered oligonucleotide or salt thereof of any one of claims 1-18, the nucleic acid construct of claim 19, the vector of any one of claims 20-21, or the pharmaceutical composition of claim 22.

27. The engineered oligonucleotide or salt thereof of any one of claims 1-18, the nucleic acid construct of claim 19, the vector of any one of claims 20-21, or the pharmaceutical composition of claim 22 for use in therapy.