TARGETED INHIBITION USING ENGINEERED OLIGONUCLEOTIDES

STATEMENT OF GOVERNMENT SUPPORT

[0001] This invention was made with Government support under Grant No. U43CA221567 awarded by the National Cancer Institute and support from SBIR Contract No. HHSN272201800034C awarded by the National Institute of Allergy and Infection Disease. The Government has certain rights in the invention.

CROSS-REFERENCE TO RELATED APPLICATIONS(S)

[0002] This application claims priority to, and the benefit of United States Provisional Application No. 63/004,045, filed April 2, 2020, for all subject matter common to both applications. The disclosure of said provisional application is hereby incorporated by reference in its entirety.

SUMMARY

[0003] Disclosed herein are engineered oligonucleotides or salts thereof that can comprise a polynucleotide sequence. In some embodiments, an engineered oligonucleotide or salt thereof can be 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. In some embodiments, when an engineered oligonucleotide or salt thereof at least partially binds to a first RNA: a first region of at least seven contiguous bases in the engineered oligonucleotide can be complementary to contiguous nucleic acids contained within the first RNA and a second region of at least five contiguous bases in the engineered oligonucleotide can be complementary to contiguous nucleic acids contained within the first RNA. In some embodiments, when an engineered oligonucleotide or salt thereof at least partially binds to a second RNA: a first region of at least seven contiguous bases in the engineered oligonucleotide can be complementary to contiguous nucleotides contained within a second RNA, and a second region of at least five

contiguous bases in the engineered oligonucleotide can be complementary to contiguous nucleotides contained within the second RNA. In some embodiments, a predicted Gibbs free energy (ΔG) of binding of an engineered oligonucleotide to a first and a second RNA can range, 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. In some embodiments, an engineered oligonucleotide or salt thereof can be an antisense oligonucleotide, a synthetic microRNA (miRNA), or a small interfering RNA (siRNA). In some embodiments, an engineered oligonucleotide or salt thereof can comprise one or more nucleotide insertions, nucleotide deletions, nucleotide substitutions, or any combination thereof, relative to one or more otherwise comparable non-coding RNAs (ncRNAs). In some embodiments, an engineered oligonucleotide or salt thereof, when at least partially bound to the first or the second RNA, can have 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. In some embodiments, an engineered oligonucleotide or salt thereof can be from about 5 to about 50 nucleotides in length. In some embodiments, an engineered oligonucleotide or salt thereof can comprise a ribose sugar. In some embodiments, an engineered oligonucleotide or salt thereof can comprise a deoxyribose sugar. In some embodiments, an ncRNA can be an miR-30 mircro 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. In some embodiments, an engineered oligonucleotide or salt thereof can have 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:

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modified backbone or phosphate linkage, or any combination thereof relative to a naturally occurring base, sugar, backbone, or phosphate linkage. In some embodiments, a chemical modification can be 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. In some embodiments, an engineered oligonucleotide or salt thereof, when chemically modified, can 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 can be independently uracil, guanine, adenine, cytosine, or other natural nucleotide; each mN can be independently a 2'-O-methyl-modified uracil, guanine, adenine, or cytosine; each s can be independently a phosphothionate-modified backbone; each fN can be independently 2'fluoro-modified uracil, guanine, adenine, or cytosine; and each a can be from 8-10, each b can be from 7-10, each c can be from 2-4, each h can be from 5-7, each i can be 0 or 1, and each j can be from 3-4. In some embodiments, an engineered oligonucleotide or salt thereof can have 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

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the ncRNA into a second isolated mammalian cell comprising the mRNA sequence, and (c) 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. In some embodiments, an engineered oligonucleotide or salt thereof, when contacted with the mRNA sequence, can produce 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: (a) transfecting the engineered oligonucleotide or salt thereof into a first isolated mammalian cell comprising the mRNA sequence, (b) transfecting the ncRNA into a second isolated mammalian cell comprising the mRNA sequence, and (c) 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. In some embodiments, an engineered oligonucleotide or salt thereof when contacted with the mRNA sequence can produce 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. In some embodiments, an engineered oligonucleotide or salt thereof when contacted with the mRNA sequence can produce 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. In some embodiments, a first isolated mammalian cell and second isolated mammalian cell can be a human cell or a mouse cell. In some embodiments, a first isolated mammalian cell can be a human cell, wherein the human cell can be a cancer cell, a fibroblast, a leukocyte, an epithelial cell, a squamous cell, a myoblast, a muscle cell In some embodiments, at least about 80% of an initial amount of the engineered oligonucleotide or salt thereof can remain 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%. In some embodiments, a time period can be from about 1 month to about 1 year. In some embodiments, a disease or condition can comprise a cancer. In some embodiments, at least a portion of the first or the second RNA can be encoded by an oncogene. In some embodiments, an oncogene can comprise ABL1, ABL2, AKT1, AKT2, AKT3, ATF1, BCL11A, BCL2, BCL3, BCL6, BCR, BRAF, CARD11, CBLB, CBLC, CCND1, CCND2, CCND3, CDX2, CTNNB1, DDB2, BBIT3, 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. In some embodiments, an oncogene can comprise 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. In some embodiments, an engineered oligonucleotide or salt thereof can be selective for an RNA sequence encoding ITGA6, SERPINE1, EGFR, MDTH or any combination thereof, among a plurality of RNA sequences. In some embodiments, a disease or condition can comprise fibrosis. In some embodiments, at least

a portion of the first or the second RNA can be 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. In some embodiments, at least a portion of an first or the second RNA can be 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. In some embodiments, 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 can be selected from the group consisting of: PDGFB, PDGFC, PDGFRB, and any combination thereof. In some embodiments, at least a portion of the first or the second RNA can be encoded by the TGF-β signaling gene, wherein the TGF-β signaling gene is WISP1, TGFB2, or any combination thereof. In some embodiments, at least a portion of the first or the second RNA can be encoded by the collagen remodeling gene, wherein the collagen remodeling gene is LOXL2. In some embodiments, at least a portion of the first or the second RNA can be 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. In some embodiments, at least a portion of the first or the second RNA can be encoded by the Wnt signaling gene, wherein the Wnt signaling gene comprises WISP1. In some embodiments, at least a portion of the first or the second RNA can be encoded by the HDGF signaling gene, wherein the HDGF signaling gene comprises HDGF. In some embodiments, the disease or condition can comprise a viral infection. In some embodiments, the viral infection can be an HCV Genotype 1 infection. In some embodiments, at least a portion of the first or the second

RNA can be encoded in an HCV Genotype 1 genome. In some embodiments, the first or the second RNA can comprise 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. In some embodiments, the viral infection can be a coronavirus infection. In some embodiments, the coronavirus can be SARS-CoV-2. In some embodiments, at least a portion of the first or the second RNA can be encoded in a SARS-CoV-2 genome. In some embodiments, the first or the second RNA can comprise 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. In some embodiments, the first or the second RNA can comprise 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. In some embodiments, the coronavirus can be SARS-CoV. In some embodiments, at least a portion of the first or the second RNA can be encoded in a SARS-CoV genome. In some embodiments, the first or the second RNA can comprise 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. In some embodiments, the first or the second RNA can comprise 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. In some embodiments, the coronavirus can be MERS-CoV. In some embodiments, at least a portion of the first or the second RNA can be encoded in a MERS-CoV genome. In some embodiments, the first or the second RNA can comprise at least about 90% sequence identity to any one of SEQ ID NO: 532 to SEQ ID NO: 554. In some embodiments, the coronavirus can be CoV-HKU1. In some embodiments, at least a portion of the first or the second RNA can be encoded in a CoV-HKU1 genome. In some embodiments, the first or the second RNA can comprise at least about 90% sequence identity to any one of SEQ ID NO: 555 to SEQ ID NO: 586. In some embodiments, the viral infection can be an HIV infection. In some embodiments, at least a portion of the first or the second RNA can be encoded by an HIV genome. In some embodiments, the first or the second RNA can comprise at least about 90% sequence identity to

SEQ ID NO: 470, as determined by a BLAST pairwise sequence alignment algorithm. In some embodiments, the first or the second RNA can comprise 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. In some embodiments, the disease or condition can comprise a neuromuscular disorder including a muscular dystrophy or a myopathy. In some embodiments, the disease or condition can be 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. In some embodiments, the disease or condition can be caused by an inherited or spontaneous autosomal dominant mutation. In some embodiments, at least a portion of the first or the second RNA can be 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, TMEM 108, TMEM259, TNFSF4, TNIP1, TRNP1, USH1G, WRNIP1, XIAP, ZNF574 gene or any combination thereof. In some embodiments, a first or the second RNA can comprise 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. In some embodiments, at least one base of

a nucleotide in the engineered oligonucleotide may not be complementary to the first or the second RNA.

[0004] Also disclosed herein are engineered oligonucleotides or salts thereof that can comprise a polynucleotide sequence of from about 5 nucleotides to about 50 nucleotides. In some embodiments, the engineered oligonucleotide or salt thereof can comprise: 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. In some embodiments, the engineered oligonucleotide or salt thereof can comprise 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, wherein the otherwise comparable oligonucleotide lacks the at least one base in the engineered oligonucleotide that is not complementary to the mRNA sequence.

[0005] Also disclosed herein are engineered oligonucleotides or salts thereof that can comprise 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. In some embodiments, the structure and chemistry can be optimized to impart greater than or equal to 100X stability to natural nucleases compared to an unmodified sequence or a comparable ncRNA.

[0006] Also disclosed herein are engineered passenger oligonucleotides or salts thereof that can comprise a polynucleotide sequence, wherein the engineered passenger oligonucleotide or salt thereof can be at least partially complementary to at least a portion of an engineered oligonucleotide or salt thereof as described herein. In some embodiments, an engineered passenger oligonucleotide or salt thereof can be from about 5 to about 50 nucleotides in length. In some embodiments, the engineered passenger oligonucleotide or salt thereof can comprise a ribose sugar. In some embodiments, the engineered passenger oligonucleotide or salt thereof can comprise a deoxyribose sugar. In some embodiments, the engineered passenger oligonucleotide or salt thereof can have 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. In some embodiments, the engineered passenger oligonucleotide can form a secondary structure comprising a stem-loop. In some embodiments, the engineered passenger oligonucleotide or salt thereof can comprise 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. In some embodiments, the

chemical modification can be 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. In some embodiments, the engineered passenger oligonucleotide or salt thereof, when chemically modified, can comprise the formula: CAP–mNmNmN$(N)_k$mNmNmN; wherein CAP can be selected from a 5'-terminal methyl group (5'-OMethyl) or alkylamino group such as amino-carbon 6 chain (5'-Amino C6); each N can be independently uracil, guanine, adenine, or cytosine; each mN can be independently a 2'-O-methyl-modified uracil, guanine, adenine, or cytosine; and each k can be from 12-19. In some embodiments, the engineered passenger oligonucleotide or salt thereof can have 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. In some embodiments, the engineered passenger oligonucleotide or salt thereof can comprise a sugar modification. In some embodiments, the sugar modification can comprise a glycosylated base. In some embodiments, the structure and chemistry can be optimized to impart greater than or equal to 100X stability to natural nucleases compared to an unmodified sequence or a comparable ncRNA.

[0007] Also disclosed herein are nucleic acid constructs that can comprise: (a) a first strand comprising an engineered oligonucleotide or salt thereof as described herein and (b) a second strand comprising an engineered passenger oligonucleotide or salt thereof as described herein with a sequence complementary to at least a portion of the first strand.

[0008] Also disclosed herein are vectors that can comprise an engineered oligonucleotide or salt thereof as described herein or a nucleic acid construct as described herein. In some embodiments, the vector can be present in a liposome, a nanoparticle, or any combination thereof. In some embodiments, the vector can be a viral vector. In some embodiments, the viral vector can be an adeno-associated viral (AAV) vector.

[0009] Also disclosed herein are isolated cells that can comprise an engineered oligonucleotide or salt as described herein, a nucleic acid construct as described herein, or a vector as described herein.

[0010] Also disclosed herein are pharmaceutical compositions that can comprise: (a) an engineered oligonucleotide or salt thereof as described herein, a nucleic acid construct as described herein, or a vector as described herein; and (b) a pharmaceutically acceptable excipient, diluent, or carrier. In some embodiments, a pharmaceutical composition can be in unit dose form. In some embodiments, a pharmaceutical composition can be encapsulated. In some embodiments, a pharmaceutical composition can be in the form of a liquid.

[0011] Also disclosed herein are methods of treating a subject in need thereof that can comprise: administering to the subject a therapeutically effective amount of: an engineered oligonucleotide or salt thereof as described herein, a nucleic acid construct as described herein, a vector as described herein, or a pharmaceutical composition as described herein. In some embodiments, the administering can be by an intravenous injection, an intramuscular injection, an intrathecal injection, an intraorbital injection, a subcutaneous injection, or any combination thereof. In some embodiments, the administering can be oral, otic, ocular, rectal, or any combination thereof. In some embodiments, the method can further comprise a second administering comprising a second therapy to the subject. In some embodiments, the administering and the second administering can be concurrent. In some embodiments, the administering and the second administering can be sequential. In some embodiments, the subject can have or can be at risk of developing a disease or condition. In some embodiments, the disease or condition can be a cancer. In some embodiments, the cancer can be a head cancer, a neck cancer, skin cancer, a

cervical cancer, a prostate cancer, or any combination thereof. In some embodiments, the disease or condition can be a viral infection. In some embodiments, the viral infection can be a SARS-CoV infection, a SARS-COV-2 infection, a MERS-CoV infection, a CoV-HKU1 infection, an HIV infection, or an HCV infection. In some embodiments, the disease or condition can be a fibrosis. In some embodiments, the disease or condition can be muscular dystrophy. In some embodiments, the subject can be a mammal. In some embodiments, the mammal can be a human. In some embodiments, the subject may have been diagnosed with a disease or condition by a diagnostic test. In some embodiments, a diagnostic test can comprise an imaging procedure, a blood count analysis, a tissue pathology analysis, a biomarker analysis, or any combination thereof.

[0012] Also disclosed herein are methods that can comprise: contacting an engineered oligonucleotide or salt thereof as described herein, a nucleic acid construct as described herein, or a vector as described herein, with an isolated cell or an isolated tissue.

[0013] Also disclosed herein are as described herein kits that can comprise an engineered oligonucleotide or salt thereof as described herein in a container, a nucleic acid construct as described herein in a container, a vector as described herein in a container, or a pharmaceutical composition as described herein in a container.

INCORPORATION BY REFERENCE

[0014] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

DESCRIPTION OF THE DRAWINGS

[0015] The novel features of exemplary embodiments are set forth with particularity in the appended claims. A better understanding of the features and advantages will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of exemplary embodiments are utilized, and the accompanying drawings of which:

[0016] FIG. 1A shows natural miR-30 guide strand sequences and examples of engineered family members.

[0017] FIG. 1B shows natural miR-30 passenger strand sequences and examples of engineered family members.

[0018] FIG. 2A shows free energy (ΔG) and hybridization between natural miR-30a-5p sequence and target sites in the 3'UTRs of ITGA6, SERPINE1, and EGFR transcripts.

[0019] FIG. 2B shows free energy (ΔG) and hybridization between engineered family G007-30 (SEQ ID NO: 39) containing the 'G' insertion at position 13 and the ITGA6, SERPINE1, and EGFR target sites.

[0020] FIG. 2C shows that a mimic containing the same 'G' insertion at position 13 as found in G007-30 can demonstrate improved knockdown of select oncogenic targets.

[0021] FIG. 3 shows a schematic visualization of miR-30-5p target sites in the MTDH 3'UTR.

[0022] FIG. 4A shows anti-tumor activity of miR-30 mimics in cancer cell lines.

[0023] FIG. 4B shows knock-down of a luciferase reporter containing cancer-relevant miR-30 target sites with its 3' UTR by miR-30 mimics.

[0024] FIG. 4C shows the anti-tumor activity of native miR-30a and exemplar engineered mimics in additional cell lines with different genetic backgrounds.

[0025] FIG. 4D shows anti-tumor activity of a panel of engineered miR-30 mimics in additional cancel cell lines with different histology and genetic backgrounds.

[0026] FIG. 5A shows an example of Urea-PAGE resolving a nucleic acid marker (M) and sample comprising mimic duplex, guide strand, and degraded fragments (≤n-1)

[0027] FIG 5B shows duplex stability of engineered miR-30 miRNA mimics in human serum.

[0028] FIG. 6A shows structure of engineered mimic duplexes with passenger strands sequence and chemical modifications which alter the mimic structure.

[0029] FIG 6B shows exemplar duplex stability of engineered miR-30 miRNA mimics in human serum.

[0030] FIG. 7A shows exemplar structure of engineered mimic duplexes with passenger strands sequence and chemical modifications which alter the mimic structure.

[0031] FIG. 7B shows anti-tumor activity of exemplar engineered miR-30 mimics in cancer cell lines. .

[0032] FIG. 7C shows knock-down of a luciferase reporter by engineered miR-30 mimics with varied structure but identical guide strands.

[0033] FIG. 8A shows the structure of two blunting modifications that can be made to the 5' terminus of the guide strand. **FIG. 8B** shows blunted anti-tumor activity of mimics with 5' modified guide strands.

[0034] FIG. 9A shows structure of exemplar engineered miR-30 mimic duplexes.

[0035] FIG. 9B shows anti-tumor activity of exemplar engineered miR-30 mimics in cancer cell lines.

[0036] FIG. 9C shows knock-down of a luciferase reporter by exemplar engineered miR-30 mimics with varied structure but identical guide strands.

[0037] FIG. 10A displays improved anticancer activity and silencing of exemplar engineered mimic M30-043. **FIG. 10B** shows knockdown of luciferase activity by exemplar engineered mimic M30-043.

[0038] FIG. 11A shows reductions in innate TNFα production after exposure of PBMCs to engineered miR-30 mimics

[0039] FIG. 11B shows reductions in innate IFNα production after exposure of PBMCs to engineered miR-30 mimics.

[0040] FIG. 12A shows production of cisplatin resistant cancer cell lines.

[0041] FIG. 12B shows preservation of engineered miR-30 mimic activity in cisplatin resistant cancer cell lines.

[0042] FIG. 12C shows resensitization of resistance cell lines to cisplatin by engineered miR-30 mimic treatment.

[0043] FIG. 12D shows sensitization of cancer cell lines to EGFR inhibitor cetuximab by engineered miR-30 mimic treatment.

[0044] FIG. 13A shows luciferase images of anti-tumor activity in orthotopic HNSCC tumors by engineered miR-30 mimics. **FIG. 13B** shows quantification of luciferase activity in orthotopic HNSCC tumors by engineered miR-30 mimics.

[0045] FIG. 13C shows anti-tumor activity of engineered miR-30 mimic M30-040 in a subcutaneous HNSCC mouse model.

[0046] FIG. 14A shows luciferase images of anti-tumor activity in orthotopic HNSCC tumors by engineered miR-30 mimic M30-048 with local treatment. **FIG. 14B** shows quantification of luciferase activity in orthotopic HNSCC tumors by engineered miR-30 mimic M30-048 with local treatment.

[0047] FIG. 15 shows natural miR-29 guide strand sequences and examples of engineered family members.

[0048] FIG. 16 shows a schematic visualization of a human host cell gene TET-1 and improved predicted binding by engineered miR-29 mimics.

[0049] FIG. 17 figure shows that engineered miR-29 mimics can have equivalent or greater knockdown activity compared to native miR-29b in a luciferase cell line.

[0050] FIG. 18A shows sequence and structure of native miR-29b-1 duplex and engineered miR-29 mimics.

[0051] FIG. 18B shows duplex stability of native and engineered miR-29 miRNA mimics in human serum.

[0052] FIG. 19A shows sequence and structure of exemplar engineered miR-29 mimics.

[0053] FIG. 19B shows duplex stability of exemplar engineered miR-29 miRNA mimics in human serum.

[0054] FIG. 20A shows sequence and structure of native miR-29a duplex and exemplar engineered miR-29a mimics.

[0055] FIG. 20B shows sequence and structure of native miR-29b duplex and exemplar engineered miR-29b mimics.

[0056] FIG. 20C shows improvement of luciferase knockdown activity by exemplar engineered mimics of miR-29a and miR-29b.

[0057] FIG. 21 shows engineered mimics of miR-29 display reduced innate immune stimulation.

[0058] FIG. 22A shows schematic visualization of an native and engineered miR-29-3p guide strands binding to HIV-1 NEF RNA.

[0059] FIG. 22B shows inhibition of HIV-1 replication by exemplar engineered miR-29 mimics.

[0060] FIG. 22C shows decreased GFP reporter expression by M29-012 and M29-028 mimics.

~~[0060]~~**[0061] FIG. 23A, FIG. 23B and FIG. 23C** shows improved knockdown of HIV-1 relevant host mRNAs by engineered mimics of miR-29.

~~[0061]~~**[0062] FIG. 24A** shows calculated free energy of binding to predicted target sites in the SARS-CoV viral genome by natural and engineered miR-29-3p guide strands.

~~[0062]~~**[0063] FIG. 24B** shows calculated free energy of binding to predicted target sites in the SARS-CoV viral genome by natural and engineered miR-30-5p guide strands.

~~[0063]~~**[0064] FIG. 25A** shows calculated free energy of binding to predicted target sites in the SARS-CoV-2 viral genome by natural and engineered miR-29-3p guide strands.

~~[0064]~~**[0065] FIG. 25B** shows calculated free energy of binding to predicted target sites in the SARS-CoV-2 viral genome by natural and engineered miR-30-5p guide strands.

~~[0065]~~**[0066] FIG. 25C** shows inhibition of SARS-CoV-2 viral replication by exemplar engineered miR-29 and miR-30 mimics.

~~[0066]~~**[0067] FIG. 26** shows calculated free energy of binding to predicted target sites in the HCV-1 viral genome by natural and engineered miR-29-3p guide strands.

~~[0067]~~[0068] **FIG. 27** shows cell killing activity of anti-cancer engineered artificial miRNA mimic ENG-miR-1 in normal and cancer cell lines.

~~[0068]~~[0069] **FIG. 28** shows simultaneous knockdown of DUX4 and DBET RNA transcripts in FSHD patient myoblasts by multi-targeted ASOs.

~~[0069]~~[0070] **FIG. 29** is a diagram showing a method and system as disclosed herein.

~~[0070]~~[0071] **FIG. 30** shows a computer control system that is programmed or otherwise configured to implement methods provided herein.

SEQUENCE LISTING

~~[0071]~~[0072] Any nucleic acid and amino acid sequences listed herein or in the accompanying Sequence Listing are shown using standard letter abbreviations for nucleotide bases and amino acids, as defined in 37 C.F.R. 1.822.

~~[0072]~~[0073] SEQ ID NOs: 1-37 are the nucleotide sequences of exemplary mature miRNAs.

~~[0073]~~[0074] SEQ ID NOs: 38-45, 52-89, and 624-825 are modified miR-30 guide strand nucleotide sequences.

~~[0074]~~[0075] SEQ ID NOs: 46-51, 90-99, and 900 are modified miR-30 passenger strand nucleotide sequences.

~~[0075]~~[0076] SEQ ID NOs: 100-154, 620, and 835-837 are modified miR-29 guide strand nucleotide sequences.

~~[0076]~~[0077] SEQ ID NOs: 155-183 and 838-839 are modified miR-29 passenger strand nucleotide sequences.

~~[0077]~~[0078] SEQ ID NOs: 184-201 are modified miR-26 guide strand nucleotide sequences.

~~[0078]~~[0079] SEQ ID NOs: 202-204 are modified miR-26 passenger strand nucleotide sequences.

~~[0079]~~[0080] SEQ ID NOs: 205-222 are modified miR-27 guide strand nucleotide sequences.

~~[0080]~~[0081] SEQ ID NOs: 223-224 are modified miR-27 passenger strand nucleotide sequences.

~~[0081]~~[0082] SEQ ID NOs: 225-233 are modified miR-101 guide strand nucleotide sequences.

~~[0082]~~[0083] SEQ ID NOs: 234 is a modified miR-101 passenger strand nucleotide sequence.

~~[0083]~~[0084] SEQ ID NOs: 235-243 are modified miR-145 guide strand nucleotide sequences.

~~[0084]~~[0085] SEQ ID NOs: 244 is a modified miR-145 passenger strand nucleotide sequence.

~~[0085]~~[0086] SEQ ID NOs: 245-443 and 840-899 are modified miR-205 guide strand nucleotide sequences.

~~[0086]~~[0087] SEQ ID NOs: 444 is a modified miR-205 passenger strand nucleotide sequence.

~~[0087]~~[0088] SEQ ID NOs: 445-453 are modified miR-338 guide strand nucleotide sequences.

~~[0088]~~[0089] SEQ ID NOs: 454 is a modified miR-338 passenger strand nucleotide sequence.

~~[0089]~~[0090] SEQ ID NOs: 455-463 are modified miR-375 guide strand nucleotide sequences.

~~[0090]~~[0091] SEQ ID NOs: 464 is a modified miR-375 passenger strand nucleotide sequence.

~~[0091]~~[0092] SEQ ID NOs: 465 is an engineered guide strand nucleotide sequence.

~~[0092]~~[0093] SEQ ID NOs: 466 is an engineered passenger strand nucleotide sequence.

~~[0093]~~[0094] SEQ ID NOs: 901-949 are antisense nucleotide sequences.

~~[0094]~~[0095] SEQ ID NO: 467-619, 621-623, 826-834, 950-1120 are target nucleotide sequence.

DETAILED DESCRIPTION

Definitions

~~[0095]~~[0096] Unless otherwise indicated, open terms for example “contain,” “containing,” “include,” “including,” and the like mean comprising.

~~[0096]~~[0097] The singular forms “a”, “an”, and “the” are used herein to include plural references unless the context clearly dictates otherwise. Accordingly, unless the contrary is indicated, the numerical parameters set forth in this application are approximations that can vary depending upon the desired properties sought to be obtained.

~~[0097]~~[0098] As used herein, the term “about” or “approximately” can mean within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, *e.g.*, the limitations of the

measurement system. For example, “about” can mean plus or minus 10%, per the practice in the art. Alternatively, “about” can mean a range of plus or minus 20%, plus or minus 10%, plus or minus 5%, or plus or minus 1% of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, within 5-fold, or within 2-fold, of a value. Where particular values are described in the application and claims, unless otherwise stated the term “about” meaning within an acceptable error range for the particular value should be assumed. Also, where ranges and/or subranges of values are provided, the ranges and/or subranges can include the endpoints of the ranges and/or subranges.

~~[0098]~~[0099] The term “substantially” as used herein can refer to a value approaching 100% of a given value. In some cases, the term can refer to an amount that can be at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.9%, or 99.99% of a total amount. In some cases, the term can refer to an amount that can be about 100% of a total amount.

~~[0099]~~[00100] The term “homology” can refer to a % identity of a sequence to a reference sequence. As a practical matter, whether any particular sequence can be at least 50%, 60%, 70%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to any sequence described herein (which can correspond with a particular nucleic acid sequence described herein), such particular polypeptide sequence can be determined conventionally using known computer programs such the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, Wis. 53711). When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence, the parameters can be set such that the percentage of identity is calculated over the full length of the reference sequence and that gaps in homology of up to 5% of the total reference sequence are allowed.

~~[00100]~~[00101] For example, in a specific embodiment the identity between a reference sequence (query sequence, i.e., a sequence as described herein) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). In

some cases, parameters for a particular embodiment in which identity is narrowly construed, used in a FASTDB amino acid alignment, can include: Scoring Scheme=PAM (Percent Accepted Mutations) 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject sequence, whichever is shorter. According to this embodiment, if the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction can be made to the results to take into consideration the fact that the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity can be corrected by calculating the number of residues of the query sequence that are lateral to the N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. A determination of whether a residue is matched/aligned can be determined by results of the FASTDB sequence alignment. This percentage can be then subtracted from the percent identity, calculated by the FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score can be used for the purposes of this embodiment. In some cases, only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence are considered for this manual correction. For example, a 90 residue subject sequence can be aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C-termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues

were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for.

~~[00101]~~[00102] In some cases, an engineered oligonucleotide or salt thereof can comprise at least about: 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% sequence identity to an oligonucleotide of any SEQ ID NO as described herein. In some cases, an engineered oligonucleotide or salt thereof can comprise at least about: 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% sequence identity to at least 10 contiguous bases of an oligonucleotide of any one of SEQ ID NOs as described herein.

Table 1 – Natural Human miRNAs

miRNA Oligo	Sequence (5′-3′)	SEQ ID NO:
miR-30a-5p	UGUAAACAUCCUCGACUGGAAG	1
miR-30b-5p	UGUAAACAUCCUACACUCAGCU	2
miR-30c-5p	UGUAAACAUCCUACACUCUCAGC	3
miR-30d-5p	UGUAAACAUCCCCGACUGGAAG	4
miR-30e-5p	UGUAAACAUCCUUGACUGGAAG	5
miR-30a-3p	CUUUCAGUCGGAUGUUUGCAGC	6
miR-30b-3p	CUGGGAGGUGGAUGUUUACUUC	7
miR-30c-1-3p	CUGGGAGAGGGUUGUUUACUCC	8
miR-30c-2-3p	CUGGGAGAAGGCUGUUUACUCU	9
miR-30d-3p	CUUUCAGUCAGAUGUUUGCUGC	10
miR-30e-3p	CUUUCAGUCGGAUGUUUACAGC	11
miR-29a-3p	UAGCACCAUCUGAAAUCGGUUA	12
miR-29b-3p	UAGCACCAUUUGAAAUCAGUGUU	13
miR-29c-3p	UAGCACCAUUUGAAAUCGGUUA	14
miR-29a-5p	ACUGAUUUCUUUUGGUGUUCAG	15
miR-29b-1-5p	GCUGGUUUCAUAUGGUGGUUUAGA	16
miR-29b-2-5p	CUGGUUUCACAUGGUGGCUUAG	17
miR-29c-5p	UGACCGAUUUCUCCUGGUGUUC	18
miR-26a-5p	UUCAAGUAAUCCAGGAUAGGCU	19
miR-26b-5p	UUCAAGUAAUUCAGGAUAGGU	20
miR-26a-1-3p	CCUAUUCUUGGUUACUUGCACG	21
miR-26a-2-3p	CCUAUUCUUGAUUACUUGUUUC	22
miR-26b-3p	CCUGUUCUCCAUUACUUGGCUC	23
miR-27a-5p	AGGGCUUAGCUGCUUGUGAGCA	24

miRNA Oligo	Sequence (5′-3′)	SEQ ID NO:
miR-27b-5p	AGAGCUUAGCUGAUUGGUGAAC	25
miR-27a-3p	UUCACAGUGGCUAAGUUCCGC	26
miR-27b-3p	UUCACAGUGGCUAAGUUCUGC	27
miR-101-3p	UACAGUACUGUGAUAACUGAA	28
miR-101-5p	CAGUUAUCACAGUGCUGAUGCU	29
miR-145-5p	GUCCAGUUUUCCCAGGAAUCCCU	30
miR-145-3p	GGAUUCCUGGAAAUACUGUUCU	31
miR-205-5p	UCCUUCAUUCCACCGGAGUCUG	32
miR-205-3p	GAUUUCAGUGGAGUGAAGUUC	33
miR-338-3p	UCCAGCAUCAGUGAUUUUGUUG	34
miR-338-5p	AACAAUAUCCUGGUGCUGAGUG	35
miR-375-3p	UUUGUUCGUUCGGCUCGCGUGA	36
miR-375-5p	GCGACGAGCCCCUCGCACAAACC	37

Table 2 – natural miRNA mimic composition

miRNA Name	Guide Strand	Passenger Strand
miR-30a	miR-30a-5p (SEQ ID NO. 1)	miR-30a-3p (SEQ ID NO. 6)
miR-30b	miR-30b-5p (SEQ ID NO. 2)	miR-30b-3p (SEQ ID NO. 7)
miR-30c-1	miR-30c-5p (SEQ ID NO. 3)	miR-30c-1-3p (SEQ ID NO. 8)
miR-30c-2	miR-30c-5p (SEQ ID NO. 3)	miR-30c-2-3p (SEQ ID NO. 9)
miR-30d	miR-30d-5p (SEQ ID NO. 4)	miR-30d-3p (SEQ ID NO. 10)
miR-30e	miR-30e-5p (SEQ ID NO. 5)	miR-30e-3p (SEQ ID NO. 11)
miR-29a	miR-29a-3p (SEQ ID NO. 12)	miR-29a-5p (SEQ ID NO. 15)
miR-29b-1	miR-29b-3p (SEQ ID NO. 13)	miR-29b-1-5p (SEQ ID NO. 16)
miR-29b-2	miR-29b-3p (SEQ ID NO. 13)	miR-29b-2-5p (SEQ ID NO. 17)
miR-29c	miR-29c-3p (SEQ ID NO. 14)	miR-29c-5p (SEQ ID NO. 18)
miR-26a-1	miR-26a-5p (SEQ ID NO. 19)	miR-26a-1-3p (SEQ ID NO. 21)
miR-26a-2	miR-26a-5p (SEQ ID NO. 19)	miR-26a-2-3p (SEQ ID NO. 22)
miR-26b	miR-26b-5p (SEQ ID NO. 20)	miR-26b-3p (SEQ ID NO. 23)
miR-27a	miR-27a-5p (SEQ ID NO.24)	miR-27a-3p (SEQ ID NO. 26)
miR-27b	miR-27b-5p (SEQ ID NO. 25)	miR-27b-3p (SEQ ID NO. 27)
miR-101	miR-101-3p (SEQ ID NO. 28)	miR-101-5p (SEQ ID NO. 29)
miR-145	miR-145-5p (SEQ ID NO. 30)	miR-145-3p (SEQ ID NO. 31)
miR-205	miR-205-5p (SEQ ID NO. 32)	miR-205-3p (SEQ ID NO. 33)
miR-338	miR-338-3p (SEQ ID NO. 34)	miR-338-5p (SEQ ID NO. 35)
miR-375	miR-375-3p (SEQ ID NO. 36)	miR-375-5p (SEQ ID NO. 37)

Table 3 – Engineered miRNAs

Oligo	Sequence (5′-3′)	SEQ ID NO:
G006-30	UGUAAACAUCCUGCGACUGGAA	38
G007-30	UGUAAACAUCCUGCGACUGGAAG	39
G061-30	UGUAAACAUCCCGCGACUGGAAG	40
G062-30	UGUAAACAUCCUGUGACUGGAAG	41
G063-30	UGUAAACAUCCCGUGACUGGAAG	42
G064-30	UGUAAACAUCCUGACACUCUCAGC	43
G065-30	UGUAAACAUCCUGACACUCUCAG	44

Oligo	Sequence (5′-3′)	SEQ ID NO:
G066-30	UGUAAACAUCCUGACACUCUCA	45
G075-30	UGUAAACAUCCUGACACUCAGCU	624
G076-30	UGUAAACAUCCCGUGACAGGAAG	625
G077-30	UGUAAACAUCCUGCGACUAGGAA	626
G078-30	UGUAAACAUCCUGCGACUGGUAA	627
G079-30	UGUAAACAUCCCUGACUGGAAG	628
G080-30	UGUAAACAUCCUCGACUCAGCU	629
G081-30	UGUAAACAUCCUCGACUCUCAGC	630
G082-30	UGUAAACAUCCUUCACUCAGCU	631
G083-30	UGUAAACAUCCUUCACUCUCAGC	632
G084-30	UGUAAACAUCCCACACUCAGCU	633
G085-30	UGUAAACAUCCCACACUCUCAGC	634
G086-30	UGUAAACAUCCCUCACUCAGCU	635
G087-30	UGUAAACAUCCCUCACUCUCAGC	636
G088-30	UGUAAACAUCCUGCGACUCAGCU	637
G089-30	UGUAAACAUCCUCGACAGGAAG	638
G090-30	UGUAAACAUCCUGCGACAGGAAG	639
G091-30	UGUAAACAUCCUCGACAUGGAAG	640
G092-30	UGUAAACAUCCUCGAACUGGAAG	641
G093-30	UGUAAACAUCCUGCGAACUGGAA	642
G094-30	UGUAAACAUCCCUGACAGGAAG	643
P001-30	CCAGUCGAGGAUGUUUACA	46
P002-30	CCAGUCGCAGGAUGUUUACA	47
P003-30	UCCAGUCGAGGAUGUUUACA	48
P004-30	UCCAGUCGCAGGAUGUUUACA	49
P005-30	UCCAGUCGGAUGUUUACA	50
P125-30	UUCAGUCGGAUGUUUGCAGC	51
G008-30	fUmGfUmAfAmAfCmAfUmCfCmUmGfCmGfAmCfUmGfGmAdAymG	52
G009-30	fUmGfUmAfAmAfCmAfUmCfCmUmGfCmGfAmCfUmGfGmAfAymG	53
G010-30	fUmGfUmAfAmAfCmAfUmCfCmUmGsfCmGfAmCfUmGfGmAsfAsmG	54
G011-30	UGUAAACAUCmCmUmCmGmAmCmUmGGAAG	55
G012-30	fUmGfUmAfAmAfCmAfUmCfCmUmGyfCmGfAmCfUmGfGmAsfAsmG	56
G014-30	fUmGfUmAfAmAfCmAfUmCfCmUsmGfCmGfAmCfUmGfGmAsfAsmG	57
G025-30	fUmGfUmAfAmAfCmAfUmCfCmUsmGsfCmGfAmCfUmGfGmAsfAsmG	58
G026-30	fUmGfUmAfAmAfCmAfUmCfCmUymGfCmGfAmCfUmGfGmAsfAsmG	59
G027-30	UGUAAACAUCmCmUmGmCmGmAmCmUGGfAymA	60
G028-30	UGUAAACAUCmCmUmGmCmGmAmCmUGGsfAsmA	61
G029-30	UGUAAACAUCmCmUmGmCmGmAmCmUmGGAfAymG	62
G030-30	UGUAAACAUCmCmUmGmCmGmAmCmUmGGfAymA	63
G031-30	UGUAAACAUCmCmUmGmCmGmAmCmUmGGsfAsmA	64

Oligo	Sequence (5′-3′)	SEQ ID NO:
G032-30	fUmGfUmAfAmAfCmAfUmCfCmUmGfCmGfAmCfUmGfGmAsfAsmG	65
G033-30	UGUAAACAUCmCmUmGsmCmGmAmCmUmGGAsfAsmA	644
G034-30	UGUAAACAUCmCmUmGymCmGmAmCmUmGGAsfAsmA	66
G035-30	mUsmGUAAACAUCmCmUmGmCmGmAmCmUmGGAsfAsmG	67
G038-30	UGUAAACAUCmCmUsmGmCmGmAmCmUmGGsfAsmA	645
G039-30	fUmGfUAAACAfUmCfCmUfCmGfAmCfUmGfGmAsfAsmG	68
G042-30	fUmGfUmAfAmAfCmAfUmCfCmUfCmGfAmCfUmGfGmAsfAsmG	69
G056-30	UGUAAACAUCmCmUsmGsmCmGmAmCmUmGGsfAsmA	70
G057-30	UGUAAACAUCmCmUymGmCmGmAmCmUmGGsfAsmA	71
G058-30	UGUAAACAUfCmCfUmGfCmGfAmCfUGGsfAsmA	72
G059-30	UGUAAACAUmCfCmUfGmCfGmAfCmUGGsfAsmA	73
G060-30	UGUAAACAUmCmCmUmGmCmGmAmCmUGGsfAsmA	74
G067-30	UGUAAACAUCmCmUmsGmCmGmAmCmUmGGsfAsmA	75
G068-30	UGUAAACAUCmCmUmGmsCmGmAmCmUmGGAsfAsmA	76
G069-30	UGUAAACAUCmCmUmAmCmAmCmUmCAGsfCsmU	77
G070-30	UGUAAACAUCmCmCmCmGmAmCmUmGGAsfAsmG	78
G071-30	UGUAAACAUCmCmCmGmCmGmAmCmUmGGAsfAsmG	79
G072-30	mUsmGUAAACAUCmCmUmGmCmGmAmCmUmGGmAsfAsmG	80
G073-30	mUsmGUAAACAUmCmCmUmGmCmGmAmCmUGGmAsfAsmG	81
G074-30	mUsmGsmUAAACAUCmCmUmGmCmGmAmCmUmGGmAsfAsmG	82
G095-30	UGUAAACAUCmCmCmUmGmAmCmAmGGApfApmG	646
G096-30	UGUAAACAUCmCmCmUmGmAmCmAGGApfApmG	647
G097-30	UGUAAACAUCmCmCmUmGmAmCAGGApfApmG	648
G098-30	UGUAAACAUmCmCmCmUmGmAmCmAmGGApfApmG	649
G099-30	UGUAAACAUmCmCmCmUmGmAmCmAGGApfApmG	650
G100-30	UGUAAACAUmCmCmCmUmGmAmCAGGApfApmG	651
G101-30	UGUAAACAmUmCmCmCmUmGmAmCmAmGGApfApmG	652
G102-30	UGUAAACAmUmCmCmCmUmGmAmCmAGGApfApmG	653
G103-30	UGUAAACAmUmCmCmCmUmGmAmCAGGApfApmG	654
G104-30	UGUAAACAUCmCmUmGmCmGmAmAmCmUGGpfApmA	655
G105-30	UGUAAACAUCmCmUmGmCmGmAmAmCUGGpfApmA	656
G106-30	UGUAAACAUCmCmUmGmCmGmAmACUGGpfApmA	657
G107-30	UGUAAACAUmCmCmUmGmCmGmAmAmCmUGGpfApmA	658
G108-30	UGUAAACAUmCmCmUmGmCmGmAmAmCUGGpfApmA	659
G109-30	UGUAAACAUmCmCmUmGmCmGmAmACUGGpfApmA	660
G110-30	UGUAAACAmUmCmCmUmGmCmGmAmAmCmUGGpfApmA	661
G111-30	UGUAAACAmUmCmCmUmGmCmGmAmAmCUGGpfApmA	662
G112-30	UGUAAACAmUmCmCmUmGmCmGmAmACUGGpfApmA	663
G113-30	UGUAAACAUCmCmUmCmGmAmAmCmUmGGApfApmG	664
G114-30	UGUAAACAUCmCmUmCmGmAmAmCmUGGApfApmG	665
G115-30	UGUAAACAUCmCmUmCmGmAmAmCUGGApfApmG	666
G116-30	UGUAAACAUmCmCmUmCmGmAmAmCmUmGGApfApmG	667
G117-30	UGUAAACAUmCmCmUmCmGmAmAmCmUGGApfApmG	668
G118-30	UGUAAACAUmCmCmUmCmGmAmAmCUGGApfApmG	669
G119-30	UGUAAACAmUmCmCmUmCmGmAmAmCmUmGGApfApmG	670
G120-30	UGUAAACAmUmCmCmUmCmGmAmAmCmUGGApfApmG	671

Oligo	Sequence (5′-3′)	SEQ ID NO:
G121-30	fUmGfUmAfAmAfCmAfUmCfCmUfCmGfAmCfUmGfGmAdAymG	83
G122-30	fUmGfUAAACAfUmCfCmUfCGACUGfGmAsfAsmG	84
G123-30	UGUAAACAmUmCmCmUmCmGmAmAmCUGGApfApmG	672
G124-30	UGUAAACAUCmCmUmCmGmAmCmAmUmGGApfApmG	673
G125-30	UGUAAACAUCmCmUmCmGmAmCmAmUGGApfApmG	674
G126-30	UGUAAACAUCmCmUmCmGmAmCmAUGGApfApmG	675
G127-30	UGUAAACAUmCmCmUmCmGmAmCmAmUmGGApfApmG	676
G128-30	OMe-dTmGfUmAfAmAfCmAfUmCfCmUmGfCmGfAmCfUmGfGmAsfAsmG	85
G129-30	UGUAAACAUCmCmUmCmGmAmCmUmGGAsfAsmG	86
G130-30	UGUAAACAUCmCmUmGmCmGmAmCmUmGGAAG	87
G131-30	UGUAAACAUmCmCmUmCmGmAmCmAmUGGApfApmG	677
G132-30	UGUAAACAUCmCmUmGmCmGmAmCmUmGGAsfAsmG	88
G133-30	UGUAAACAUCmCmUmGmCmGmAmCmUmGGAA	89
G134-30	UGUAAACAUmCmCmUmCmGmAmCmAUGGApfApmG	678
G135-30	UGUAAACAmUmCmCmUmCmGmAmCmAmUmGGApfApmG	679
G136-30	UGUAAACAmUmCmCmUmCmGmAmCmAmUGGApfApmG	680
G137-30	UGUAAACAmUmCmCmUmCmGmAmCmAUGGApfApmG	681
G138-30	UGUAAACAUCmCmUmGmCmGmAmCmAmGGApfApmG	682
G139-30	UGUAAACAUCmCmUmGmCmGmAmCmAGGApfApmG	683
G140-30	UGUAAACAUCmCmUmGmCmGmAmCAGGApfApmG	684
G141-30	UGUAAACAUmCmCmUmGmCmGmAmCmAmGGApfApmG	685
G142-30	UGUAAACAUmCmCmUmGmCmGmAmCmAGGApfApmG	686
G143-30	UGUAAACAUmCmCmUmGmCmGmAmCAGGApfApmG	687
G144-30	UGUAAACAmUmCmCmUmGmCmGmAmCmAmGGApfApmG	688
G145-30	UGUAAACAmUmCmCmUmGmCmGmAmCmAGGApfApmG	689
G146-30	UGUAAACAmUmCmCmUmGmCmGmAmCAGGApfApmG	690
G147-30	UGUAAACAUCmCmUmCmGmAmCmAmGGApfApmG	691
G148-30	UGUAAACAUCmCmUmCmGmAmCmAGGApfApmG	692
G149-30	UGUAAACAUCmCmUmCmGmAmCAGGApfApmG	693
G150-30	UGUAAACAUmCmCmUmCmGmAmCmAmGGApfApmG	694
G151-30	UGUAAACAUmCmCmUmCmGmAmCmAGGApfApmG	695
G152-30	UGUAAACAUmCmCmUmCmGmAmCAGGApfApmG	696
G153-30	UGUAAACAmUmCmCmUmCmGmAmCmAmGGApfApmG	697
G154-30	UGUAAACAmUmCmCmUmCmGmAmCmAGGApfApmG	698
G155-30	UGUAAACAmUmCmCmUmCmGmAmCAGGApfApmG	699
G156-30	UGUAAACAUCmCmUmGmCmGmAmCmUmCAGpfCpmU	700
G157-30	UGUAAACAUCmCmUmGmCmGmAmCmUCAGpfCpmU	701
G158-30	UGUAAACAUCmCmUmGmCmGmAmCUCAGpfCpmU	702
G159-30	UGUAAACAUmCmCmUmGmCmGmAmCmUmCAGpfCpmU	703
G160-30	UGUAAACAUmCmCmUmGmCmGmAmCmUCAGpfCpmU	704
G161-30	UGUAAACAUmCmCmUmGmCmGmAmCUCAGpfCpmU	705
G162-30	UGUAAACAmUmCmCmUmGmCmGmAmCmUmCAGpfCpmU	706
G163-30	UGUAAACAmUmCmCmUmGmCmGmAmCmUCAGpfCpmU	707
G164-30	UGUAAACAmUmCmCmUmGmCmGmAmCUCAGpfCpmU	708
G165-30	UGUAAACAUCmCmCmUmCmAmCmUmCmUCApfGpmC	709
G166-30	UGUAAACAUCmCmCmUmCmAmCmUmCUCApfGpmC	710

Oligo	Sequence (5′-3′)	SEQ ID NO:
G167-30	UGUAAACAUCmCmCmUmCmAmCmUCUCApfGpmC	711
G168-30	UGUAAACAUmCmCmCmUmCmAmCmUmCmUCApfGpmC	712
G169-30	UGUAAACAUmCmCmCmUmCmAmCmUmCUCApfGpmC	713
G170-30	UGUAAACAUmCmCmCmUmCmAmCmUCUCApfGpmC	714
G171-30	UGUAAACAmUmCmCmCmUmCmAmCmUmCmUCApfGpmC	715
G172-30	UGUAAACAmUmCmCmCmUmCmAmCmUmCUCApfGpmC	716
G173-30	UGUAAACAmUmCmCmCmUmCmAmCmUCUCApfGpmC	717
G174-30	UGUAAACAUCmCmCmUmCmAmCmUmCAGpfCpmU	718
G175-30	UGUAAACAUCmCmCmUmCmAmCmUCAGpfCpmU	719
G176-30	UGUAAACAUCmCmCmUmCmAmCUCAGpfCpmU	720
G177-30	UGUAAACAUmCmCmCmUmCmAmCmUmCAGpfCpmU	721
G178-30	UGUAAACAUmCmCmCmUmCmAmCmUCAGpfCpmU	722
G179-30	UGUAAACAUmCmCmCmUmCmAmCUCAGpfCpmU	723
G180-30	UGUAAACAmUmCmCmCmUmCmAmCmUmCAGpfCpmU	724
G181-30	UGUAAACAmUmCmCmCmUmCmAmCmUCAGpfCpmU	725
G182-30	UGUAAACAmUmCmCmCmUmCmAmCUCAGpfCpmU	726
G183-30	UGUAAACAUCmCmCmAmCmAmCmUmCmUCApfGpmC	727
G184-30	UGUAAACAUCmCmCmAmCmAmCmUmCUCApfGpmC	728
G185-30	UGUAAACAUCmCmCmAmCmAmCmUCUCApfGpmC	729
G186-30	UGUAAACAUmCmCmCmAmCmAmCmUmCmUCApfGpmC	730
G187-30	UGUAAACAUmCmCmCmAmCmAmCmUmCUCApfGpmC	731
G188-30	UGUAAACAUmCmCmCmAmCmAmCmUCUCApfGpmC	732
G189-30	UGUAAACAmUmCmCmCmAmCmAmCmUmCmUCApfGpmC	733
G190-30	UGUAAACAmUmCmCmCmAmCmAmCmUmCUCApfGpmC	734
G191-30	UGUAAACAmUmCmCmCmAmCmAmCmUCUCApfGpmC	735
G192-30	UGUAAACAUCmCmCmAmCmAmCmUmCAGpfCpmU	736
G193-30	UGUAAACAUCmCmCmAmCmAmCmUCAGpfCpmU	737
G194-30	UGUAAACAUCmCmCmAmCmAmCUCAGpfCpmU	738
G195-30	UGUAAACAUmCmCmCmAmCmAmCmUmCAGpfCpmU	739
G196-30	UGUAAACAUmCmCmCmAmCmAmCmUCAGpfCpmU	740
G197-30	UGUAAACAUmCmCmCmAmCmAmCUCAGpfCpmU	741
G198-30	UGUAAACAmUmCmCmCmAmCmAmCmUmCAGpfCpmU	742
G199-30	UGUAAACAmUmCmCmCmAmCmAmCmUCAGpfCpmU	743
G200-30	UGUAAACAmUmCmCmCmAmCmAmCUCAGpfCpmU	744
G201-30	UGUAAACAUCmCmUmUmCmAmCmUmCmUCApfGpmC	745
G202-30	UGUAAACAUCmCmUmUmCmAmCmUmCUCApfGpmC	746
G203-30	UGUAAACAUCmCmUmUmCmAmCmUCUCApfGpmC	747
G204-30	UGUAAACAUmCmCmUmUmCmAmCmUmCmUCApfGpmC	748
G205-30	UGUAAACAUmCmCmUmUmCmAmCmUmCUCApfGpmC	749
G206-30	UGUAAACAUmCmCmUmUmCmAmCmUCUCApfGpmC	750
G207-30	UGUAAACAmUmCmCmUmUmCmAmCmUmCmUCApfGpmC	751
G208-30	UGUAAACAmUmCmCmUmUmCmAmCmUmCUCApfGpmC	752
G209-30	UGUAAACAmUmCmCmUmUmCmAmCmUCUCApfGpmC	753
G210-30	UGUAAACAUCmCmUmUmCmAmCmUmCAGpfCpmU	754
G211-30	UGUAAACAUCmCmUmUmCmAmCmUCAGpfCpmU	755
G212-30	UGUAAACAUCmCmUmUmCmAmCUCAGpfCpmU	756
G213-30	UGUAAACAUmCmCmUmUmCmAmCmUmCAGpfCpmU	757
G214-30	UGUAAACAUmCmCmUmUmCmAmCmUCAGpfCpmU	758

Oligo	Sequence (5′-3′)	SEQ ID NO:
G215-30	UGUAAACAUmCmCmUmUmCmAmCUCAGpfCpmU	759
G216-30	UGUAAACAmUmCmCmUmUmCmAmCmUmCAGpfCpmU	760
G217-30	UGUAAACAmUmCmCmUmUmCmAmCmUCAGpfCpmU	761
G218-30	UGUAAACAmUmCmCmUmUmCmAmCUCAGpfCpmU	762
G219-30	UGUAAACAUCmCmUmCmGmAmCmUmCmUCApfGpmC	763
G220-30	UGUAAACAUCmCmUmCmGmAmCmUmCUCApfGpmC	764
G221-30	UGUAAACAUCmCmUmCmGmAmCmUCUCApfGpmC	765
G222-30	UGUAAACAUmCmCmUmCmGmAmCmUmCmUCApfGpmC	766
G223-30	UGUAAACAUmCmCmUmCmGmAmCmUmCUCApfGpmC	767
G224-30	UGUAAACAUmCmCmUmCmGmAmCmUCUCApfGpmC	768
G225-30	UGUAAACAmUmCmCmUmCmGmAmCmUmCmUCApfGpmC	769
G226-30	UGUAAACAmUmCmCmUmCmGmAmCmUmCUCApfGpmC	770
G227-30	UGUAAACAmUmCmCmUmCmGmAmCmUCUCApfGpmC	771
G228-30	UGUAAACAUCmCmUmCmGmAmCmUmCAGpfCpmU	772
G229-30	UGUAAACAUCmCmUmCmGmAmCmUCAGpfCpmU	773
G230-30	UGUAAACAUCmCmUmCmGmAmCUCAGpfCpmU	774
G231-30	UGUAAACAUmCmCmUmCmGmAmCmUmCAGpfCpmU	775
G232-30	UGUAAACAUmCmCmUmCmGmAmCmUCAGpfCpmU	776
G233-30	UGUAAACAUmCmCmUmCmGmAmCUCAGpfCpmU	777
G234-30	UGUAAACAmUmCmCmUmCmGmAmCmUmCAGpfCpmU	778
G235-30	UGUAAACAmUmCmCmUmCmGmAmCmUCAGpfCpmU	779
G236-30	UGUAAACAmUmCmCmUmCmGmAmCUCAGpfCpmU	780
G237-30	UGUAAACAUCmCmCmUmGmAmCmUmGGApfApmG	781
G238-30	UGUAAACAUCmCmCmUmGmAmCmUGGApfApmG	782
G239-30	UGUAAACAUCmCmCmUmGmAmCUGGApfApmG	783
G240-30	UGUAAACAUmCmCmCmUmGmAmCmUmGGApfApmG	784
G241-30	UGUAAACAUmCmCmCmUmGmAmCmUGGApfApmG	785
G242-30	UGUAAACAUmCmCmCmUmGmAmCUGGApfApmG	786
G243-30	UGUAAACAmUmCmCmCmUmGmAmCmUmGGApfApmG	787
G244-30	UGUAAACAmUmCmCmCmUmGmAmCmUGGApfApmG	788
G245-30	UGUAAACAmUmCmCmCmUmGmAmCUGGApfApmG	789
G246-30	UGUAAACAUCmCmUmGmCmGmAmCmUmGGUpfApmA	790
G247-30	UGUAAACAUCmCmUmGmCmGmAmCmUGGUpfApmA	791
G248-30	UGUAAACAUCmCmUmGmCmGmAmCUGGUpfApmA	792
G249-30	UGUAAACAUmCmCmUmGmCmGmAmCmUmGGUpfApmA	793
G250-30	UGUAAACAUmCmCmUmGmCmGmAmCmUGGUpfApmA	794
G251-30	UGUAAACAUmCmCmUmGmCmGmAmCUGGUpfApmA	795
G252-30	UGUAAACAmUmCmCmUmGmCmGmAmCmUmGGUpfApmA	796
G253-30	UGUAAACAmUmCmCmUmGmCmGmAmCmUGGUpfApmA	797
G254-30	UGUAAACAmUmCmCmUmGmCmGmAmCUGGUpfApmA	798
G255-30	UGUAAACAUCmCmUmGmCmGmAmCmUmAGGpfApmA	799
G256-30	UGUAAACAUCmCmUmGmCmGmAmCmUAGGpfApmA	800
G257-30	UGUAAACAUCmCmUmGmCmGmAmCUAGGpfApmA	801
G258-30	UGUAAACAUmCmCmUmGmCmGmAmCmUmAGGpfApmA	802
G259-30	UGUAAACAUmCmCmUmGmCmGmAmCmUAGGpfApmA	803
G260-30	UGUAAACAUmCmCmUmGmCmGmAmCUAGGpfApmA	804
G261-30	UGUAAACAmUmCmCmUmGmCmGmAmCmUmAGGpfApmA	805
G262-30	UGUAAACAmUmCmCmUmGmCmGmAmCmUAGGpfApmA	806

Oligo	Sequence (5′-3′)	SEQ ID NO:
G263-30	UGUAAACAmUmCmCmUmGmCmGmAmCUAGGpfApmA	807
G264-30	UGUAAACAUCmCmCmGmUmGmAmCmAmGGApfApmG	808
G265-30	UGUAAACAUCmCmCmGmUmGmAmCmAGGApfApmG	809
G266-30	UGUAAACAUCmCmCmGmUmGmAmCAGGApfApmG	810
G267-30	UGUAAACAUmCmCmCmGmUmGmAmCmAmGGApfApmG	811
G268-30	UGUAAACAUmCmCmCmGmUmGmAmCmAGGApfApmG	812
G269-30	UGUAAACAUmCmCmCmGmUmGmAmCAGGApfApmG	813
G270-30	UGUAAACAmUmCmCmCmGmUmGmAmCmAmGGApfApmG	814
G271-30	UGUAAACAmUmCmCmCmGmUmGmAmCmAGGApfApmG	815
G272-30	UGUAAACAmUmCmCmCmGmUmGmAmCAGGApfApmG	816
G273-30	UGUAAACAUCmCmUmGmAmCmAmCmUmCAGpfCpmU	817
G274-30	UGUAAACAUCmCmUmGmAmCmAmCmUCAGpfCpmU	818
G275-30	UGUAAACAUCmCmUmGmAmCmAmCUCAGpfCpmU	819
G276-30	UGUAAACAUmCmCmUmGmAmCmAmCmUmCAGpfCpmU	820
G277-30	UGUAAACAUmCmCmUmGmAmCmAmCmUCAGpfCpmU	821
G278-30	UGUAAACAUmCmCmUmGmAmCmAmCUCAGpfCpmU	822
G279-30	UGUAAACAmUmCmCmUmGmAmCmAmCmUmCAGpfCpmU	823
G280-30	UGUAAACAmUmCmCmUmGmAmCmAmCmUCAGpfCpmU	824
G281-30	UGUAAACAmUmCmCmUmGmAmCmAmCUCAGpfCpmU	825
P008-30	Amino C6-mCmUmGGGAGGUGGAUGUUUACmUmUmC	90
P009-30	Amino C6-mCmUmUUCAGUCAGAUGUUUGCmUmGmC	91
P010-30	Amino C6-mUsmCsmCAGUCmGmAGGAUGUUUmAsmCsmA	92
P011-30	Amino C6-mUsmCsmCAGUmCmGmAmGGAUGUUUmAsmCsmA	93
P013-30	Amino C6-mUsmCsmCAGUmCmGmAmGmGmAmUmGmUmUmUmAsmCsmA	94
P014-30	Amino C6-mUmCmCAGUCGGAUGUUUmAmCmA	95
P015-30	Amino C6-mUsmCsmCAGUmCfGmAmGGAUGUUUmAsmCsmA	900
P123-30	Amino C6-mUmCmCAGUCGAGGAUGUUUmAmCmA	96
P126-30	Amino C6-mUmCmCAGUCGCAGGAUGUUUmAmCmA	97
P128-30	Amino C6-mCmCmAGUCGAGGAUGUUUmAmCmA	98
P131-30	Amino C6-mCmCmAGUCGCAGGAUGUUUmAmCmA	99
G001-29	UAGCACCAUCUGAAAGCAGUGUU	100
G002-29	UAGCACCAUCUGAAAUCAGUGU	101
G003-29	UAGCACCAUCUGAAAUCAGUGUU	102
G004-29	UAGCACCAUUUGAAGUCAGUGUU	103
G005-29	UAGCACCAUUUGAAGGUCAGUGU	104
G006-29	UAGCACCAUCUGAAGUCAGUGUU	105
G007-29	UAGCACCAUCUGAAGGUCAGUGU	106
G008-29	UAGCACCAUCUGAAGGCAGUGU	107
G013-29	UAGCACCAUUUGAAAUCAGUGU	108
G019-29	UAGCACCAUCUGAAGGCAGUGUU	109
G020-29	UAGCACCAUCUGAAGGUCAGUGUU	110
G021-29	UAGCACCAUUUGAAAGCAGUGU	111
G022-29	UAGCACCAUUUGAAAGCAGUGUU	112
G023-29	UAGCACCAUUUGAAAGUCAGU	113
G024-29	UAGCACCAUUUGAAAGUCAGUGU	114
G025-29	UAGCACCAUUUGAAGGCAGUGU	115
G026-29	UAGCACCAUUUGAAGGUCAGUG	116

Oligo	Sequence (5′-3′)	SEQ ID NO:
G027-29	UAGCACCAUUUGAAGGUCAGUGUU	117
G028-29	UAGCACCAUUUGAAGUCAGUGU	118
G029-29	UAGCACCAUUUGAAAGUCAGUGUU	119
G030-29	UAGCACCAUUUGAAAGUCAGUG	120
G031-29	UAGCACCAUUUGAAGGCAGUGUU	121
G032-29	UAGCACCAUCUGAAGGUCAGUG	122
G033-29	UAGCACCAUCUGAAGGUCAGU	123
G034-29	UAGCACCAUCUGAAGUCAGUGU	124
G035-29	UAGCACCAUCUGAAAGCAGUGU	125
G036-29	UAGCACCAUCUGAAAGCAGUG	126
P001-29	ACUGAUUUCUUUUGGUGUUAG	155
P002-29	ACCGAUUUCUUUUGGUGUUA	156
P003-29	ACCGAUUUCAGAUGGUGUUA	157
P010-29	CGCUGGUUUCAUAUGGUGUUAGA	158
P015-29	GCUGGUUUCAUAUGGUGGUUUA	159
P016-29	GCUGGUUUCAGAUGGUGGUUUA	160
P017-29	GCUGGUUUCAGAUGGUGUUA	161
P018-29	ACUGAUUUCAGAUGGUGUUA	162
P019-29	CACUGAUUUCAGAUGGUGUUA	163
P020-29	CACUGACUUCAGAUGGUGUUA	164
P021-29	ACUGACUUUCAGAUGGUGUUA	165
P022-29	ACUGACCUUCAGAUGGUGUUA	166
P023-29	CUGACUUUCAGAUGGUGUUA	167
P024-29	ACUGCUUUCAGAUGGUGUUA	168
P025-29	ACUGACUUCAGAUGGUGUUA	169
G009-29	mUfAmGfCmAfCmCfAmUfUmUfGmAfAmAfUmCfAmGfUmGyfUymU	127
G010-29	mUfAmGfCmAfCmCfAmUfCmUfGmAfAmAfUmCfAmGfUmGyfUymU	128
G011-29	mUfAmGfCmAfCmCfAmUfCmUfGmAfAmGfUmCfAmGfUmGyfUymU	129
G012-29	mUfAmGfCmAfCmCfAmUfCmUfGmAfAmGfGmCfAmGfUymGyfU	130
G014-29	mUfAmGfCmAfCmCfAmUfCmUfGmAfAmGfUmCfAmGfUymGyfU	131
G015-29	UAGCACCAUUmUmGmAmAmAmUmCmAmGUGyfUymU	620
G016-29	UAGCACCAUCmUmGmAmAmAmUmCmAmGUGyfUymU	835
G017-29	UAGCACCAUCmUmGmAmAmGmGmUmCmAGUyfGymU	836
G018-29	UAGCACCAUCmUmGmAmAmGmGmCmAmGUGyfGymU	837
G037-29	mUfAmGfCmAfCmCfAmUfUmUfGmAfAmAfUmCfAmGfUmGsfUsmU	132
G038-29	mUfAmGfCmAfCmCfAmUfCmUfGmAfAmAfUmCfAmGfUmGsfUsmU	133
G039-29	mUfAmGfCmAfCmCfAmUfCmUfGmAfAmGfUmCfAmGfUmGsfUsmU	134
G040-29	mUfAmGfCmAfCmCfAmUfCmUfGmAfAmGfGmCfAmGfUsmGsfU	135
G041-29	mUfAmGfCmAfCmCfAmUfCmUfGmAfAmGfUmCfAmGfUsmGsfU	136
G042-29	UAGCACCAUmUmUmGmAmAmGmGmUmCAGUGU	137
G043-29	UAGCACCAUmUmUmGmAmAmGmGmUmCAGUsfGsmU	138
G044-29	UAGCACCAUmUmUmGmAmAmGmGmUCAGUG	139

Oligo	Sequence (5′-3′)	SEQ ID NO:
G045-29	UAGCACCAUmUmUmGmAmAmGmGmUCAGsfUsmG	140
G046-29	UAGCACCAUmCmUmGmAmAmGmGmUmCAGUsfGsmU	141
G047-29	UAGCACCAUmCmUmGmAmAmGmGmUCAGsfUsmG	142
G048-29	UAGCACCAUmUmUmGmAmAmAmUmCAGUGUU	143
G049-29	UAGCACCAUmUmUmGmAmAmAmUmCAGUGsfUsmU	144
G050-29	UAGCACCAUmCmUmGmAmAmAmUmCAGUGUU	145
G051-29	UAGCACCAUmCmUmGmAmAmAmUmCAGUGsfUsmU	146
G052-29	UAGCACCAUmCmUmGmAmAmGmUmCAGUGUU	147
G053-29	UAGCACCAUmCmUmGmAmAmGmUmCAGUGsfUsmU	148
G054-29	UAGCACCAUmUfUmGfAmAfAmUfCAGUGsfUsmU	149
G055-29	UAGCACCAUmCfUmGfAmAfAmUfCAGUGsfUsmU	150
G056-29	UAGCACCAUmCfUmGfAmAfGmUfCAGUGsfUsmU	151
G057-29	UAGCACCAUmCfUmGfAmAfGmGfCAGUsfGsmU	152
G058-29	mUfAmGfCmAfCmCfAmUfUmUfGmAfAmAfUmCfAmGfUsmGsfU	153
G059-29	mUfAmGfCmAfCmCfAmUfCmUfGmAfAmAfUmCfAmGfUsmGsfU	154
P004-29	Amino C6-mGmCmUGGUUUCAUAUGGUGGUmUmUmA	170
P005-29	Amino C6-mGmCmUGGUUUCAGAUGGUGGUmUmUmA	171
P006-29	Amino C6-mGmCmUGGUUUCAGAUGGUGmUmUmA	172
P007-29	Amino C6-mAmCmUGAUUUCAGAUGGUGmUmUmA	173
P008-29	Amino C6-mAmCmCGAUUUCUUUUGGUGmUmUmA	174
P009-29	Amino C6-mAmCmCGAUUUCAGAUGGUGmUmUmA	175
P011-29	Amino C6-mCmAmCUGAUUUCAGAUGGUGmUmUmA	176
P012-29	Amino C6-mCmAmCUmGAUUUCAGAUmGGmUGmUmUmA	838
P013-29	Amino C6-mAmCmUGACUUUCAGAUGGUGmUmUmA	177
P014-29	Amino C6-mCmAmCUmGmCUUUCAGAUGGUGmUmUmA	839
P026-29	Amino C6-mCmAmCUGAUUUCAGAUGGUGmUmUA	178
P027-29	Amino C6-mCmAmCUGACUUCAGAUGGUGmUmUmA	179
P028-29	Amino C6-mAmCmUGACCUUCAGAUGGUGmUmUmA	180
P029-29	Amino C6-mCmUmGACUUUCAGAUGGUGmUmUmA	181
P030-29	Amino C6-mAmCmUGCUUUCAGAUGGUGmUmUmA	182
P031-29	Amino C6-mAmCmUGACUUCAGAUGGUGmUmUmA	183
G001-26	UUCAAGUAAUmCmCmAmGmGmAmUmAGGsfCsmU	184
G002-26	UUCAAGUAAUmUmCmAmGmGmAmUAGsfGsmU	185
G003-26	UUCAAGUAAUmCmCmAmGmGmAmUAGGsfCsmU	186
G004-26	UUCAAGUAAUmCmCmAmGmGmAUAGGsfCsmU	187
G005-26	UUCAAGUAAmUmCmCmAmGmGmAmUmAGGsfCsmU	188
G006-26	UUCAAGUAAmUmCmCmAmGmGmAmUAGGsfCsmU	189
G007-26	UUCAAGUAAmUmCmCmAmGmGmAUAGGsfCsmU	190
G008-26	UUCAAGUAmAmUmCmCmAmGmGmAmUmAGGsfCsmU	191
G009-26	UUCAAGUAmAmUmCmCmAmGmGmAmUAGGsfCsmU	192
G010-26	UUCAAGUAmAmUmCmCmAmGmGmAUAGGsfCsmU	193
G011-26	UUCAAGUAAUmUmCmAmGmGmAUAGsfGsmU	194
G012-26	UUCAAGUAAUmUmCmAmGmGAUAGsfGsmU	195
G013-26	UUCAAGUAAmUmUmCmAmGmGmAmUAGsfGsmU	196
G014-26	UUCAAGUAAmUmUmCmAmGmGmAUAGsfGsmU	197
G015-26	UUCAAGUAAmUmUmCmAmGmGAUAGsfGsmU	198
G016-26	UUCAAGUAmAmUmUmCmAmGmGmAmUAGsfGsmU	199
G017-26	UUCAAGUAmAmUmUmCmAmGmGmAUAGsfGsmU	200

Oligo	Sequence (5′-3′)	SEQ ID NO:
G018-26	UUCAAGUAmAmUmUmCmAmGmGAUAGsfGsmU	201
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P002-26	Amino C6-mCmCmUAUUCUUGAUUACUUGUmUmUmC	203
P003-26	Amino C6-mCmCmUGUUCUCCAUUACUUGGmCmUmC	204
G002-27	AGGGCUUAGCmUmGmCmUmUmGmUmGAGsfCsmA	205
G003-27	AGGGCUUAGCmUmGmCmUmUmGmUGAGsfCsmA	206
G004-27	AGGGCUUAGCmUmGmCmUmUmGUGAGsfCsmA	207
G005-27	AGGGCUUAGmCmUmGmCmUmUmGmUmGAGsfCsmA	208
G006-27	AGGGCUUAGmCmUmGmCmUmUmGmUGAGsfCsmA	209
G007-27	AGGGCUUAGmCmUmGmCmUmUmGUGAGsfCsmA	210
G008-27	AGGGCUUAmGmCmUmGmCmUmUmGmUmGAGsfCsmA	211
G009-27	AGGGCUUAmGmCmUmGmCmUmUmGmUGAGsfCsmA	212
G010-27	AGGGCUUAmGmCmUmGmCmUmUmGUGAGsfCsmA	213
G011-27	AGAGCUUAGCmUmGmAmUmUmGmGmUGAsfAsmC	214
G012-27	AGAGCUUAGCmUmGmAmUmUmGmGUGAsfAsmC	215
G013-27	AGAGCUUAGCmUmGmAmUmUmGGUGAsfAsmC	216
G014-27	AGAGCUUAGmCmUmGmAmUmUmGmGmUGAsfAsmC	217
G015-27	AGAGCUUAGmCmUmGmAmUmUmGmGUGAsfAsmC	218
G016-27	AGAGCUUAGmCmUmGmAmUmUmGGUGAsfAsmC	219
G017-27	AGAGCUUAmGmCmUmGmAmUmUmGmGmUGAsfAsmC	220
G018-27	AGAGCUUAmGmCmUmGmAmUmUmGmGUGAsfAsmC	221
G019-27	AGAGCUUAmGmCmUmGmAmUmUmGGUGAsfAsmC	222
P001-27	Amino C6-mUmUmCACAGUGGCUAAGUUCmCmGmC	223
P002-27	Amino C6-mUmUmCACAGUGGCUAAGUUCmUmGmC	224
G001-101	UACAGUACUGmUmGmAmUmAmAmCUGsfAsmA	225
G002-101	UACAGUACUGmUmGmAmUmAmACUGsfAsmA	226
G003-101	UACAGUACUGmUmGmAmUmAACUGsfAsmA	227
G004-101	UACAGUACUmGmUmGmAmUmAmAmCUGsfAsmA	228
G005-101	UACAGUACUmGmUmGmAmUmAmACUGsfAsmA	229
G006-101	UACAGUACUmGmUmGmAmUmAACUGsfAsmA	230
G007-101	UACAGUACmUmGmUmGmAmUmAmAmCUGsfAsmA	231
G008-101	UACAGUACmUmGmUmGmAmUmAmACUGsfAsmA	232
G009-101	UACAGUACmUmGmUmGmAmUmAACUGsfAsmA	233
P001-101	Amino C6-mCmAmGUUAUCACAGUGCUGAUmGmCmU	234
G001-145	GUCCAGUUUUmCmCmCmAmGmGmAmAmUCCsfCsmU	235
G002-145	GUCCAGUUUUmCmCmCmAmGmGmAmAUCCsfCsmU	236
G003-145	GUCCAGUUUUmCmCmCmAmGmGmAAUCCsfCsmU	237
G004-145	GUCCAGUUUmUmCmCmCmAmGmGmAmAmUCCsfCsmU	238
G005-145	GUCCAGUUUmUmCmCmCmAmGmGmAmAUCCsfCsmU	239
G006-145	GUCCAGUUUmUmCmCmCmAmGmGmAAUCCsfCsmU	240
G007-145	GUCCAGUUmUmUmCmCmCmAmGmGmAmAmUCCsfCsmU	241
G008-145	GUCCAGUUmUmUmCmCmCmAmGmGmAmAUCCsfCsmU	242
G009-145	GUCCAGUUmUmUmCmCmCmAmGmGmAAUCCsfCsmU	243
P001-145	Amino C6-mGmGmAUUCCUGGAAAUACUGUmUmCmU	244
G001-205	UCCUUCAUACCACCGGAGUGUG	245
G002-205	UCCUUCAUACCCACCGGAGUCUG	246
G003-205	UCCUUCAUACCUCCGGAGUCUG	247
G004-205	UCCUUCAUACCUCCGGAGUGUG	248

Oligo	Sequence (5′-3′)	SEQ ID NO:
G005-205	UCCUUCAUAUCCACCGGAGUGCU	249
G006-205	UCCUUCAUAUCCACCGGAGUGUG	250
G007-205	UCCUUCAUAUCCUCCGGAGUGCU	251
G008-205	UCCUUCAUAUCCUCCGGAGUGUG	252
G009-205	UCCUUCAUCCCACCGGAGUGUG	253
G010-205	UCCUUCAUCCCUCCGGAGUCUG	254
G011-205	UCCUUCAUCCCUCCGGAGUGUG	255
G012-205	UCCUUCAUCUCCACCGGAGUGCU	256
G013-205	UCCUUCAUCUCCACCGGAGUGUG	257
G014-205	UCCUUCAUCUCCUCCGGAGUGCU	258
G015-205	UCCUUCAUUCCACCGGAGUGCUG	259
G016-205	UCCUUCAUUCCACCGGAGUGUG	260
G017-205	UCCUUCAUUCCAUCGGAGUGCUG	261
G018-205	UCCUUCAUUCCUCCGGAGUCUG	262
G019-205	UCCUUCAUUCCUCCGGAGUGUG	263
G200-205	UCCUUCAUACCACCGGAGUCUG	840
G201-205	UCCUUCAUCCCACCGGAGUCUG	841
G202-205	UCCUUCAUAUCCACCGGAGUCUG	842
G203-205	UCCUUCAUCUCCACCGGAGUCUG	843
G204-205	UCCUUCAUCACCACCGGAGUCUG	844
G205-205	UCCUUCAUAUCCUCCGGAGUCUG	845
G020-205	UCCUUCAUUCmCmAmCmCmGmGmAmGUCsfUsmG	264
G021-205	UCCUUCAUUCmCmAmCmCmGmGmAGUCsfUsmG	265
G022-205	UCCUUCAUUCmCmAmCmCmGmGAGUCsfUsmG	266
G023-205	UCCUUCAUUmCmCmAmCmCmGmGmAmGUCsfUsmG	267
G024-205	UCCUUCAUUmCmCmAmCmCmGmGmAGUCsfUsmG	268
G025-205	UCCUUCAUUmCmCmAmCmCmGmGAGUCsfUsmG	269
G026-205	UCCUUCAUmUmCmCmAmCmCmGmGmAmGUCsfUsmG	270
G027-205	UCCUUCAUmUmCmCmAmCmCmGmGmAGUCsfUsmG	271
G028-205	UCCUUCAUmUmCmCmAmCmCmGmGAGUCsfUsmG	272
G029-205	UCCUUCAUACmCmAmCmCmGmGmAmGUGsfUsmG	273
G030-205	UCCUUCAUACmCmAmCmCmGmGmAGUGsfUsmG	274
G031-205	UCCUUCAUACmCmAmCmCmGmGAGUGsfUsmG	275
G032-205	UCCUUCAUAmCmCmAmCmCmGmGmAmGUGsfUsmG	276
G033-205	UCCUUCAUAmCmCmAmCmCmGmGmAGUGsfUsmG	277
G034-205	UCCUUCAUAmCmCmAmCmCmGmGAGUGsfUsmG	278
G035-205	UCCUUCAUmAmCmCmAmCmCmGmGmAmGUGsfUsmG	279
G036-205	UCCUUCAUmAmCmCmAmCmCmGmGmAGUGsfUsmG	280
G037-205	UCCUUCAUmAmCmCmAmCmCmGmGAGUGsfUsmG	281
G038-205	UCCUUCAUACmCmCmAmCmCmGmGmAmGUCsfUsmG	282
G039-205	UCCUUCAUACmCmCmAmCmCmGmGmAGUCsfUsmG	283
G040-205	UCCUUCAUACmCmCmAmCmCmGmGAGUCsfUsmG	284
G041-205	UCCUUCAUAmCmCmCmAmCmCmGmGmAmGUCsfUsmG	285
G042-205	UCCUUCAUAmCmCmCmAmCmCmGmGmAGUCsfUsmG	286
G043-205	UCCUUCAUAmCmCmCmAmCmCmGmGAGUCsfUsmG	287
G044-205	UCCUUCAUmAmCmCmCmAmCmCmGmGmAmGUCsfUsmG	288
G045-205	UCCUUCAUmAmCmCmCmAmCmCmGmGmAGUCsfUsmG	289
G046-205	UCCUUCAUmAmCmCmCmAmCmCmGmGAGUCsfUsmG	290

Oligo	Sequence (5′-3′)	SEQ ID NO:
G047-205	UCCUUCAUACmCmUmCmCmGmGmAmGUCsfUsmG	291
G048-205	UCCUUCAUACmCmUmCmCmGmGmAGUCsfUsmG	292
G049-205	UCCUUCAUACmCmUmCmCmGmGAGUCsfUsmG	293
G050-205	UCCUUCAUAmCmCmUmCmCmGmGmAmGUCsfUsmG	294
G051-205	UCCUUCAUAmCmCmUmCmCmGmGmAGUCsfUsmG	295
G052-205	UCCUUCAUAmCmCmUmCmCmGmGAGUCsfUsmG	296
G053-205	UCCUUCAUmAmCmCmUmCmCmGmGmAmGUCsfUsmG	297
G054-205	UCCUUCAUmAmCmCmUmCmCmGmGmAGUCsfUsmG	298
G055-205	UCCUUCAUmAmCmCmUmCmCmGmGAGUCsfUsmG	299
G056-205	UCCUUCAUACmCmUmCmCmGmGmAmGUGsfUsmG	300
G057-205	UCCUUCAUACmCmUmCmCmGmGmAGUGsfUsmG	301
G058-205	UCCUUCAUACmCmUmCmCmGmGAGUGsfUsmG	302
G059-205	UCCUUCAUAmCmCmUmCmCmGmGmAmGUGsfUsmG	303
G060-205	UCCUUCAUAmCmCmUmCmCmGmGmAGUGsfUsmG	304
G061-205	UCCUUCAUAmCmCmUmCmCmGmGAGUGsfUsmG	305
G062-205	UCCUUCAUmAmCmCmUmCmCmGmGmAmGUGsfUsmG	306
G063-205	UCCUUCAUmAmCmCmUmCmCmGmGmAGUGsfUsmG	307
G064-205	UCCUUCAUmAmCmCmUmCmCmGmGAGUGsfUsmG	308
G065-205	UCCUUCAUAUmCmCmAmCmCmGmGmAmGUGsfCsmU	309
G066-205	UCCUUCAUAUmCmCmAmCmCmGmGmAGUGsfCsmU	310
G067-205	UCCUUCAUAUmCmCmAmCmCmGmGAGUGsfCsmU	311
G068-205	UCCUUCAUAmUmCmCmAmCmCmGmGmAmGUGsfCsmU	312
G069-205	UCCUUCAUAmUmCmCmAmCmCmGmGmAGUGsfCsmU	313
G070-205	UCCUUCAUAmUmCmCmAmCmCmGmGAGUGsfCsmU	314
G071-205	UCCUUCAUmAmUmCmCmAmCmCmGmGmAmGUGsfCsmU	315
G072-205	UCCUUCAUmAmUmCmCmAmCmCmGmGmAGUGsfCsmU	316
G073-205	UCCUUCAUmAmUmCmCmAmCmCmGmGAGUGsfCsmU	317
G074-205	UCCUUCAUAUmCmCmAmCmCmGmGmAmGUGsfUsmG	318
G075-205	UCCUUCAUAUmCmCmAmCmCmGmGmAGUGsfUsmG	319
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G078-205	UCCUUCAUAmUmCmCmAmCmCmGmGmAGUGsfUsmG	322
G079-205	UCCUUCAUAmUmCmCmAmCmCmGmGAGUGsfUsmG	323
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G081-205	UCCUUCAUmAmUmCmCmAmCmCmGmGmAGUGsfUsmG	325
G082-205	UCCUUCAUmAmUmCmCmAmCmCmGmGAGUGsfUsmG	326
G083-205	UCCUUCAUAUmCmCmUmCmCmGmGmAmGUGsfCsmU	327
G084-205	UCCUUCAUAUmCmCmUmCmCmGmGmAGUGsfCsmU	328
G085-205	UCCUUCAUAUmCmCmUmCmCmGmGAGUGsfCsmU	329
G086-205	UCCUUCAUAmUmCmCmUmCmCmGmGmAmGUGsfCsmU	330
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G090-205	UCCUUCAUmAmUmCmCmUmCmCmGmGmAGUGsfCsmU	334
G091-205	UCCUUCAUmAmUmCmCmUmCmCmGmGAGUGsfCsmU	335
G092-205	UCCUUCAUAUmCmCmUmCmCmGmGmAmGUGsfUsmG	336
G093-205	UCCUUCAUAUmCmCmUmCmCmGmGmAGUGsfUsmG	337
G094-205	UCCUUCAUAUmCmCmUmCmCmGmGAGUGsfUsmG	338

Oligo	Sequence (5′-3′)	SEQ ID NO:
G095-205	UCCUUCAUAmUmCmCmUmCmCmGmGmAmGUGsfUsmG	339
G096-205	UCCUUCAUAmUmCmCmUmCmCmGmGmAGUGsfUsmG	340
G097-205	UCCUUCAUAmUmCmCmUmCmCmGmGAGUGsfUsmG	341
G098-205	UCCUUCAUmAmUmCmCmUmCmCmGmGmAmGUGsfUsmG	342
G099-205	UCCUUCAUmAmUmCmCmUmCmCmGmGmAGUGsfUsmG	343
G100-205	UCCUUCAUmAmUmCmCmUmCmCmGmGAGUGsfUsmG	344
G101-205	UCCUUCAUCCmCmAmCmCmGmGmAmGUGsfUsmG	345
G102-205	UCCUUCAUCCmCmAmCmCmGmGmAGUGsfUsmG	346
G103-205	UCCUUCAUCCmCmAmCmCmGmGAGUGsfUsmG	347
G104-205	UCCUUCAUCmCmCmAmCmCmGmGmAmGUGsfUsmG	348
G105-205	UCCUUCAUCmCmCmAmCmCmGmGmAGUGsfUsmG	349
G106-205	UCCUUCAUCmCmCmAmCmCmGmGAGUGsfUsmG	350
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G109-205	UCCUUCAUmCmCmCmAmCmCmGmGAGUGsfUsmG	353
G110-205	UCCUUCAUCCmCmUmCmCmGmGmAmGUCsfUsmG	354
G111-205	UCCUUCAUCCmCmUmCmCmGmGmAGUCsfUsmG	355
G112-205	UCCUUCAUCCmCmUmCmCmGmGAGUCsfUsmG	356
G113-205	UCCUUCAUCmCmCmUmCmCmGmGmAmGUCsfUsmG	357
G114-205	UCCUUCAUCmCmCmUmCmCmGmGmAGUCsfUsmG	358
G115-205	UCCUUCAUCmCmCmUmCmCmGmGAGUCsfUsmG	359
G116-205	UCCUUCAUmCmCmCmUmCmCmGmGmAmGUCsfUsmG	360
G117-205	UCCUUCAUmCmCmCmUmCmCmGmGmAGUCsfUsmG	361
G118-205	UCCUUCAUmCmCmCmUmCmCmGmGAGUCsfUsmG	362
G119-205	UCCUUCAUCCmCmUmCmCmGmGmAmGUGsfUsmG	363
G120-205	UCCUUCAUCCmCmUmCmCmGmGmAGUGsfUsmG	364
G121-205	UCCUUCAUCCmCmUmCmCmGmGAGUGsfUsmG	365
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G123-205	UCCUUCAUCmCmCmUmCmCmGmGmAGUGsfUsmG	367
G124-205	UCCUUCAUCmCmCmUmCmCmGmGAGUGsfUsmG	368
G125-205	UCCUUCAUmCmCmCmUmCmCmGmGmAmGUGsfUsmG	369
G126-205	UCCUUCAUmCmCmCmUmCmCmGmGmAGUGsfUsmG	370
G127-205	UCCUUCAUmCmCmCmUmCmCmGmGAGUGsfUsmG	371
G128-205	UCCUUCAUCUmCmCmAmCmCmGmGmAmGUGsfCsmU	372
G129-205	UCCUUCAUCUmCmCmAmCmCmGmGmAGUGsfCsmU	373
G130-205	UCCUUCAUCUmCmCmAmCmCmGmGAGUGsfCsmU	374
G131-205	UCCUUCAUCmUmCmCmAmCmCmGmGmAmGUGsfCsmU	375
G132-205	UCCUUCAUCmUmCmCmAmCmCmGmGmAGUGsfCsmU	376
G133-205	UCCUUCAUCmUmCmCmAmCmCmGmGAGUGsfCsmU	377
G134-205	UCCUUCAUmCmUmCmCmAmCmCmGmGmAmGUGsfCsmU	378
G135-205	UCCUUCAUmCmUmCmCmAmCmCmGmGmAGUGsfCsmU	379
G136-205	UCCUUCAUmCmUmCmCmAmCmCmGmGAGUGsfCsmU	380
G137-205	UCCUUCAUCUmCmCmAmCmCmGmGmAmGUGsfUsmG	381
G138-205	UCCUUCAUCUmCmCmAmCmCmGmGmAGUGsfUsmG	382
G139-205	UCCUUCAUCUmCmCmAmCmCmGmGAGUGsfUsmG	383
G140-205	UCCUUCAUCmUmCmCmAmCmCmGmGmAmGUGsfUsmG	384
G141-205	UCCUUCAUCmUmCmCmAmCmCmGmGmAGUGsfUsmG	385
G142-205	UCCUUCAUCmUmCmCmAmCmCmGmGAGUGsfUsmG	386

Oligo	Sequence (5′-3′)	SEQ ID NO:
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G144-205	UCCUUCAUmCmUmCmCmAmCmCmGmGmAGUGsfUsmG	388
G145-205	UCCUUCAUmCmUmCmCmAmCmCmGmGAGUGsfUsmG	389
G146-205	UCCUUCAUCUmCmCmUmCmCmGmGmAmGUGsfCsmU	390
G147-205	UCCUUCAUCUmCmCmUmCmCmGmGmAGUGsfCsmU	391
G148-205	UCCUUCAUCUmCmCmUmCmCmGmGAGUGsfCsmU	392
G149-205	UCCUUCAUCmUmCmCmUmCmCmGmGmAmGUGsfCsmU	393
G150-205	UCCUUCAUCmUmCmCmUmCmCmGmGmAGUGsfCsmU	394
G151-205	UCCUUCAUCmUmCmCmUmCmCmGmGAGUGsfCsmU	395
G152-205	UCCUUCAUmCmUmCmCmUmCmCmGmGmAmGUGsfCsmU	396
G153-205	UCCUUCAUmCmUmCmCmUmCmCmGmGmAGUGsfCsmU	397
G154-205	UCCUUCAUmCmUmCmCmUmCmCmGmGAGUGsfCsmU	398
G155-205	UCCUUCAUUCmCmAmCmCmGmGmAmGmUGCsfUsmG	399
G156-205	UCCUUCAUUCmCmAmCmCmGmGmAmGUGCsfUsmG	400
G157-205	UCCUUCAUUCmCmAmCmCmGmGmAGUGCsfUsmG	401
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G161-205	UCCUUCAUmUmCmCmAmCmCmGmGmAmGmUGCsfUsmG	405
G162-205	UCCUUCAUmUmCmCmAmCmCmGmGmAmGUGCsfUsmG	406
G163-205	UCCUUCAUmUmCmCmAmCmCmGmGmAGUGCsfUsmG	407
G164-205	UCCUUCAUUCmCmAmCmCmGmGmAmGUGsfUsmG	408
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G166-205	UCCUUCAUUCmCmAmCmCmGmGAGUGsfUsmG	410
G167-205	UCCUUCAUUmCmCmAmCmCmGmGmAmGUGsfUsmG	411
G168-205	UCCUUCAUUmCmCmAmCmCmGmGmAGUGsfUsmG	412
G169-205	UCCUUCAUUmCmCmAmCmCmGmGAGUGsfUsmG	413
G170-205	UCCUUCAUmUmCmCmAmCmCmGmGmAmGUGsfUsmG	414
G171-205	UCCUUCAUmUmCmCmAmCmCmGmGmAGUGsfUsmG	415
G172-205	UCCUUCAUmUmCmCmAmCmCmGmGAGUGsfUsmG	416
G173-205	UCCUUCAUUCmCmAmUmCmGmGmAmGmUGCsfUsmG	417
G174-205	UCCUUCAUUCmCmAmUmCmGmGmAmGUGCsfUsmG	418
G175-205	UCCUUCAUUCmCmAmUmCmGmGmAGUGCsfUsmG	419
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G177-205	UCCUUCAUUmCmCmAmUmCmGmGmAmGUGCsfUsmG	421
G178-205	UCCUUCAUUmCmCmAmUmCmGmGmAGUGCsfUsmG	422
G179-205	UCCUUCAUmUmCmCmAmUmCmGmGmAmGmUGCsfUsmG	423
G180-205	UCCUUCAUmUmCmCmAmUmCmGmGmAmGUGCsfUsmG	424
G181-205	UCCUUCAUmUmCmCmAmUmCmGmGmAGUGCsfUsmG	425
G182-205	UCCUUCAUUCmCmUmCmCmGmGmAmGUCsfUsmG	426
G183-205	UCCUUCAUUCmCmUmCmCmGmGmAGUCsfUsmG	427
G184-205	UCCUUCAUUCmCmUmCmCmGmGAGUCsfUsmG	428
G185-205	UCCUUCAUUmCmCmUmCmCmGmGmAmGUCsfUsmG	429
G186-205	UCCUUCAUUmCmCmUmCmCmGmGmAGUCsfUsmG	430
G187-205	UCCUUCAUUmCmCmUmCmCmGmGAGUCsfUsmG	431
G188-205	UCCUUCAUmUmCmCmUmCmCmGmGmAmGUCsfUsmG	432
G189-205	UCCUUCAUmUmCmCmUmCmCmGmGmAGUCsfUsmG	433
G190-205	UCCUUCAUmUmCmCmUmCmCmGmGAGUCsfUsmG	434

Oligo	Sequence (5′-3′)	SEQ ID NO:
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G192-205	UCCUUCAUUCmCmUmCmCmGmGmAGUGsfUsmG	436
G193-205	UCCUUCAUUCmCmUmCmCmGmGAGUGsfUsmG	437
G194-205	UCCUUCAUUmCmCmUmCmCmGmGmAmGUGsfUsmG	438
G195-205	UCCUUCAUUmCmCmUmCmCmGmGmAGUGsfUsmG	439
G196-205	UCCUUCAUUmCmCmUmCmCmGmGAGUGsfUsmG	440
G197-205	UCCUUCAUmUmCmCmUmCmCmGmGmAmGUGsfUsmG	441
G198-205	UCCUUCAUmUmCmCmUmCmCmGmGmAGUGsfUsmG	442
G199-205	UCCUUCAUmUmCmCmUmCmCmGmGAGUGsfUsmG	443
G206-205	UCCUUCAUACmCmAmCmCmGmGmAmGUCpfUpmG	846
G207-205	UCCUUCAUACmCmAmCmCmGmGmAGUCpfUpmG	847
G208-205	UCCUUCAUACmCmAmCmCmGmGAGUCpfUpmG	848
G209-205	UCCUUCAUAmCmCmAmCmCmGmGmAmGUCpfUpmG	849
G210-205	UCCUUCAUAmCmCmAmCmCmGmGmAGUCpfUpmG	850
G211-205	UCCUUCAUAmCmCmAmCmCmGmGAGUCpfUpmG	851
G212-205	UCCUUCAUmAmCmCmAmCmCmGmGmAmGUCpfUpmG	852
G213-205	UCCUUCAUmAmCmCmAmCmCmGmGmAGUCpfUpmG	853
G214-205	UCCUUCAUmAmCmCmAmCmCmGmGAGUCpfUpmG	854
G215-205	UCCUUCAUCCmCmAmCmCmGmGmAmGUCpfUpmG	855
G216-205	UCCUUCAUCCmCmAmCmCmGmGmAGUCpfUpmG	856
G217-205	UCCUUCAUCCmCmAmCmCmGmGAGUCpfUpmG	857
G218-205	UCCUUCAUCmCmCmAmCmCmGmGmAmGUCpfUpmG	858
G219-205	UCCUUCAUCmCmCmAmCmCmGmGmAGUCpfUpmG	859
G220-205	UCCUUCAUCmCmCmAmCmCmGmGAGUCpfUpmG	860
G221-205	UCCUUCAUmCmCmCmAmCmCmGmGmAmGUCpfUpmG	861
G222-205	UCCUUCAUmCmCmCmAmCmCmGmGmAGUCpfUpmG	862
G223-205	UCCUUCAUmCmCmCmAmCmCmGmGAGUCpfUpmG	863
G224-205	UCCUUCAUAUmCmCmAmCmCmGmGmAmGUCpfUpmG	864
G225-205	UCCUUCAUAUmCmCmAmCmCmGmGmAGUCpfUpmG	865
G226-205	UCCUUCAUAUmCmCmAmCmCmGmGAGUCpfUpmG	866
G227-205	UCCUUCAUAmUmCmCmAmCmCmGmGmAmGUCpfUpmG	867
G228-205	UCCUUCAUAmUmCmCmAmCmCmGmGmAGUCpfUpmG	868
G229-205	UCCUUCAUAmUmCmCmAmCmCmGmGAGUCpfUpmG	869
G230-205	UCCUUCAUmAmUmCmCmAmCmCmGmGmAmGUCpfUpmG	870
G231-205	UCCUUCAUmAmUmCmCmAmCmCmGmGmAGUCpfUpmG	871
G232-205	UCCUUCAUmAmUmCmCmAmCmCmGmGAGUCpfUpmG	872
G233-205	UCCUUCAUCUmCmCmAmCmCmGmGmAmGUCpfUpmG	873
G234-205	UCCUUCAUCUmCmCmAmCmCmGmGmAGUCpfUpmG	874
G235-205	UCCUUCAUCUmCmCmAmCmCmGmGAGUCpfUpmG	875
G236-205	UCCUUCAUCmUmCmCmAmCmCmGmGmAmGUCpfUpmG	876
G237-205	UCCUUCAUCmUmCmCmAmCmCmGmGmAGUCpfUpmG	877
G238-205	UCCUUCAUCmUmCmCmAmCmCmGmGAGUCpfUpmG	878
G239-205	UCCUUCAUmCmUmCmCmAmCmCmGmGmAmGUCpfUpmG	879
G240-205	UCCUUCAUmCmUmCmCmAmCmCmGmGmAGUCpfUpmG	880
G241-205	UCCUUCAUmCmUmCmCmAmCmCmGmGAGUCpfUpmG	881
G242-205	UCCUUCAUCAmCmCmAmCmCmGmGmAmGUCpfUpmG	882
G243-205	UCCUUCAUCAmCmCmAmCmCmGmGmAGUCpfUpmG	883
G244-205	UCCUUCAUCAmCmCmAmCmCmGmGAGUCpfUpmG	884

Oligo	Sequence (5′-3′)	SEQ ID NO:
G245-205	UCCUUCAUCmAmCmCmAmCmCmGmGmAmGUCpfUpmG	885
G246-205	UCCUUCAUCmAmCmCmAmCmCmGmGmAGUCpfUpmG	886
G247-205	UCCUUCAUCmAmCmCmAmCmCmGmGAGUCpfUpmG	887
G248-205	UCCUUCAUmCmAmCmCmAmCmCmGmGmAmGUCpfUpmG	888
G249-205	UCCUUCAUmCmAmCmCmAmCmCmGmGmAGUCpfUpmG	889
G250-205	UCCUUCAUmCmAmCmCmAmCmCmGmGAGUCpfUpmG	890
G251-205	UCCUUCAUAUmCmCmUmCmCmGmGmAmGUCpfUpmG	891
G252-205	UCCUUCAUAUmCmCmUmCmCmGmGmAGUCpfUpmG	892
G253-205	UCCUUCAUAUmCmCmUmCmCmGmGAGUCpfUpmG	893
G254-205	UCCUUCAUAmUmCmCmUmCmCmGmGmAmGUCpfUpmG	894
G255-205	UCCUUCAUAmUmCmCmUmCmCmGmGmAGUCpfUpmG	895
G256-205	UCCUUCAUAmUmCmCmUmCmCmGmGAGUCpfUpmG	896
G257-205	UCCUUCAUmAmUmCmCmUmCmCmGmGmAmGUCpfUpmG	897
G258-205	UCCUUCAUmAmUmCmCmUmCmCmGmGmAGUCpfUpmG	898
G259-205	UCCUUCAUmAmUmCmCmUmCmCmGmGAGUCpfUpmG	899
P001-205	Amino C6-mGmAmUUUCAGUGGAGUGAAGmUmUmC	444
G001-338	UCCAGCAUCAmGmUmGmAmUmUmUmUGUsfUsmG	445
G002-338	UCCAGCAUCAmGmUmGmAmUmUmUUGUsfUsmG	446
G003-338	UCCAGCAUCAmGmUmGmAmUmUUUGUsfUsmG	447
G004-338	UCCAGCAUCmAmGmUmGmAmUmUmUmUGUsfUsmG	448
G005-338	UCCAGCAUCmAmGmUmGmAmUmUmUUGUsfUsmG	449
G006-338	UCCAGCAUCmAmGmUmGmAmUmUUUGUsfUsmG	450
G007-338	UCCAGCAUmCmAmGmUmGmAmUmUmUmUGUsfUsmG	451
G008-338	UCCAGCAUmCmAmGmUmGmAmUmUmUUGUsfUsmG	452
G009-338	UCCAGCAUmCmAmGmUmGmAmUmUUUGUsfUsmG	453
P001-338	Amino C6-mAmAmCAAUAUCCUGGUGCUGAmGmUmG	454
G001-375	UUUGUUCGUUmCmGmGmCmUmCmGmCGUsfGsmA	455
G002-375	UUUGUUCGUUmCmGmGmCmUmCmGCGUsfGsmA	456
G003-375	UUUGUUCGUUmCmGmGmCmUmCGCGUsfGsmA	457
G004-375	UUUGUUCGUmUmCmGmGmCmUmCmGmCGUsfGsmA	458
G005-375	UUUGUUCGUmUmCmGmGmCmUmCmGCGUsfGsmA	459
G006-375	UUUGUUCGUmUmCmGmGmCmUmCGCGUsfGsmA	460
G007-375	UUUGUUCGmUmUmCmGmGmCmUmCmGmCGUsfGsmA	461
G008-375	UUUGUUCGmUmUmCmGmGmCmUmCmGCGUsfGsmA	462
G009-375	UUUGUUCGmUmUmCmGmGmCmUmCGCGUsfGsmA	463
P001-375	Amino C6-mGmCmGACGAGCCCCUCGCACAAmAmCmC	464
G001-E1	UUGAGAAGGAGGCUGCUGAGA	465
P001-E1	UCAGCAGCCUCCUUCUAA	466

Table 4 – Mimic/mimetic composition

Mimic name	Guide Strand	Passenger Strand
M30-021	G039-30 (SEQ ID NO. 67)	P014-30 (SEQ ID NO. 95)
M30-025	G032-30 (SEQ ID NO. 65)	P014-30 (SEQ ID NO. 95)
M30-033	G042-30 (SEQ ID NO. 69)	P014-30 (SEQ ID NO. 95)
M30-034	G042-30 (SEQ ID NO. 69)	P123-30 (SEQ ID NO. 96)
M30-035	G121-30 (SEQ ID NO. 83)	P123-30 (SEQ ID NO. 96)
M30-036	G122-30 (SEQ ID NO. 84)	P123-30 (SEQ ID NO. 96)

Mimic name	Guide Strand	Passenger Strand
M30-037	G011-30 (SEQ ID NO. 55)	P123-30 (SEQ ID NO. 96)
M30-038	G121-30 (SEQ ID NO. 83)	P014-30 (SEQ ID NO. 95)
M30-039	G039-30 (SEQ ID NO. 67)	P123-30 (SEQ ID NO. 96)
M30-040	G032-30 (SEQ ID NO. 65)	P123-30 (SEQ ID NO. 96)
M30-042	G128-30 (SEQ ID NO. 85)	P123-30 (SEQ ID NO. 96)
M30-043	G129-30 (SEQ ID NO. 86)	P123-30 (SEQ ID NO. 96)
M30-044	G032-30 (SEQ ID NO. 65)	P126-30 (SEQ ID NO. 97)
M30-046	G130-30 (SEQ ID NO. 87)	P123-30 (SEQ ID NO. 96)
M30-047	G130-30 (SEQ ID NO. 87)	P126-30 (SEQ ID NO. 97)
M30-048	G132-30 (SEQ ID NO. 88)	P123-30 (SEQ ID NO. 96)
M30-049	G133-30 (SEQ ID NO. 89)	P131-30 (SEQ ID NO. 99)
M29-002	miR-29a-3p (SEQ ID NO. 12)	P009-29 (SEQ ID NO. 175)
M29-004	miR-29b-3p (SEQ ID NO. 13)	P004-29 (SEQ ID NO. 170)
M29-005	miR-29b-3p (SEQ ID NO. 13)	P005-29 (SEQ ID NO. 171)
M29-006	miR-29b-3p (SEQ ID NO. 13)	P006-29 (SEQ ID NO. 172)
M29-007	miR-29b-3p (SEQ ID NO. 13)	P007-29 (SEQ ID NO. 173)
M29-008	miR-29b-3p (SEQ ID NO. 13)	P011-29 (SEQ ID NO. 176)
M29-009	G013-29 (SEQ ID NO. 108)	P007-29 (SEQ ID NO. 173)
M29-010	G013-29 (SEQ ID NO. 108)	P006-29 (SEQ ID NO. 172)
M29-011	G003-29 (SEQ ID NO. 102)	P007-29 (SEQ ID NO. 173)
M29-012	G003-29 (SEQ ID NO. 102)	P011-29 (SEQ ID NO. 176)
M29-013	G004-29 (SEQ ID NO. 103)	P011-29 (SEQ ID NO. 176)
M29-014	G004-29 (SEQ ID NO. 103)	P007-29 (SEQ ID NO. 173)
M29-015	G005-29 (SEQ ID NO. 104)	P011-29 (SEQ ID NO. 176)
M29-016	G005-29 (SEQ ID NO. 104)	P007-29 (SEQ ID NO. 173)
M29-017	G006-29 (SEQ ID NO. 105)	P011-29 (SEQ ID NO. 176)
M29-018	G006-29 (SEQ ID NO. 105)	P007-29 (SEQ ID NO. 173)
M29-019	G007-29 (SEQ ID NO. 106)	P011-29 (SEQ ID NO. 176)
M29-020	G007-29 (SEQ ID NO. 106)	P007-29 (SEQ ID NO. 173)
M29-023	miR-29a-3p (SEQ ID NO. 12)	P008-29 (SEQ ID NO. 174)
M29-024	G009-29 (SEQ ID NO. 127)	P007-29 (SEQ ID NO. 173)
M29-025	G009-29 (SEQ ID NO. 127)	P011-29 (SEQ ID NO. 176)
M29-026	G009-29 (SEQ ID NO. 127)	P005-29 (SEQ ID NO. 171)
M29-027	G010-29 (SEQ ID NO. 128)	P007-29 (SEQ ID NO. 173)
M29-028	G010-29 (SEQ ID NO. 128)	P011-29 (SEQ ID NO. 176)
M29-029	G011-29 (SEQ ID NO. 129)	P007-29 (SEQ ID NO. 173)
M29-030	G011-29 (SEQ ID NO. 129)	P011-29 (SEQ ID NO. 176)
M29-031	G012-29 (SEQ ID NO. 130)	P007-29 (SEQ ID NO. 173)
M29-032	G012-29 (SEQ ID NO. 130)	P011-29 (SEQ ID NO. 176)
M29-033	G014-29 (SEQ ID NO. 131)	P007-29 (SEQ ID NO. 173)
M29-034	G014-29 (SEQ ID NO. 131)	P011-29 (SEQ ID NO. 176)
M29-035	G015-29 (SEQ ID NO. 620)	P011-29 (SEQ ID NO. 176)
M29-036	G015-29 (SEQ ID NO. 620)	P012-29 (SEQ ID NO. 838)
M29-037	G016-29 (SEQ ID NO. 835)	P011-29 (SEQ ID NO. 176)
M29-038	G016-29 (SEQ ID NO. 835)	P012-29 (SEQ ID NO. 838)
M29-039	G007-29 (SEQ ID NO. 106)	P013-29 (SEQ ID NO. 177)
M29-040	G017-29 (SEQ ID NO. 836)	P013-29 (SEQ ID NO. 177)
M29-041	G018-29 (SEQ ID NO. 837)	P014-29 (SEQ ID NO. 839)
E1-001	G001-E1 (SEQ ID NO. 465)	P001-E1 (SEQ ID NO. 466)

~~[00102]~~[00103] For example, an engineered oligonucleotide or salt thereof can comprise at least about 80% sequence identity to an oligonucleotide of 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. For example, an engineered oligonucleotide or salt thereof can comprise at least about 90% sequence identity to an oligonucleotide of 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. In some cases, an engineered oligonucleotide or salt thereof can comprise from about 80% to 100% sequence identity to an oligonucleotide of 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. In some cases, an engineered oligonucleotide or salt thereof can comprise from about 85% to 100% sequence identity to an oligonucleotide of 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. In some cases, an engineered oligonucleotide or salt thereof can comprise at least 80% sequence identity to at least about 10 contiguous bases of 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. In some cases, an engineered oligonucleotide or salt thereof can comprise at least 85% sequence identity to at least about 10 contiguous bases of 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.

~~[00103]~~[00104] In some cases, the engineered oligonucleotide can comprise at least about: 70%, 75%, 80%, 85%, 90%, 95% sequence identity to any one of SEQ ID NOs: 1-5, 12-14, 19-20, 24-25, 28, 30, 32, 34, 36, 38-45, 100-126, 245-263, 465, 624-643, 840-845, and 901-949, or any combination thereof.

~~[00104]~~[00105] In some cases, a second strand can comprise at least about: 70%, 75%, 80%, 85%, 90%, 95% sequence identity to any one of SEQ ID NOs: 6-11, 15-18, 21-23, 26-27, 29, 31, 33, 35, 37, 46-51, 90-99, 155-183, 202-204, 223-224, 234-244, 444, 454, 464, 466, 838-839, or any combination thereof. In some cases, the second strand can comprise at least about: 70%, 75%, 80%, 85%, 90%, 95% sequence identity to any one of: SEQ ID NOs: 51, 95-99, or any combination thereof.

~~[00105]~~[00106] For example, an engineered oligonucleotide or salt thereof can comprise at least about 80% sequence identity to an oligonucleotide of any one of SEQ ID NO: 587, SEQ ID NO: 588, SEQ ID NO: 589, SEQ ID NO: 500, SEQ ID NO: 513, SEQ ID NO: 518, SEQ ID NO: 476, SEQ ID NO: 481, or SEQ ID NO: 495. For example, an engineered oligonucleotide or salt thereof can comprise at least about 90% sequence identity to an oligonucleotide of any one of SEQ ID NO: 587, SEQ ID NO: 588, SEQ ID NO: 589, SEQ ID NO: 500, SEQ ID NO: 513, SEQ ID NO: 518, SEQ ID NO: 476, SEQ ID NO: 481, or SEQ ID NO: 495. In some cases, an engineered oligonucleotide or salt thereof can comprise from about 80% to 100% sequence identity to an oligonucleotide of any one of SEQ ID NO: 587, SEQ ID NO: 588, SEQ ID NO: 589, SEQ ID NO: 500, SEQ ID NO: 513, SEQ ID NO: 518, SEQ ID NO: 476, SEQ ID NO: 481, or SEQ ID NO: 495. In some cases, an engineered oligonucleotide or salt thereof can comprise from about 85% to 100% sequence identity to an oligonucleotide of any one of SEQ ID NO: 587, SEQ ID NO: 588, SEQ ID NO: 589, SEQ ID NO: 500, SEQ ID NO: 513, SEQ ID NO: 518, SEQ ID NO: 476, SEQ ID NO: 481, or SEQ ID NO: 495. In some cases, an engineered oligonucleotide or salt thereof can comprise at least 80% sequence identity to at least about 10 contiguous bases of any one of SEQ ID NO: 587, SEQ ID NO: 588, SEQ ID NO: 589, SEQ ID NO: 500, SEQ ID NO: 513, SEQ ID NO: 518, SEQ ID NO: 476, SEQ ID NO: 481, or SEQ ID NO: 495. In some cases, an engineered oligonucleotide or salt thereof can comprise at least 85% sequence identity to at least about 10 contiguous bases of any one of SEQ ID NO: 587, SEQ ID NO: 588, SEQ ID NO: 589, SEQ ID NO: 500, SEQ ID NO: 513, SEQ ID NO: 518, SEQ ID NO: 476, SEQ ID NO: 481, or SEQ ID NO: 495.

~~[00106]~~[00107] In some cases, an engineered oligonucleotide or salt thereof can comprise at least about: 1%, 2%, 5%, 7%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20% lower Gibbs free energy (ΔG) of binding to the RNA sequence at about 37 degrees Celsius and at about pH 7.2 . In some cases, an engineered oligonucleotide or salt thereof can bind the RNA sequence at about 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 or 40 degrees Celsius. In some cases, an engineered oligonucleotide or salt thereof can bind the RNA sequence at a pH of about 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, or 7.8.

~~[00107]~~[00108] The terms “administer,” “administering”, “administration,” and the like, as used herein, can refer to methods that can be used to enable delivery of compounds or compositions to the desired site of biological action. Delivery can include direct application to the affect tissue or region of the body. Delivery can include a parenchymal injection, an intra-thecal injection, an intra-ventricular injection, or an intra-cisternal injection. A composition provided herein can be administered by any method. A method of administration can be by inhalation, intraarterial injection, intracerebroventricular injection, intracisternal injection, intramuscular injection, intraorbital injection, intraparenchymal injection, intraperitoneal injection, intraspinal injection, intrathecal injection, intravenous injection, intraventricular injection, stereotactic injection, subcutaneous injection, or any combination thereof. Delivery can include parenteral administration (including intravenous, subcutaneous, intrathecal, intraperitoneal, intramuscular, intravascular or infusion), oral administration, inhalation administration, intraduodenal administration, rectal administration. Delivery can include topical administration (such as a lotion, a cream, an ointment) to an external surface of a surface, such as a skin. In some instances, a subject can administer the composition in the absence of supervision. In some instances, a subject can administer the composition under the supervision of a medical professional (e.g., a physician, nurse, physician’s assistant, orderly, hospice worker, etc.). In some cases, a medical professional can administer the composition. In some cases, a cosmetic professional can administer the composition.

~~[00108]~~[00109] The term “subject,” “host,” “individual,” and “patient” are as used interchangeably here-in to refer to animals, typically mammalian animals. Any suitable mammal can be administered a composition as described herein (such as an engineered oligonucleotide) or treated by a method as described herein. Non-limiting examples of mammals include humans, non-human primates (e.g., apes, gibbons, chimpanzees, orangutans, monkeys, macaques, and the like), domestic animals (e.g., dogs and cats), farm animals (e.g., horses, cows, goats, sheep, pigs) and experimental animals (e.g., mouse, rat, rabbit, guinea pig). Mammals can be any age or at any stage of development, for example a mammal can be neonatal, infant, adolescent, adult or in utero. In some embodiments a mammal can be a human. Humans can be more than about: 1, 2, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 years of age. Humans can be less than about: 1, 2, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 years of age. A mammal can be male or female. In some embodiments a subject can be a human. In some embodiments, a subject may be suspected of having a disease or condition. The subject can be a patient, such as a patient being treated for a condition or a disease, such as a cancer, a fibrosis condition, or a viral infection patient. The subject may be predisposed to a risk of developing a condition or a disease such as cancer. The subject may be in remission from a condition or a disease, such as a cancer patient. The subject may be healthy.

~~[00109]~~[00110] The term “mammalian cell” can refer to any mammalian cell, typically a human cell. In some embodiments the human cell can be a cell of head or neck tissue, a skin cell, a cervical cell, a prostate cell, a stem cell, a bone cell, a blood cell, a muscle cell, a fat cell, a nerve cell, an endothelial cell, sperm cell, egg cell, cancer cell, barrier cell, hormone-secreting cell, exocrine-secretory cell, epithelial cell, oral cell, sensory transducer cell, autonomic neuron cell, peripheral neuron cell, central nervous neuron cell, secretory cell, barrier cell, muscle cell, cardiac muscle cell, white blood cell, germ cell, nurse cell, kidney cell, or any combination thereof.

~~[00110]~~[00111] As used herein, cancer refers to a disease caused by an uncontrolled division of abnormal cells in a part of the body. Those cells can be of different types selected from a list maintained by the National Cancer Institute (https://www.cancer.gov/types).

~~[00111]~~[00112] As used herein, "treating" of cancer can include one or more of: reducing the frequency and/or severity of symptoms, elimination of symptoms and/or their underlying cause, and improvement or remediation of damage. For example, treatment of cancer can include, for example, relieving the pain experienced by a mammal suffering from cancer, and/or causing the regression or disappearance of cancer. Treating may also include: reduced malaise, cessation of cancer side effects, abatement of tumors, or any combination thereof. Treating can include administering an engineered oligonucleotide 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, and 840-899, or any combination thereof. As used herein, “treating” of fibrosis, scarring, or both can include one or more of: reducing the frequency and/or severity of symptoms, elimination of symptoms and/or their underlying cause, and improvement or remediation of damage. For example, treatment of fibrosis can include, for example, relieving shortness of breath experienced by a mammal suffering from pulmonary fibrosis, and/or causing the regression or disappearance of fibrosis. Treating may also include: reduced malaise, cessation of fibrosis or scarring side effects, abatement of fibrotic tissue, or any combination thereof. Treating can include administering an engineered oligonucleotide of SEQ ID NOs: 1-5, 12-14, 19-20, 38-45, 52-89, 100-154, 184-201, 620, 624-825, and 835-837, or any combination thereof. As used herein, “treating” of a viral infection can include one or more of: reducing the frequency and/or severity of symptoms, elimination of symptoms and/or their underlying cause, elimination of the infectious disease, and improvement or remediation of damage. For example, treatment of a viral infection can include, for example, relieving the cough experienced by a mammal suffering from a viral infection, and/or causing the regression or disappearance of a viral infection. Treating may also include: reduced malaise, cessation of viral infection side effects, abatement of a viral infection, or any combination thereof. Treating can include administering an

engineered oligonucleotide of SEQ ID NOs: 1-5, 12-14, 19-20, 38-45, 52-89, 100-154, 184-201, 620, 624-825, and 835-837, or any combination thereof.

~~[00112]~~[00113] As used herein, "treating" of muscular dystrophy can include one or more of: reducing the frequency and/or severity of symptoms, elimination of symptoms and/or their underlying cause, and improvement or remediation of damage. For example, treatment of muscular dystrophy can include, for example, relieving the muscle weakness experienced by a mammal suffering from muscular dystrophy, and/or causing the regression or disappearance of muscle weakness. Treating may also include: reduced malaise, cessation of myotonia, abatement of muscle pain, or any combination thereof. Treating can include administering an engineered oligonucleotide of SEQ ID NOs: 12-14, 30, 100-154, 235-243, 620, 835-837, and 901-949, or any combination thereof.

Table 5 – ASOs

Oligo	Sequence (5′-3′)	SEQ ID NO:	Targeted mRNA SEQ ID NOs:
AS-DX-003	TCCAAACGAGTCTCCG	901	954, 1017, 1046, 1112
AS-DX-004	GATTCTGAAACCAGA	902	958, 994, 1004, 1040, 1057, 1111
AS-DX-005	GCGGGCGCCCTGCCAC	903	1030, 1047, 1104
AS-DX-006	TCATCCAGCAGCAGGC	904	981, 1025, 1068, 1069, 1113
AS-DX-007	TAGCCAGCCAGGTGTT	905	966, 967, 997, 1056
AS-DX-008	CAGCGTCGGAAGGTGG	906	955, 999, 1071, 1092, 1118
AS-DX-009	TAGACAGCGTCGGAAG	907	1021, 1051, 1094
AS-DX-010	ATAGGATCCACAGGGA	908	1032, 1065, 1107
AS-DX-011	TCTATAGGATCCACAG	909	1032, 1067, 1075, 1106
AS-DX-012	GCACTAATCATCCAGG	910	957, 1035, 1042
AS-DX-014	CAGCGTCGGAAGGTG	911	955, 999, 1071, 1092, 1118
AS-DX-015	CCTAGACAGCGTCGGAAGGT	912	955, 999, 1071, 1092, 1118
AS-DX-018	ATAGGATCCACAGGGAGG	913	1012, 1065

Oligo	Sequence (5′-3′)	SEQ ID NO:	Targeted mRNA SEQ ID NOs:
AS-DX-019	CGGCTCTGGGATCCCCGG	914	973, 1011
AS-DX-021	GGGGCGGAGACACGCCC	915	986, 1028
AS-DX-022	AGAAGGCAGGAATCCCAG	916	976, 1019
AS-DX-023	GCAGGAATCCCAGGCCGG	917	972, 1010
AS-DX-025	GGAGTCTCTCACCGGGCC	918	984, 1026, 1076
AS-DX-036	GCGAGGCGGCCTCTTCCG	919	964, 989, 1033, 1064
AS-DX-037	GCCTCCAGCTCCCCCGGG	920	980, 992, 1024
AS-DX-038	GGTGTCGGGAGGGCCAT	921	1006, 1039, 1108
AS-DX-055	CGGTATTCTTCCTCGCTG	922	952, 963, 991, 1036, 1082
AS-DX-060	GGGCATTTTAATATATCTCTGAACT	923	1003, 1074, 1085
AS-DX-061	TATCTTCTGAACTAATCATCCA	924	957, 1035, 1042
AS-DX-062	CAGGAGATGTAACTCTAATCCAG	925	1018, 1059, 1090, 1101, 1105, 1119
AS-DX-063	CTCTCACCGGGCCTAGACCTAGAAG	926	987, 1034, 1077, 1109
AS-DX-064	TGCGCACTGCGCGCAGGTCTAGCCA	927	1014, 1043, 1091, 1103
AS-DX-065	ACTGCGCGCAGGTCTAGCCAGGAAG	928	1031, 1001, 1072, 1084, 1089
AS-DX-066	CGGGGTGCGCACTGCGCGCAGGTCT	929	998, 1048, 1049, 1050, 1097, 1102
AS-DX-067	TGCGCACTGCGCGCAGGTCTAGCCAGGAAG	930	960, 978, 1001
AS-DX-068	ACTGCGCGCAGGTCTAGCCAGGAAGCGGGC	931	974, 1031, 1089, 1110
AS-DX-069	ACCCGACCCCGTCCCAACCCCGCGT	932	968, 1000, 1081, 1095
AS-DX-070	TGGGCTGGTGGAGAGGCAG	933	975, 1013, 1054, 1120
AS-DX-074	TTCCCTGCATGTTTCCGGGTGCCCG	934	983, 1061
AS-DX-075	CTTCCCTGCATGTTTCCGG	935	971, 1063
AS-DX-076	TGTGGCTCTCGTTCATTTC	936	977, 1096
AS-DX-077	CTCCGTGGGAGTCTTGAGTGTGCCA	937	950, 961, 982, 1070, 1073

Oligo	Sequence (5′-3′)	SEQ ID NO:	Targeted mRNA SEQ ID NOs:
AS-DX-078	TGGAACTGAACCTCCGTGG	938	965, 988, 1066
AS-DX-080	CACCCCTTCATGAATGGCGCC	939	979, 995, 1052, 1083
AS-DX-081	ACAGGCTCCACCCCTTCATG	940	970, 1044, 1045, 1088, 1114
AS-DX-082	TTCCGCTCAAAGCAGGCCTC	941	953, 1022, 1116
AS-DX-083	AAAGCGATCCTTCTCAAAGGCTCGG	942	993, 1023, 1041, 1078
AS-DX-084	CCTGCGCGGGCGCCCTGCCGC	943	951, 1030, 1098, 1115
AS-DX-085	TATCTCTGAACTAATCATC	944	956, 1005, 1053
AS-DX-086	AGCGCCTGGCGGCGGAACGCAGACC	945	990, 1058, 1093
AS-DX-087	ATCTCTGCCCGCCTTCCCTCCCGCC	946	985, 1087, 1100
AS-DX-088	AAACCAGATCTGAATCCTGGAC	947	959, 962, 1029, 1055, 1060
AS-DX-089	TTTCTAGGAGAGGTTGCGCCTG	948	969, 1008, 1079
AS-DX-097	CCTAGACAGCGTCGGAAGGTAG	949	955, 999, 1071, 1092, 1118

~~[00113]~~[00114] A regulatory non-coding RNA (ncRNA) comprises short non-coding RNA sequences expressed in a genome that regulates expression or function of other biomolecules in mammalian cells. An ncRNA is generally < 200 nucleotides in length and can be single stranded or double stranded, and may form non-linear secondary or tertiary structures. An ncRNA can comprise exogenously derived small interfering RNA (siRNA), MicroRNA (miRNA), small nuclear RNA (U-RNA), Small nucleolar RNA (snoRNA), Piwi-interacting RNA (piRNA), repeat associated small interfering RNA (rasiRNA), small rDNA-derived RNA (srRNA), transfer RNA derived small RNA (tsRNA), ribosomal RNA derived small RNA (rsRNA), large non-coding RNA derived small RNA (lncsRNA), or a messenger RNA derived small RNA (msRNA).

~~[00114]~~[00115] An engineered oligonucleotide can comprise DNA or RNA. In some cases, an engineered oligonucleotide can comprise a plurality of nucleotides. In some cases, an engineered oligonucleotide can comprise an artificial nucleic acid analogue. In some cases, an engineered

oligonucleotide can comprise DNA, can comprise cell-free DNA, cDNA, fetal DNA, viral DNA, or maternal DNA. In some cases, an engineered oligonucleotide can comprise an shRNA, or siRNA, an ncRNA mimic, a short-harpin RNA (shRNA), a dicer-dependent siRNA (di-siRNA), an antisense oligonucleotide (ASO), a gapmer, a mixmer, double-stranded RNAs (dsRNA), single stranded RNAi, (ssRNAi), DNA-directed RNA interference (ddRNAi), an RNA activating oligonucleotide (RNAa), or an exon skipping oligonucleotide. In some cases, an engineered oligonucleotide can comprise a completely synthetic miRNA. A completely synthetic miRNA is one that is not derived or based upon an ncRNA. Instead, a completely synthetic miRNA may be based upon an analysis of multiple potential target sequences or may be based upon isolated natural non-coding sequences that are not ncRNAs. One example of a completely synthetic miRNA is E1-001 (Table 4).

~~[00115]~~[00116] A diagnostic test can comprise an imaging procedure, a blood count analysis, a tissue pathology analysis, a biomarker analysis, a biopsy, a magnetic resonance image procedure, a physical examination, a urine test, an ultrasonography procedure, a genetic test, a liver function test, a positron emission tomography procedure, a X-ray, serology, an angiography procedure, an electrocardiography procedure, an endoscopy, a diagnostic polymerase chain reaction test (PCR), a pap smear, a hematocrit test, a skin allergy test, a urine test, a colonoscopy, an enzyme-linked immunosorbent assay (ELISA), microscopy analysis, bone marrow examination, rapid diagnostic test, pregnancy test, organ function test, toxicology test, infectious disease test, bodily fluids test, or any combination thereof.

~~[00116]~~[00117] A pharmaceutical composition can comprise a first active ingredient. The first active ingredient can comprise an engineered oligonucleotide as described herein. The pharmaceutical composition can be formulated in unit dose form. The pharmaceutical composition can comprise a pharmaceutically acceptable excipient, diluent, or carrier. The pharmaceutical composition can comprise a second, third, or fourth active ingredient, such as a second engineered oligonucleotide.

~~[00117]~~[00118] A composition described herein can compromise an excipient. An excipient can comprise a pH agent (to minimize oxidation or degradation of a component of the composition), a stabilizing agent (to prevent modification or degradation of a component of the composition), a buffering agent (to enhance temperature stability), a solubilizing agent (to increase protein solubility), or any combination thereof. An excipient can comprise a surfactant, a sugar, an amino acid, an antioxidant, a salt, a non-ionic surfactant, a solubilizer, a triglyceride, an alcohol, or any combination thereof. An excipient can comprise sodium carbonate, acetate, citrate, phosphate, poly-ethylene glycol (PEG), human serum albumin (HSA), sorbitol, sucrose, trehalose, polysorbate 80, sodium phosphate, sucrose, disodium phosphate, mannitol, polysorbate 20, histidine, citrate, albumin, sodium hydroxide, glycine, sodium citrate, trehalose, arginine, sodium acetate, acetate, HCl, disodium edetate, lecithin, glycerin, xanthan rubber, soy isoflavones, polysorbate 80, ethyl alcohol, water, teprenone, or any combination thereof. An excipient can be an excipient described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986).

~~[00118]~~[00119] Administration or application of a composition disclosed herein can be performed for a treatment duration of at least about at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 days consecutive or nonconsecutive days. In some cases, a treatment duration can be from about 1 to about 30 days, from about 2 to about 30 days, from about 3 to about 30 days, from about 4 to about 30 days, from about 5 to about 30 days, from about 6 to about 30 days, from about 7 to about 30 days, from about 8 to about 30 days, from about 9 to about 30 days, from about 10 to about 30 days, from about 11 to about 30 days, from about 12 to about 30 days, from about 13 to about 30 days, from about 14 to about 30 days, from about 15 to about 30 days, from about 16 to about 30 days, from about 17 to about 30 days, from about 18 to about 30 days, from about 19 to about 30 days, from about 20 to about 30 days,

from about 21 to about 30 days, from about 22 to about 30 days, from about 23 to about 30 days, from about 24 to about 30 days, from about 25 to about 30 days, from about 26 to about 30 days, from about 27 to about 30 days, from about 28 to about 30 days, or from about 29 to about 30 days.

~~[00119]~~[00120] Administration or application of a composition disclosed herein can be performed for a treatment duration of at least about 1 week, at least about 1 month, at least about 1 year, at least about 2 years, at least about 3 years, at least about 4 years, at least about 5 years, at least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, at least about 10 years, at least about 15 years, at least about 20 years, or more. Administration can be performed repeatedly over a lifetime of a subject, such as once a month or once a year for the lifetime of a subject. Administration can be performed repeatedly over a substantial portion of a subject's life, such as once a month or once a year for at least about 1 year, 5 years, 10 years, 15 years, 20 years, 25 years, 30 years, or more.

~~[00120]~~[00121] Administration or application of composition disclosed herein can be performed at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 times a day. In some cases, administration or application of composition disclosed herein can be performed at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 times a week. In some cases, administration or application of composition disclosed herein can be performed at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, or 90 times a month.

~~[00121]~~[00122] In some cases, a composition can be administered/applied as a single dose or as divided doses. In some cases, the compositions described herein can be administered at a first time point and a second time point. In some cases, a composition can be administered such that a first administration is administered before the other with a difference in administration time of 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 16 hours, 20 hours, 1 day, 2 days, 4 days, 7 days, 2

weeks, 4 weeks, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year or more.

~~[00122]~~[00123] In some cases, an engineered oligonucleotide or salt thereof comprising a modification when contacted with an mRNA sequence can produce lower activity of a polypeptide encoded by the mRNA sequence as compared to contacting an equivalent amount of an otherwise comparable oligonucleotide that lacks the modification with the mRNA sequence. In some cases, the lower activity can be at least about 1.2-fold lower. In some cases, the lower activity can be at least about 1.5-fold lower. In some cases, the lower activity can be at least about 1.7-fold lower. In some cases, the lower activity can be at least about 2.0-fold lower. In some cases, the lower activity can be about: 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5-fold lower. In some cases, the lower activity can be from about 1.2-fold to about 2.0-fold lower. In some cases, the lower activity can be from about 1.1-fold to about 1.5-fold lower. In some cases, the lower activity can be from about 1.1-fold to about 2.5-fold lower. In some cases, the lower activity can be from about 1.2-fold to about 3.0-fold lower. In some cases, the lower activity can be at least about 1.2-fold to about at least 10-fold lower expression. In some cases, the lower activity can be at least about 14-fold lower. In some cases, the lower expression can be at least about 18-fold lower expression. In some cases, the lower activity can be about: 1.2, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20-fold lower. In some cases, the lower activity can be from about 1.2-fold to about 14-fold. In some cases, the lower activity can be from about 1.1-fold to about 20-fold lower. In some cases, the lower activity can be from about 1.2-fold to about 30-fold lower.

~~[00123]~~[00124] In some cases, an engineered oligonucleotide or salt thereof comprising a modification when stored in a closed container placed in a room for a time period will remain at least about 80% of an initial amount of the engineered oligonucleotide or salt thereof. In some cases, the engineered oligonucleotide will remain at least about 70% the initial amount. In some cases, the engineered oligonucleotide will remain at least about 90% the initial amount. In some cases, the engineered oligonucleotide will remain at least about: 60%, 65%, 70%, 75%, 80%,

85%, 90%, 95%, 99%. In some cases, the engineered nucleotide can be at least about 60% to about at least 80%. In some cases, the engineered nucleotide can be at least about 80% to at least about 99%. In some cases, the time period of storage can be at least 1 month. In some cases, the time period of storage can be at least about 3 months. In some cases, the time period of storage can be at least about 1 year. In some cases, the time period of storage can be at least about 1, 2, 4, 6, 8, 12, 18, 24, 36, 48 or 60 months. In some cases, the time period of storage can be at least about 1 month to about at least 1 year. In some cases, the time period of storage can be at least about 6 months to at least about 2 years. In some cases, the time period of storage can be at least about 1 month to at least about 5 years.

The term "tissue" as used herein, can be any tissue sample. A tissue can be a tissue suspected or confirmed of having a disease or condition. A tissue can be a sample that may be substantially healthy, substantially benign, or otherwise substantially free of a disease or a condition. A tissue can be a tissue removed from a subject, such as a tissue biopsy, a tissue resection, an aspirate (such as a fine needle aspirate), a tissue washing, a cytology specimen, a bodily fluid, or any combination thereof. A tissue can comprise cancerous cells, tumor cells, non-cancerous cells, or a combination thereof. A tissue can comprise a blood sample (such as a cell-free DNA sample). A tissue can be a sample that may be genetically modified.

In some cases, a disease or condition can comprise a viral infection, a fibrosis condition, a cancer, a muscular dystrophy, or any combination thereof. In some cases, the disease or condition can comprise the viral infection. The viral infection can comprise a SARS-CoV infection, a SARS-CoV-2 infection, a MERS-CoV infection, a CoV-HKU1 infection, an HIV infection, an HCV infection, or any combination thereof. The viral infection can comprise a coronavirus infection. A coronavirus can be a SARS-CoV, a SARS-CoV-2, a CoV-HKU1, or a MERS-CoV. In some cases, the viral infection can comprise an HCV genotype 1 infection. In some cases, at least a portion of the RNA sequence can be encoded by a SARS-CoV genome, a MERS-CoV genome, a CoV-HKU1 genome, an HIV genome, or any combination thereof. In some cases, an engineered oligonucleotide can be selective for an RNA sequence. In some cases, an RNA

sequence can comprise at least about: 70%, 75%, 80%, 85%, 90%, 95% sequence identity to an RNA sequence of SEQ ID NOS: 500-531, 829-831 (Table 6), SEQ ID NOS: 474-499, 826-828 (Table 6), SEQ ID NOS: 532-554 (Table 6), SEQ ID NOS: 555-586 (Table 6), or any combination thereof. In some cases, a subject may suffer from a SARS-CoV-2 infection and the RNA sequence can comprise at least about: 70%, 75%, 80%, 85%, 90%, 95% sequence identity to an RNA sequence of SEQ ID NOS: 500-531, 829-831 (Table 6). In some cases, a subject may suffer from a SARS-CoV infection and the RNA sequence can comprise at least about: 70%, 75%, 80%, 85%, 90%, 95% sequence identity to an RNA sequence of SEQ ID NOS: 474-499, 826-828 (Table 6). In some cases, a subject may suffer from a MERS-CoV infection and the RNA sequence can comprise at least about: 70%, 75%, 80%, 85%, 90%, 95% sequence identity to an RNA sequence of SEQ ID NOS: 532-554 (Table 6). In some cases, a subject may suffer from a CoV-HKU1 infection and the RNA sequence can comprise at least about: 70%, 75%, 80%, 85%, 90%, 95% sequence identity to an RNA sequence of SEQ ID NOS: 555-586 (Table 6). In some cases, at least a portion of the RNA sequence can be encoded in an HIV genome. In some cases, the RNA sequence can comprise at least about: 75%, 80%, 85%, 90%, 95% or more sequence identity to SEQ ID NO: 470, as determined by a BLAST pairwise sequence alignment algorithm. In some cases, the viral infection can be an HIV infection. In some cases, the RNA sequence can comprise at least about: 70%, 75%, 80%, 85%, 90%, 95% or more 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.

Table 6 – Target sequences

Name	Sequence	SEQ ID NO
ITGA6 3'UTR	AUUCUUAGUCACAAAAUAUAUUUUGUUUACAA	467
SERPINE1 3'UTR	AUUUUGGAGUGUAGGUGACUUGUUUACU	468
EGFR 3'UTR	UAGACCCACAGACUGGUUUUGCAACGUUUACAC	469
HIV-1 NEF site	UCCACUGACCUUUGGAUGGUGCUA	470
TET1 3' UTR site 01	UCACUCAGUUUGGUGCUU	471
TET1 3' UTR site 02	ACUCUACACAGCUUCUGGUGCUU	472
TET1 3' UTR site 03	GUAUGGAAAACCUAAUGGUGCUU	473

SARS-CoV Site 01	CUCAUGGAAAGUGAACUUGUCAUUGGUGCUG	474
SARS-CoV Site 02	UCCUUCCCACAAGCAGCCCCGCAUGGUGUUG	475
SARS-CoV Site 03	ACUGCCACUGCUGGAUGGACAUUUGGUGCUG	476
SARS-CoV Site 04	AUUGUGGCUUAUACUAUGUCUUUAGGUGCUG	477
SARS-CoV Site 05	AGACAAAUAGCGCCAGGACAAACUGGUGUUA	478
SARS-CoV Site 06	UACAACAUGAGAGUUAUUCACUUUGGUGCUG	479
SARS-CoV Site 07	GACCUUUUUAGAAACGCCCGUAAUGGUGUUU	480
SARS-CoV Site 08	UGUAUUACACGAUGCAAUUUAGGUGGUGCUG	481
SARS-CoV Site 09	ACACAUCACGAUAAAUUCACUGAUGGUGUUU	482
SARS-CoV Site 10	CCACAUACAGUCUUGCAGGCUGUAGGUGCUU	483
SARS-CoV Site 11	CUAGUAAGAAAAAUAUUUGUAGAUGGUGUU C	484
SARS-CoV Site 12	AACAUGGACCAAGAGUCCUUUGGUGGUGCUU	485
SARS-CoV Site 13	CUUAAACAACCUAAAUAGAGGUAUGGUGCUG	486
SARS-CoV Site 14	UUGUCUGUUUUGCUAUCCAUGCAGGGUGCUG	487
SARS-CoV Site 15	AACCGUUACUUCAGGCUUACUCUUGGUGUUU	488
SARS-CoV Site 16	UUUGAUGUUGUUAGACAAUGCUCUGGUGUUA	489
SARS-CoV Site 17	GCAUGCUACAAUGGUUCACCAUCUGGUGUUU	490
SARS-CoV Site 18	GCUCUAAAUGACUUUAGCAACUCAGGUGCUG	491
SARS-CoV Site 19	UUUACUCCUCUUGUGCAACCUGUGGGUGCUU	492
SARS-CoV Site 20	UUUGGUGUACUCUUAUCUAAUUUUGGUGCUC	493
SARS-CoV Site 21	AGACAACGUUCAAACCAAACACUUGGUGUUU	494
SARS-CoV Site 22	CACUAUUCAGCGAGUUUCAAGAAAGGUGCUA	495
SARS-CoV Site 23	CAGUUUGGUCCAACAUACUUGGAUGGUGCUG	496
SARS-CoV Site 24	CCAUUGUUGUCAGCAGGCAUAUUUGGUGCUA	497
SARS-CoV Site 25	UGUGGUUUUCCCUCACAGGCUGCUGGUGUUA	498
SARS-CoV Site 26	GUUACCAAGGGAAAGCCCGUAAAAGGUGCUU	499
SARS-CoV Site 27	AUUUUAGAAGAUGAGUUUACA	826
SARS-CoV Site 28	AUUUAGGUGGUGCUGUUUGCA	827
SARS-CoV Site 29	CUUCCUUCAGGCUGUUUGC	828
SARS CoV-2 Site 01	GGGCCAGAAGCUGGACUUCCCUAUGGUGCUA	500
SARS CoV-2 Site 02	UCAACUCAAUUGAGUACAGACACUGGUGUUG	501
SARS CoV-2 Site 03	ACUUCUGGUUGGACCUUUGGUGCAGGUGCUG	502
SARS CoV-2 Site 04	UCAUAUGGUUUCCAACCCACUAAUGGUGUUG	503
SARS CoV-2 Site 05	CAGGCCGGUAGCACACCUUGUAAUGGUGUUG	504
SARS CoV-2 Site 06	GAUUCUUCUUCAGGUUGGACAGCUGGUGCUG	505
SARS CoV-2 Site 07	AACCCUGUCCUACCAUUUAAUGAUGGUGUUU	506
SARS CoV-2 Site 08	GCAUACACUAAUUCUUUCACACGUGGUGUUU	507
SARS CoV-2 Site 09	UAUAAUAUGAGAGUUAUACAUUUUGGUGCU G	508
SARS CoV-2 Site 10	UUCAAUUAUUAUAAGAAAGUUGAUGGUGUU G	509
SARS CoV-2 Site 11	GACUUAUUUAGAAAUGCCCGUAAUGGUGUUC	510
SARS CoV-2 Site 12	GCUCCAGCACAUAUAUCUACUAUUGGUGUUU	511
SARS CoV-2 Site 13	AACACUGUUUACACAAAAGUUGAUGGUGUUG	512
SARS CoV-2 Site 14	UGUAUAACACGUUGCAAUUUAGGUGGUGCUG	513
SARS CoV-2 Site 15	AAUUCACAGACUUCAUUAAGAUGUGGUGCUU	514
SARS CoV-2 Site 16	CUAGUGAGAAAAAUAUUUGUUGAUGGUGUU C	515
SARS CoV-2 Site 17	CUUUCUGUUUUGCUUUCCAUGCAGGGUGCUG	516
SARS CoV-2 Site 18	AACCGCUACUUUAGACUGACUCUUGGUGUUU	517

SARS CoV-2 Site 19	ACAGCAAGAACUGUGUAUGAUGAUGGUGCUA	518
SARS CoV-2 Site 20	GCUUGUUACAAUGGUUCACCAUCUGGUGUUU	519
SARS CoV-2 Site 21	CUAAAGAGACGUGUAGUCUUUAAUGGUGUUU	520
SARS CoV-2 Site 22	ACACCAGUUUACUCAUUCUUACCUGGUGUUU	521
SARS CoV-2 Site 23	UUUACACCACUAAUUCAACCUAUUGGUGCUU	522
SARS CoV-2 Site 24	GGCACUUGUGAAAGAUCAGAAGCUGGUGUUU	523
SARS CoV-2 Site 25	GAAAACAUGACACCCCGUGACCUUGGUGCUU	524
SARS CoV-2 Site 26	GUCGAAUGUACAACUAUUGUUAAUGGUGUUA	525
SARS CoV-2 Site 27	AAACCAGUUACUUAUAAAUUGGAUGGUGUUG	526
SARS CoV-2 Site 28	AAAGAAACUUUGUAUUGCAUAGACGGUGCUU	527
SARS CoV-2 Site 29	AUACAAGAGGGUGUGGUUGAUUAUGGUGCU A	528
SARS CoV-2 Site 30	CCAUUAUUAUCAGCUGGUAUUUUUGGUGCUG	529
SARS CoV-2 Site 31	GUUGUAAUGGCCUACAUUACAGGUGGUGUUG	530
SARS CoV-2 Site 32	AACUGGAACACUAAACAUAGCAGUGGUGUUA	531
SARS CoV-2 Site 33	ACCAUCUGGUGUUUAC	829
SARS CoV-2 Site 34	GUCAGUUAGGUGGUUUACA	830
SARS CoV-2 Site 35	UUUGUGCUUGCUGCUGUUUACA	831
MERS-CoV Site 01	AUUAAUAGUGUGGUCCAAAAGGAUGGUGUU G	532
MERS-CoV Site 02	CUUAAGCAUGGCGGUGGUAUCGCUGGUGCUA	533
MERS-CoV Site 03	CAGCUUGGAUGCGUUUUCUUUAAUGGUGCUG	534
MERS-CoV Site 04	AUGGCUUAUGGCAAUUGCACAUUUGGUGCUC	535
MERS-CoV Site 05	CAAACCGUUCUGCAAUGUGUAAUUGGUGCUU	536
MERS-CoV Site 06	CAAAUUGUCUUGCGUAAUUCUAAUGGUGCUU	537
MERS-CoV Site 07	UUCACUGCUAACAAAAUUGUUGGUGGUGCUC	538
MERS-CoV Site 08	GUUGCAGUAAUUGCUGGAGUUGCUGGUGCUC	539
MERS-CoV Site 09	UUUAACAAGUAUAAGUACUUCUCUGGUGCUA	540
MERS-CoV Site 10	CAUAUAGAACAUCCUGAUGUCUCUGGUGUUU	541
MERS-CoV Site 11	UUUGUUGAAAAUCCCAGUGUUAUUGGUGUUU	542
MERS-CoV Site 12	UCGCUUGGCAAAUGAGUGUGCUCAGGUGCUA	543
MERS-CoV Site 13	ACUGCUAAUGUCAGUGCACUUAUGGGUGCUA	544
MERS-CoV Site 14	AGCUGGAUAGGCUUCGAUGUUGAGGGUGCUC	545
MERS-CoV Site 15	GUGAACUUUGUUGUUCAGCCAGUUGGUGUUG	546
MERS-CoV Site 16	UCUCUGCAUCAGGUUUCCGCCUUUGGUGUUA	547
MERS-CoV Site 17	GUUGUUAAACAAGGCCAUUUUAUUGGUGUUG	548
MERS-CoV Site 18	GGUCCUGAUUAUGCUUACUUCAAUGGUGCUA	549
MERS-CoV Site 19	ACUAUUAAAGAAAAUAUAGAUGGUGGUGCU A	550
MERS-CoV Site 20	AAUUGCGUGGAAUAUUCCCUCUAUGGUGUUU	551
MERS-CoV Site 21	UCCCUCUAUGGUGUUUCGGGCCGUGGUGUUU	552
MERS-CoV Site 22	GCUAGCGAGCUAUCUAAUACUUUUGGUGCUA	553
MERS-CoV Site 23	CUCAAAAUGGCUGGCAUGCAUUUCGGUGCUU	554
CoV-HKU1 Site 01	AGUGAAGUUAAAGCCCAAUCAUCUGGUGUUA	555
CoV-HKU1 Site 02	AAUCUUGAACAAAAUCAUAUUCUUGGUGUUA	556
CoV-HKU1 Site 03	UUGAUAUUAAUGCGUAUGCUAAUUGGUGUU G	557
CoV-HKU1 Site 04	AUAGAUGUUUUGCUUACUGUAGAUGGUGUU A	558
CoV-HKU1 Site 05	GGUAUUAAACAAGAAAGUCGUGUUGGUGUU G	559

CoV-HKU1 Site 06	GAUUUAGGUGUUCUUAUACAGAAUGGUGCUA	560
CoV-HKU1 Site 07	GCUAGUUUUAAAGUUAUUGAUAAUGGUGUU G	561
CoV-HKU1 Site 08	CCACAUCCUUAUUGUUAUUCAGAUGGUGUUA	562
CoV-HKU1 Site 09	CAUUUGCAAUGGAUUGUUAUGUAUGGUGCUA	563
CoV-HKU1 Site 10	UUAUUUUCAUAUUGUAGGAAAAUUGGUGUU A	564
CoV-HKU1 Site 11	CCUUACACUCCAAAAUAUACUUUUGGUGUUG	565
CoV-HKU1 Site 12	UCUGACGUUUAUCAACAAUUGGCUGGUGUUA	566
CoV-HKU1 Site 13	AUGUAUAUUAAUACACAUAUGAUUGGUGUU A	567
CoV-HKU1 Site 14	UCUUCAACAAUUAGAUUGCAGGCUGGUGUUG	568
CoV-HKU1 Site 15	UAUUAUGAGUUGACUAAAAGUUGUGGUGUU G	569
CoV-HKU1 Site 16	ACUUUAGUAAAAGUAGGUUUAGUUGGUGUU U	570
CoV-HKU1 Site 17	CUUGUUAGACAAAUUUUUGUAGAUGGUGUUC	571
CoV-HKU1 Site 18	UUGAAGAGUAUAGCAGCUACUCGUGGUGUUC	572
CoV-HKU1 Site 19	AGUAUGAUGAUUUUGAGUGAUGAUGGUGUU G	573
CoV-HKU1 Site 20	UUUUGAUAAAAUGAAUUAACUAAUGGUGUU U	574
CoV-HKU1 Site 21	CCAUUGCAAAUAGGUUUUUCAACUGGUGUUG	575
CoV-HKU1 Site 22	UGUAUCACACGAUGUAAUUUAGGUGGUGCUG	576
CoV-HKU1 Site 23	GUACUUUUUGAUGGUCGUGACAAUGGUGCUU	577
CoV-HKU1 Site 24	GAAGCUUUUAGAAAAGCAAGAAAUGGUGUU U	578
CoV-HKU1 Site 25	AGAAAUAGUACAACAUGGAAUGGUGGUGCUU	579
CoV-HKU1 Site 26	UUUACAGGUUAUUUUCCUAAAUCUGGUGCUA	580
CoV-HKU1 Site 27	UAUUUUCAUUUUUAUCAAGAACGUGGUGUUU	581
CoV-HKU1 Site 28	ACUCAAUCUUUUGCACCUAAUACUGGUGUUU	582
CoV-HKU1 Site 29	UAUUCUAACACUGAAGUUUCUACUGGUGUUU	583
CoV-HKU1 Site 30	UUACAACAAUUAUUUAAUAAAUUUGGUGCUA	584
CoV-HKU1 Site 31	GACACCUCUCAUAAGAAUAAUUUUGGUGUUA	585
CoV-HKU1 Site 32	CUUGCUGAAUUAGCCCCUACACCAGGUGCUU	586
HCV-1 Site 01	GAUGUAUGGAGAAAAGUAUCCAGUGGUGUU G	587
HCV-1 Site 02	GAAGGCAAAGACAGCUAUUGAAAUGGUGUUA	588
HCV-1 Site 03	GCAUCUUGUCUGGAGAGACAAUUUGGUGUUU	589
ZEB1 3' UTR	UGUUUGAAUAUGUGGUAACAUAUGAAGGA	590
E2F1 3' UTR	UGUGCAUGUACCGGGGAAUGAAGGU	591
HER3 3' UTR	UUCACAGGCACUCCUGGAGAUAUGAAGGA	592
SHIP2 3' UTR	GGGGCGGGUGUCCGUCCGGAAAUGAAGGA	593
CSNK1G1 3' UTR Site 01	UGAAUUUUCAUUCAUCUUCUCAG	594
CSNK1G1 3' UTR Site 02	AAGGUCUGAAAUUAUCUUCUCAA	595
CSNK1G1 3' UTR Site 03	AUGUGUGGAGUUACUCUUCUCAU	596
CSNK1G1 3' UTR Site 04	AAGCAUGGCUUGCAUUUCUCAAA	597

CSNK1G1 3' UTR Site 05	CAGCCAAGAAAACGUCUUCUCAG	598
CSNK1G1 3' UTR Site 06	GGUAGUUGACAUAUUUUCUCAAA	599
ARHGAP26 3' UTR Site 01	CGAGUUUUUGUCUUUCUUCUCAG	600
ARHGAP26 3' UTR Site 02	GAGAUACAAUCCAGUCUUCUCAU	601
ARHGAP26 3' UTR Site 03	UCUUAGAAUGUUCAGUUCUCAAU	602
ARHGAP26 3' UTR Site 04	UCACAUACUAUUACGCUUCUCAA	603
ARHGAP26 3' UTR Site 05	AAGUCAGCAGGAUGUCUUCUCAC	604
RAB11FIP1 3' UTR Site 01	UGGGACCACUGUAAACUUCUCAG	605
RAB11FIP1 3' UTR Site 02	UGUAAACCUACCCAGCUUCUCAG	606
RAB11FIP1 3' UTR Site 03	AGACACAGGCAUGUGCUUCUCAG	607
RBJ 3' UTR Site 01	GAAGAGAGGUUCGUACUUCUCAU	608
RBJ 3' UTR Site 02	UUCUCAUAUAUUGAAUUCUCAAC	609
SERBP1 3' UTR Site 01	AAAAAUCUUUUUUCACUUCUCAU	610
SERBP1 3' UTR Site 02	CUACUCAAAACACAACUUCUCAG	611
CTBP1 3' UTR	GAGGCAGUUGGCAAACUUCUCAG	612
CRKL 3' UTR	AUGGAAAGGGUCUUCCUUCUCAU	613
ITGA3 3' UTR	UUCUUUGUAUAUAGGCUUCUCAC	614
ITGAV 3' UTR	UGUUUUUUGUCAUUGUUCUCAAG	615
LAMC1 3' UTR	GAGUUUCCUAGUGGGCUUCUCAA	616
G6PC2 3' UTR	AUGUUUUAUGUAACUCUUCUCAG	617
PPP2R5E 3' UTR	UGGACAGUAGAUGGACUUCUCAG	618
KLF17 3' UTR	GUCAGGGAAGAAAGACUUCUCAA	619
MTDH 3' UTR site 01	UUAACAACAGUGCCCUGUUUACA	621
MTDH 3' UTR site 02	AGGAACAUGGCAGUAUGUUUAC	622
MTDH 3' UTR site 03	AACUGUCAUGGUUUAGUUUACAA	623
IGF1R 3' UTR site	UUUUUUUUUUUUUUUUAGGACACCUGUUUACU	832
MET 3' UTR site	AAAGUGUUAUAUUUUUUAUAAAAAUGUUUAUU	833
IRS1 3' UTR site	UGGUACGAUGCAUCCAUUUCAGUUUGUUUACG	834
ACVR1	ACUCAAGACUCCCACUGUG	950
ASIC2	CGGGCGGGCGCCCGCGGAGG	951
ATG14	CAGCGAUGAAGAAACCG	952
ATP1A1	GAGGCCUGCUUUUGAGAGGAA	953
B3GTNL1	UGGAGACUGUUUGGA	954
BANF1	ACUUCCGGCGCUGUCUCGG	955
BPTF	AUGAUUGUUCAGAAUA	956
CASP8AP2	UGGAUGAUUGUUCAAAGA	957
CDX4	AUCUGGUUUCAGAAUC	958
CELF2	AGGAUUCAGAUCUGUUUU	959

CHMP7	GCCACCUGCCGCGCAGGCGCA	960
CKMT1B	ACUCAAGAUUCCCAGGAG	961
CLASP1 site 01	AUAGGAUUAGAUCGGUUU	962
CLASP1 site 02	CAGCCAGGAAGAAUACCU	963
CNOT3	UGGAAGAGGCCGCCUGGC	964
COL15A1	CACGGAGGUCAGUUCAA	965
CYP3A4	AACAGCCUGUGCUGGCUA	966
DBET Site 01	AACACCUGGCUGGCUA	967
DBET Site 02	ACGCGGGGUUGGGACGGGGUCGGGU	968
DBET Site 03	CAGGCGCAACCUCUCCUAGAAA	969
DBET Site 04	CAUGAAGGGGUGGAGCCUG	970
DBET Site 05	CCGGAAACAUGCAGGGAAG	971
DBET Site 06	CCGGCCUGGGAUUCCUGC	972
DBET Site 07	CCGGGGAUCCCAGAGCCG	973
DBET Site 08	CUCCUGGCUGCACCUGCCGCAGU	974
DBET Site 09	CUGCCUCUCCACCAGCCCA	975
DBET Site 10	CUGGGAUUCCUGCCUUCU	976
DBET Site 11	GAAAUGAACGAGAGCCACA	977
DBET Site 12	GCACCUGCCGCAGUGCACA	978
DBET Site 13	GCCAUUCAUGAAGGGGUG	979
DBET Site 14	GCCCCGGGGGAGCUGGAG	980
DBET Site 15	GCCUGCUGCUGGAUGA	981
DBET Site 16	GGCACACUCAAGACUCCCACGGAG	982
DBET Site 17	GGCACCCGGAAACAUGCAGGGAA	983
DBET Site 18	GGCCGGUGAGAGACUCC	984
DBET Site 19	GGCGGGAGGGAAGGCGGGCAGAGAU	985
DBET Site 20	GGGCGUGUCUCCGCCCC	986
DBET Site 21	UCCAGGCCGGUGAGAGACUC	987
DBET Site 22	UCCCACGGAGGUUCAGUUCCA	988
DBET Site 23	UCGGAAGAGGCGCCUCGC	989
DBET Site 24	UGCGUUCCGCCGCCAGGCGCU	990
DBET site 25	CAGCGAGGAAGAAUACCG	991
DCAF15	GCCCCGGGGGAGCCGGAG	992
DCN	GUCUUUGAGAGGAUCCCUUU	993
DLX5	AUCUGGUUUCAGAAC	994
DUSP7	GGGCCCUUCUUGAAGGGGUG	995
DUX1	GAUGGCCCUCCUGACA	996
DUX4 Site 01	AACACCUGGCUGGCUA	997
DUX4 Site 02	ACCUGCGCGCAGUGCGCACCCCG	998
DUX4 Site 03	ACCUUCCGACGCUGUCUAGG	999
DUX4 Site 04	ACGCGGGGUUGGGACGGGGUCGGGU	1000
DUX4 Site 05	AGCAGACCUGCGCGCAGUGCGCA	1001
DUX4 Site 06	AGCUCGCUGGCCUCUCUG	1002
DUX4 Site 07	AGUUCAGAGAUAUAUUAAAAUGCCC	1003
DUX4 Site 08	AUCUGGUUUCAGAAUC	1004
DUX4 Site 09	AUGAUUAGUUCAGAGAUA	1005
DUX4 Site 10	AUGGCCCUCCCGACACCC	1006
DUX4 Site 11	CAGACCUGCGCGCAGU	1007
DUX4 Site 12	CAGGCGCAACCUCUCCUAGAAA	1008
DUX4 Site 13	CCACCUUCCGACGCUG	1009
DUX4 Site 14	CCGGCCUGGGAUUCCUGC	1010

DUX4 Site 15	CCGGGGAUCCCAGAGCCG	1011
DUX4 Site 16	CCUCCCUGUGGAUCCUAU	1012
DUX4 Site 17	CCUGCCUCUCCACCAGCCC	1013
DUX4 Site 18	CCUGCGCGCAGUGCGCACCCCGGCUGACGUGC	1014
DUX4 Site 19	CCUGGAUGAUUAGUUC	1015
DUX4 Site 20	CGACACCCUCGGACAGCA	1016
DUX4 Site 21	CGGAGACUCGUUUGGA	1017
DUX4 Site 22	CUGGAUUAGAGUUACAUCUCCUG	1018
DUX4 Site 23	CUGGGAUUCCUGCCUUCU	1019
DUX4 Site 24	CUGUGGAUCCUAUAG	1020
DUX4 Site 25	CUUCCGACGCUGUCUA	1021
DUX4 Site 26	GAGCCUGCUUUGAGCGGAA	1022
DUX4 Site 27	GAGCCUUUGAGAAGGAUCGCUUU	1023
DUX4 Site 28	GCCCCGGGGGAGCUGGAG	1024
DUX4 Site 29	GCCUGCUGCUGGAUGA	1025
DUX4 Site 30	GGCCCGGUGAGAGACUCC	1026
DUX4 Site 31	GGGAGCUCGCUGGCCUCU	1027
DUX4 Site 32	GGGCGUGUCUCCGCCCC	1028
DUX4 Site 33	GUCCAGGAUUCAGAUCUGGUUU	1029
DUX4 Site 34	GUGGCAGGGCGCCCGCGCAGG	1030
DUX4 Site 35	UACCAGCAGACCUGCGCGCAGU	1031
DUX4 Site 36	UCCCUGUGGAUCCUAU	1032
DUX4 Site 37	UCGGAAGAGGCCGCCUCG	1033
DUX4 Site 38	UCUAGGCCCGGUGAGAGACU	1034
DUX4 Site 39	UGGAUGAUUAGUUCAGAG	1035
DUX4 site 40	CAGCGAGGAAGAAUACCG	1036
DUX5 Site 01	AUCUGGUUUCAGAAUC	1037
DUX5 Site 02	GAUGGCCCUCCUGACA	1038
EMILIN1	AUGGCCCCCCGCACCCUC	1039
EPG5	CUGUGGUUUCAGAAUC	1040
FAM13A	ACUUUGAAAAGGAUCUCUUU	1041
FBX03	UGGAGAUUAGAUCAGAGUG	1042
FBXL22	CCUGCGCGCACUGCGCCU	1043
FMNL3	CAGAGGGGUGGAGCCUGU	1044
FREM2	CAUAAAGGGGUGGAACCUGU	1045
FRMPD2	CGGAGACUUUUGGA	1046
GADD45A	GUGGCAGGAGCAGCCCGC	1047
GID4	CCACCCCGCGCGUGCGCGCCCCG	1048
GJD3	UGAGGCGGCGGCGCAGUGCGCCCCCG	1049
GMPR	CGCCGCCCCGCGCAGGCGCCCCCGC	1050
GNAT1	CUUCGACGCUGUCA	1051
GOSR1	GCCAUUCAUGAUGGUGUG	1052
GPRC6A	AUGUUAGUUCAGAGAA	1053
HERC1	CUGGCCUCUCCACCAGCCCUU	1054
HGF	AGGAUCAGAUCUGGUUU	1055
HOOK3	ACCACCAUGGCUGGCUA	1056
HOXC9	AUCUGGUUUCAGAAUC	1057
HSP40 Site 01	GCCUACCGCCGCCAGGCGCU	1058
HSP40 Site 02	GGUUUGAGUUACAUCUA	1059
HSP40 Site 03	UGGAGUCAGAUCUGGUUU	1060

IRF9 Site 01	CCUGGAAACAUGCAGGCAA	1061
IRF9 Site 02	CGACAGCCUGGACAGCAAC	1062
IRF9 Site 03	CUGGAAACAUGCAGGCAAG	1063
IRX5	UCGGAGGGCCGCCUCGAC	1064
ITGA10	UCUCCCUGUGGAUCCUCAU	1065
ITGA3 Site 01	CACUGAGGUCCAGUUCCA	1066
ITGA9	CUGUGGAAUCCUAUAA	1067
KCNC3	GCCUGCUGCUGGAUGA	1068
KLHL3	GCCUUUGCUGCUGGAUGA	1069
KLK6	ACUCAAGAAUCCCCGGAG	1070
LARP6	ACCUUCCUACGUGCUAGG	1071
MALT1	CAGUUGCCUAGACCUGGAGCAGU	1072
MAP3K4	ACUCAAGCCCCACGGAG	1073
MAPK10	CACAGAGAUAUUUUAAAAUUCUU	1074
MIR4661	CUGUGGAUCCUGACAGA	1075
MIR8078 Site 01	GGCCCGGUGAGAGACUCC	1076
MIR8078 Site 02	UCUAGGCCCGGUGAGAGACU	1077
MTSS1	UUUGAGAAGGAUGUUUU	1078
NDUFAF6	CUCACCUCUCCUAGAAA	1079
NEBL	AAGAUGCAGAUCUGGUUU	1080
NKX2-3	GGUAGGGACGGGGCGGGU	1081
NR2F1	CAGCGAGGAAGAAUGCCU	1082
PCID2	GCCAUUCAUGAGGGGUC	1083
PDE10A	CUGACCUGCCGCAGU	1084
PKD1L2	AACAGAGAUAUAUGUAAAAUUGCCA	1085
PKHD1	GUCCAGGACUCACAGCUGGUUU	1086
PPP1R12B	GGAGGGAAGCGGGCAGAGU	1087
PTPRN2	CAGAAGGGGGGAGCCUG	1088
PYY	CAGCAGACCUGCGCGCAGU	1089
RABGAP1L	GGAGAUAGAGUUACAUCUU	1090
rbck1	CCUGCGCCCAGUGCGGACCU	1091
RFX3	UACCUUCGACACUGUCAGG	1092
RHBDF2	UGGCUUCCGCCGCCAGGCCU	1093
SCRIB	CUUCCAGACCUGUCUA	1094
SEMA3B	UGGGACGGGGUCGCGU	1095
SETD4	GAAAUGUACCAGAGCCACA	1096
SHFL	GGCUGAGCCGCGCAGUGCGGACCCUCGC	1097
SHH	GGGGGCGCCCGCGCAGG	1098
SLC37A4	AUGAUUAUUUUAGAGAUA	1099
SLC9A8	GGCUGGGAGGGGAAGGCGGGUCAGAGAU	1100
SMAD1	GGAUUGAGAUACAUCUG	1101
SPEF1	AGAUCGCGCAGUGCGCCCCAG	1102
SPRED3	CCUGCGCGCGUGCCAC	1103
ST3GAL6	GUGGCAGGCGCCGC	1104
STAG1	GGUUUAGAGUUACAUUCU	1105
SUPV3L1 Site 01	CUGUGGAUCCUAUAA	1106
SUPV3L1 Site 02	GGCCUGUGGAUCCUAU	1107
TBC1D26	AUGGCCUUCCUGACACCC	1108
TCEA2	UCUGGGCCGGGUGAGAGAC	1109
TCF3	CUGGCUGCCCUGCGUGCAGU	1110
TM6SF1	GGCUGGUUUCAGAAUC	1111

TMEM108	CUGAGACUCGUUGGA	1112
TMEM259	GCCUGCUGCUGGAUGA	1113
TNFSF4	CAGGAAGGGUGGAGCCUGC	1114
TNIP1	GCGGCAAGGCGCCGCGCAGG	1115
TRNP1	GAGGCCUGUUUGAGGGAA	1116
USH1G	CAUCCAGGGGUGGAGCCUG	1117
WRNIP1	ACCUUCAGACGUGUCUGAGG	1118
XIAP	AGAUUAGAGUUAAUCUCCC	1119
ZNF574	UUGCCUCUCCAGCAGCCCU	1120

~~[00124]~~[00125] A condition or a disease, as disclosed herein, can include a cancer, a neurological disorder, a fibrosis disease, a scarring disease, or an autoimmune disease.

~~[00125]~~[00126] In some cases, a disease or condition may comprise a neurological disorder. In some cases, a neurological disorder may comprise Acquired Epileptiform Aphasia, Acute Disseminated Encephalomyelitis, Adrenoleukodystrophy, Agenesis of the corpus callosum, Agnosia, Aicardi syndrome, Alexander disease, Alpers' disease, Alternating hemiplegia, Alzheimer's disease, Amyotrophic lateral sclerosis (see Motor Neuron Disease), Anencephaly, Angelman syndrome, Angiomatosis, Anoxia, Aphasia, Apraxia, Arachnoid cysts, Arachnoiditis, Arnold-Chiari malformation, Arteriovenous mal-formation, Asperger's syndrome, Ataxia Telangiectasia, Attention Deficit Hyperactivity Disorder, Autism, Auditory processing disorder, Autonomic Dysfunction, , Back Pain, Batten disease, Bechet’s disease, Bell's palsy, Benign Essential Blepharospasm, Benign Focal Amyotrophy, Benign Intracranial Hypertension, Bilateral frontoparietal polymicrogyria, Binswanger's disease, Blepharo-spasm, Bloch-Sulzberger syndrome, Brachial plexus injury, Brain abscess, Brain damage, Brain in-jury, Brain tumor, Brown-Sequard syndrome, Canavan disease, Carpal tunnel syndrome (CTS), Causalgia, Central pain syndrome, Central pontine myelinolysis, Centronuclear myopathy, Cephalic disorder, Cerebral aneurysm, Cerebral arteriosclerosis, Cerebral atrophy, Cerebral gigantism, Cerebral palsy, Charcot-Marie-Tooth disease, Chiari malformation, Chorea, Chronic inflammatory de-myelinating polyneuropathy (CIDP), Chronic pain, Chronic regional pain syndrome, Coffin Lowry syndrome, Coma, including Persistent Vegetative State, Congenital facial diplegia, Corticobasal degeneration, Cranial arteritis, Craniosynostosis, Creutzfeldt-Jakob disease,

Cumulative trauma disorders, Cushing's syndrome, Cytomegalic inclusion body disease (CIBD), Cytomegalovirus Infection, , Dandy-Walker syndrome, Dawson disease, De Morsier's syndrome, Dejerine-Klumpke palsy, Dejerine-Sottas disease, Delayed sleep phase syndrome, Dementia, Dermatomyositis, Neurological Dyspraxia, Diabetic neuropathy, Diffuse sclerosis, Dysautonomia, Dyscalculia, Dysgraphia, Dyslexia, Dystonia, , Early infantile epileptic encephalopathy, Empty sella syndrome, Encephalitis, Encephalocele, Encephalotrigeminal angiomatosis, Encopresis, Epilepsy, Erb's palsy, Erythromelalgia, Essential tremor, , Fabry's disease, Fahr's syndrome, Fainting, Familial spastic paralysis, Febrile seizures, Fisher syndrome, Friedreich's ataxia, FART Syndrome, Gaucher's disease, Gerstmann's syndrome, Giant cell arteritis, Giant cell inclusion disease, Globoid cell Leukodystrophy, Gray matter heterotopia, Guillain-Barre syndrome, HTLV-1 associated myelopathy, Hallervorden-Spatz disease, Head injury, Headache, Hemifacial Spasm, Hereditary Spastic Paraplegia, Heredopathia atactica polyneuritiformis, Herpes zoster oticus, Herpes zoster, Hirayama syndrome, Holoprosencephaly, Huntington's disease, Hydranencephaly, Hydrocephalus, Hypercortisolism, Hypoxia, Immune-Mediated encephalomyelitis, Inclusion body myositis, Incontinentia pigmenti, Infantile phytanic acid storage disease, Infantile Refsum disease, Infantile spasms, Inflammatory myopathy, Intracranial cyst, Intracranial hypertension, Joubert syndrome, Kearns-Sayre syndrome, Kennedy disease, Kinsbourne syndrome, Klippel Feil syndrome, Krabbe disease, Kugelberg-Welander disease, Kuru, Lafora disease, Lambert-Eaton myasthenic syndrome, Landau-Kleffner syndrome, Lateral medullary (Wallenberg) syndrome, Learning disabilities, Leigh's disease, Lennox-Gastaut syndrome, Lesch-Nyhan syndrome, Leukodystrophy, Lewy body dementia, Lissencephaly, Locked-In syn-drome, Lou Gehrig's disease, Lumbar disc disease, Lyme disease - Neurological Sequelae, Macha-do-Joseph disease (Spinocerebellar ataxia type 3), Macrencephaly, Maple Syrup Urine Disease, Megalencephaly, Melkersson-Rosenthal syndrome, Menieres disease, Meningitis, Menkes disease, Metachromatic leukodystrophy, Microcephaly, Migraine, Miller Fisher syndrome, Mini-Strokes, Mitochondrial Myopathies, Mobius syndrome, Monomelic amyotrophy, Motor Neuron Disease, Motor skills disorder, Moyamoya disease,

Mucopolysaccharidoses, Multi-Infarct Dementia, Multi-focal motor neuropathy, Multiple sclerosis, Multiple system atrophy, Muscular dystrophy, Myalgic encephalomyelitis, Myasthenia gravis, Myelinoclastic diffuse sclerosis, Myoclonic Encephalopathy of infants, Myoclonus, Myopathy, Myotubular myopathy, Myotonia congenita, Narcolepsy, Neuro-fibromatosis, Neuroleptic malignant syndrome, Neurological manifestations of AIDS, Neurological sequelae of lupus, Neuromyotonia, Neuronal ceroid lipofuscinosis, Neuronal migration disorders, Niemann-Pick disease, Non 24-hour sleep-wake syndrome, Nonverbal learning disorder, O'Sullivan-McLeod syndrome, Occipital Neuralgia, Occult Spinal Dysraphism Sequence, Ohtahara syndrome, Olivopontocerebellar atrophy, Opsoclonus myoclonus syndrome, Optic neuritis, Orthostatic Hypotension, Overuse syndrome, Palinopsia, Paresthesia, Parkinson's disease, Paramyotonia Con-genita, Paraneoplastic diseases, Paroxysmal attacks, Parry-Romberg syndrome, Rombergs Syndrome, Pelizaeus-Merzbacher disease, Periodic Paralyses, Peripheral neuropathy, Persistent Vegetative State, Pervasive neurological disorders, Photic sneeze reflex, Phytanic Acid Storage disease, Pick's disease, Pinched Nerve, Pituitary Tumors, PMG, Polio, Polymicrogyria, Polymyositis, Porencephaly, Post-Polio syndrome, Postherpetic Neuralgia (PHN), Postinfectious Encephalomyelitis, Postural Hypotension, Prader-Willi syndrome, Primary Lateral Sclerosis, Prion diseases, Progressive Hemifacial Atrophy also known as Rombergs Syndrome, Progressive multifocal leukoencephalopathy, Progressive Sclerosing Poliodystrophy, Progressive Supranuclear Palsy, Pseudotumor cerebri, Ramsay-Hunt syndrome (Type I and Type II), Rasmussen's encephalitis, Reflex sympathetic dystrophy syndrome, Refsum disease, Repetitive motion disorders, Repetitive stress injury, Restless legs syndrome, Retrovirus-associated myelopathy, Rett syndrome, Reye's syndrome, Rombergs Syndrome, Rabies, Saint Vitus dance, Sandhoff disease, Schytsophrenia, Schilder's disease, Schizencephaly, Sensory Integration Dysfunction, Septooptic dysplasia, Shaken baby syndrome, Shingles, Shy-Drager syndrome, Sjogren's syndrome, Sleep apnea, Sleeping sickness, Snatiation, Sotos syndrome, Spasticity, Spina bifida, Spinal cord injury, Spinal cord tumors, Spinal muscular atrophy, Spinal stenosis, Steele-Richardson-Olszewski syndrome, see Progressive Supranuclear Palsy,

Spinocerebellar ataxia, Stiff-person syndrome, Stroke, Sturge-Weber syndrome, Subacute sclerosing panencephalitis, Subcortical arteriosclerotic encephalopathy, Superficial siderosis, Syden-ham's chorea, Syncope, Synesthesia, Syringomyelia, Tardive dyskinesia, Tay-Sachs disease, Temporal arteritis, Tethered spinal cord syndrome, Thomsen disease, Thoracic outlet syndrome, Tic Douloureux, Todd's paralysis, Tourette syndrome, Transient ischemic attack, Transmissible spongiform encephalopathies, Transverse myelitis, Traumatic brain injury, Tremor, Trigeminal neuralgia, Tropical spastic paraparesis, Trypanosomiasis, Tuberous sclerosis, Vasculitis including temporal arteritis, Von Hippel-Lindau disease (VHL), Viliuisk Encephalomyelitis (VE), Wallenberg's syn-drome, Werdnig-Hoffman disease, West syndrome, Whiplash, Williams syndrome, Wilson's dis-ease, X-Linked Spinal and Bulbar Muscular Atrophy, and Zellweger syndrome. Neurological conditions can comprise movement disorders, for example multiple system atrophy (MSA).

~~[00126]~~[00127] In some cases, a disease or condition may comprise an autoimmune disease. In some cases, an autoimmune disease may comprise acute disseminated encephalomyelitis (ADEM), acute necrotizing hemorrhagic leukoencephalitis, Addison's disease, agammaglobulinemia, allergic asthma, allergic rhinitis, alopecia areata, amyloidosis, ankylosing spondylitis, anti-GBM/anti-TBM nephritis, antiphospholipid syndrome (APS), autoimmune aplastic anemia, autoimmune dysautonomia, autoimmune hepatitis, autoimmune hyperlipidemia, autoimmune immunodeficiency, autoimmune inner ear disease (AIED), autoimmune myocarditis, autoimmune pancreatitis, autoimmune retinopathy, autoimmune thrombocytopenic purpura (ATP), autoimmune thyroid disease, axonal & neuronal neuropathies, Balo disease, Bechet’s disease, bullous pemphigoid, cardiomyopathy, Castlemen disease, celiac sprue (non-tropical), Chagas disease, chronic fatigue syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), chronic recurrent multifocal ostomyelitis (CRMO), Churg-Strauss syndrome, cicatricial pemphigoid/benign mucosal pemphigoid, Crohn's disease, Cogan's syndrome, cold agglutinin disease, congenital heart block, coxsackie myocarditis, CREST disease, essential mixed cryoglobulinemia, demyelinating neuropathies, dermatomyositis, Devic's

disease (neuromyelitis optica), discoid lupus, Dressler's syndrome, endometriosis, eosinophillic fasciitis, erythema nodosum, experimental allergic encephalomyelitis, Evan's syndrome, fibromyalgia, fibrosing alveolitis, giant cell arteritis (temporal arteritis), glomerulonephritis, Goodpasture's syn-drome, Grave's disease, Guillain-Barre syndrome, Hashimoto's encephalitis, Hashimoto's thyroiditis, hemolytic anemia, Henock-Schoniein purpura, herpes gestationis, hypogammaglobulinemia, idiopathic thrombocytopenic purpura (ITP), IgA nephropathy, immunoregulatory lipoproteins, inclusion body myositis, insulin-dependent diabetes (type 1), interstitial cystitis, juvenile arthritis, juvenile diabetes, Kawasaki syndrome, Lambert-Eaton syndrome, leukocytoclastic vasculitis, lichen planus, lichen sclerosis, ligneous conjunctivitis, linear IgA disease (LAD), Lupus (SLE), Lyme dis-ease, Meniere's disease, microscopic polyangitis, mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, multiple sclerosis, myasthenia gravis, myositis, narcolepsy, neuromyelitis optica (Devic's), neutropenia, ocular cicatricial pemphigoid, optic neuritis, palindromic rheumatism, PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus), paraneoplastic cerebellar degeneration, paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, Parsonnage-Turner syndrome, pars plantis (peripheral uveitis), pemphigus, peripheral neuropathy, perivenous encephalomyelitis, pernicious anemia, POEMS syn-drome, polyarteritis nodosa, type I, II & III autoimmune polyglandular syndromes, polymyalgia rheumatic, polymyositis, postmyocardial infarction syndrome, postpericardiotomy syndrome, progesterone dermatitis, primary biliary cirrhosis, primary sclerosing cholangitis, psoriasis, psoriatic arthritis, idiopathic pulmonary fibrosis, pyoderma gangrenosum, pure red cell aplasis, Raynaud's phenomena, reflex sympathetic dystrophy, Reiter's syndrome, relapsing polychondritis, restless legs syndrome, retroperitoneal fibrosis, rheumatic fever, rheumatoid arthritis, sarcoidosis, Schmidt syn-drome, scleritis, scleroderma, Slogren's syndrome, sperm and testicular autoimmunity, stiff person syndrome, subacute bacterial endocarditis (SBE), sympathetic ophthalmia, Takayasu's arteritis, temporal arteritis/giant cell arteries, thrombocytopenic purpura (TPP), Tolosa-Hunt syndrome, transverse myelitis, ulcerative colitis,

undifferentiated connective tissue disease (UCTD), uveitis, vasculitis, vesiculobullous dermatosis, vitiligo or Wegener's granulomatosis or , chronic active hepatitis, primary biliary cirrhosis, cadilated cardiomyopathy, myocarditis, autoimmune polyendocrine syndrome type I (APS-I), cystic fibrosis vasculitides, acquired hypoparathyroidism, coronary artery disease, pemphigus foliaceus, pemphigus vulgaris, Rasmussen encephalitis, autoimmune gastritis, insulin hypoglycemic syndrome (Hirata disease), Type B insulin resistance, acanthosis, systemic lupus erythematosus (SLE), pernicious anemia, treatment-resistant Lyme arthritis, polyneuropathy, demyelinating diseases, atopic dermatitis, autoimmune hypothyroidism, vitiligo, thyroid associated ophthalmopathy, autoimmune coeliac disease, ACTH deficiency, dermatomyositis, Sjogren syndrome, systemic sclerosis, progressive systemic sclerosis, morphea, primary antiphospholipid syndrome, chronic idiopathic urticaria, connective tissue syndromes, necrotizing and crescentic glomerulonephritis (NCGN), systemic vasculitis, Raynaud syndrome, chronic liver disease, visceral leishmaniasis, autoimmune C1 deficiency, membrane proliferative glomerulonephritis (MPGN), prolonged coagulation time, immunodeficiency, atherosclerosis, neuronopathy, paraneoplastic pemphigus, paraneoplastic stiff man syndrome, paraneoplastic encephalomyelitis, subacute autonomic neuropathy, cancer-associated retinopathy, paraneoplastic opsoclonus myoclonus ataxia, lower motor neuron syndrome and Lambert-Eaton myasthenic syndrome.

~~[00127]~~[00128] In some cases, a disease or a condition may comprise AIDS, anthrax, botulism, brucellosis, chancroid, chlamydial infection, cholera, coccidioidomycosis, cryptosporidiosis, cyclosporiasis, dipheheria, ehrlichiosis, arboviral encephalitis, enterohemorrhagic Escherichia coli, giardiasis, gonorrhea, dengue fever, haemophilus influenza, Hansen's disease (Leprosy), hantavirus pulmonary syn-drome, hemolytic uremic syndrome, hepatitis A, hepatitis B, hepatitis C, human immunodeficiency virus, legionellosis, listeriosis, Lyme disease, malaria, measles. Meningococcal disease, mumps, pertussis (whooping cough), plague, paralytic poliomyelitis, psittacosis, Q fever, rabies, rocky mountain spotted fever, rubella, congenital rubella syndrome , shigellosis, smallpox, streptococcal disease (invasive group A), streptococcal toxic shock

syndrome, streptococcus pneumonia, syphilis, tetanus, toxic shock syndrome, trichinosis, tuberculosis, tularemia, typhoid fever, vancomycin intermediate resistant staphylocossus aureus, varicella, yellow fever, variant Creutzfeldt-Jakob dis-ease (vCJD), Ebola hemorrhagic fever, Echinococcosis, Hendra virus infection, human monkey-pox, influenza A, influenza B, H5N1, lassa fever, Margurg hemorrhagic fever, Nipah virus, O'nyong fever, Rift valley fever, Herpes, HIV, HCV genotype 1, HCV genotype 2, HCV genotype 3, HCV genotype 4, HCV genotype 5, HCV genotype 6, SARS-CoV-2 (COVID-19), SARS-CoV (SARS), MERS-CoV (MERS), 229E coronavirus, NL63 coronavirus, OC43 coronavirus, CoV-HKU1(HKU1), alpha coronavirus, beta coronavirus, Venezuelan equine encephalitis and West Nile virus.

~~[00128]~~[00129] In some cases, a disease or condition may comprise a fibrosis disease, a scarring disease or both. In some cases, a fibrosis disease or a scarring disease may comprise, pulmonary fibrosis, cystic fibrosis, idiopathic pulmonary fibrosis, radiation induced fibrosis, myocardial fibrosis, bridging fibrosis, cirrhosis, gliosis, arterial stiffness, arthrofibrosis, Chron’s disease, Dupuytren’s contracture, keloid, mediastinal fibrosis, myelofibrosis, Peyronie’s disease, nephrogenic systemic fibrosis, progressive massive fibrosis, retroperitoneal fibrosis, scleroderma/systemic sclerosis, and adhesive capsulitis.

In some cases, a disease or condition may comprise a cancer. In some cases, a cancer may comprise thyroid cancer, adrenal cortical cancer, anal cancer, aplastic anemia, bile duct cancer, bladder cancer, bone cancer, bone metastasis, central nervous system (CNS) cancers, peripheral nervous system (PNS) cancers, breast cancer, Castleman's disease, cervical cancer, childhood Non-Hodgkin's lymphoma, lymphoma, colon and rectum cancer, endometrial cancer, esophagus cancer, Ewing's family of tumors (e.g. Ewing's sarcoma), eye cancer, gallbladder cancer, gastrointestinal carcinoid tumors, gastrointestinal stromal tumors, gestational trophoblastic disease, hairy cell leukemia, Hodgkin's disease, Kaposi's sarcoma, kidney cancer, laryngeal and hypopharyngeal cancer, acute lymphocytic leukemia, acute myeloid leukemia, children's leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, liver cancer, lung cancer, lung carcinoid tumors, Non-Hodgkin's lymphoma, male breast cancer, malignant mesothelioma,

multiple myeloma, myelodysplastic syndrome, myeloproliferative disorders, nasal cavity and paranasal cancer, nasopharyngeal cancer, neuroblastoma, oral cavity and oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, penile cancer, pituitary tumor, prostate cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma (adult soft tissue cancer), melanoma skin cancer, non-melanoma skin cancer, stomach cancer, testicular cancer, thymus cancer, uterine cancer (e.g. uterine sarcoma), vaginal cancer, vulvar cancer, or Waldenstrom's macroglobulinemia. In some cases, a cancer may be selected from a list maintained by the National Cancer Institute (https://www.cancer.gov/types).

~~[00129]~~[00130] A condition or a disease, as disclosed herein, can include hyperproliferative disorders. Malignant hyperproliferative disorders can be stratified into risk groups, such as a low risk group and a medium-to-high risk group. Hyperproliferative disorders can include but may not be limited to cancers, hyperplasia, or neoplasia. In some cases, the hyperproliferative cancer can be breast cancer such as a ductal carcinoma in duct tissue of a mammary gland, medullary carcinomas, colloid carcinomas, tubular carcinomas, and inflammatory breast cancer; ovarian cancer, including epithelial ovarian tumors such as adenocarcinoma in the ovary and an adenocarcinoma that has migrated from the ovary into the abdominal cavity; uterine cancer; cervical cancer such as adenocarcinoma in the cervix epithelial including squamous cell carcinoma and adenocarcinomas; prostate cancer, such as a prostate cancer selected from the following: an adenocarcinoma or an adenocarcinoma that has mi-grated to the bone; pancreatic cancer such as epithelioid carcinoma in the pancreatic duct tissue and an adenocarcinoma in a pancreatic duct; bladder cancer such as a transitional cell carcinoma in urinary bladder, urothelial carcinomas (transitional cell carcinomas), tumors in the urothelial cells that line the bladder, squamous cell carcinomas, adenocarcinomas, and small cell cancers; leukemia such as acute myeloid leukemia (AML), acute lymphocytic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, hairy cell leukemia, myelodysplasia, myeloproliferative disorders, acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), mastocytosis, chronic lymphocytic leukemia (CLL), multiple myeloma (MM), and myelodysplastic syndrome (MDS);

bone cancer; lung cancer such as non-small cell lung cancer (NSCLC), which may be divided into squamous cell carcinomas, adenocarcinomas, and large cell undifferentiated carcinomas, and small cell lung cancer; skin cancer such as basal cell carcinoma, melanoma, squamous cell carcinoma and actinic keratosis, which may be a skin condition that sometimes develops into squamous cell carcinoma; eye retinoblastoma; cutaneous or intraocular (eye) melanoma; primary liver cancer (cancer that begins in the liver); kidney cancer; autoimmune deficiency syndrome (AIDS)-related lympho-ma such as diffuse large B-cell lymphoma, B-cell immunoblastic lymphoma and small non-cleaved cell lymphoma; Kaposi's Sarcoma; viral-induced cancers including hepatitis B virus (HBV), hepatitis C virus (HCV),and hepatocellular carcinoma; human lymphotropic virus-type 1 (HTLV-1) and adult T-cell leukemia/lymphoma; and human papilloma virus (HPV) and cervical cancer; central nervous system (CNS) cancers such as primary brain tumor, which includes gliomas (astrocytoma, anaplastic astrocytoma, or glioblastoma multiforme), oligodendrogliomas, ependymomas, meningiomas, lymphomas, schwannomas, and medulloblastomas; peripheral nervous system (PNS) cancers such as acoustic neuromas and malignant peripheral nerve sheath tumors (MPNST) including neurofibromas and schwannomas, malignant fibrous cytomas, malignant fibrous histiocytomas, malignant meningiomas, malignant mesotheliomas, and malignant mixed Müllerian tumors; oral cavity and oropharyngeal cancer such as hypopharyngeal cancer, laryngeal cancer, nasopharyngeal cancer, and oropharyngeal cancer; stomach cancer such as lymphomas, gastric stromal tumors, and carcinoid tumors; testicular cancer such as germ cell tumors (GCTs), which include seminomas and nonseminomas, and gonadal stromal tumors, which include Leydig cell tumors and Sertoli cell tumors; thymus cancer such as to thymomas, thymic carcinomas, Hodgkin disease, non-Hodgkin lymphomas carcinoids or carcinoid tumors; rectal cancer; and colon cancer. In some cases, the dis-eases stratified, classified, characterized, or diagnosed by the methods of the present disclosure include but may not be limited to thyroid disorders such as for example benign thyroid disorders including but not limited to follicular adenomas, Hurthle cell adenomas, lymphocytic thyroiditis, and thyroid hyperplasia. In some cases, the diseases stratified, classified, characterized, or

diagnosed by the methods of the present disclosure include but may not be limited to malignant thyroid disorders such as for example follicular carcinomas, follicular variant of papillary thyroid carcinomas, medullary carcinomas, and papillary carcinomas.

~~[00130]~~[00131] Conditions or diseases of the present disclosure can include a genetic disorder. A genetic disorder may be an illness caused by abnormalities in genes or chromosomes. Genetic disorders can be grouped into two categories: single gene disorders and multifactorial and polygenic (complex) dis-orders. A single gene disorder can be the result of a single mutated gene. Inheriting a single gene disorder can include but not be limited to autosomal dominant, autosomal recessive, X-linked dominant, X-linked recessive, Y-linked and mitochondrial inheritance. In some cases, one mutated copy of the gene can be necessary for a person to be affected by an autosomal dominant disorder. Examples of autosomal dominant type of disorder can include but are not limited to Huntington's disease, Neurofibromatosis 1, Marfan Syndrome, Hereditary nonpolyposis colorectal cancer, or Hereditary multiple exostoses. In autosomal recessive disorders, two copies of the gene can be mutated for a subject to be affected by an autosomal recessive disorder. Examples of this type of disorder can include but may not be limited to cystic fibrosis, sickle-cell disease (also partial sickle-cell disease), Tay-Sachs disease, Niemann-Pick disease, or spinal muscular atrophy. X-linked dominant disorders are caused by mutations in genes on the X chromosome such as X-linked hypophosphatemic rickets. Some X-linked dominant conditions such as Rett syndrome, Incontinentia Pigmenti type 2 and Aicardi Syndrome can be fatal. X-linked recessive disorders are also caused by mutations in genes on the X chromosome. Examples of this type of disorder can include but are not limited to Hemophilia A, Duchenne muscular dystrophy, red-green color blindness, muscular dystrophy and Androgenetic alopecia. Y-linked disorders are caused by mutations on the Y chromo-some. Examples can include but are not limited to Male Infertility and hypertrichosis pinnae. The genetic disorder of mitochondrial inheritance, also known as maternal inheritance, can apply to genes in mitochondrial DNA such as in Leber's Hereditary Optic Neuropathy.

~~[00131]~~[00132] Genetic disorders may also be complex, multifactorial or polygenic. Polygenic genetic disorders can be associated with the effects of multiple genes in combination with lifestyle and environmental factors. Although complex genetic disorders can cluster in families, they do not have a clear-cut pattern of inheritance. Multifactorial or polygenic disorders can include heart disease, diabetes, asthma, autism, autoimmune diseases such as multiple sclerosis, cancers, ciliopathies, cleft palate, hypertension, inflammatory bowel disease, mental retardation or obesity.

~~[00132]~~[00133] Other genetic disorders can include but may not be limited to 1p36 deletion syndrome, 21-hydroxylase deficiency, 22q11.2 deletion syndrome, aceruloplasminemia, achondrogenesis, type II, achondroplasia, acute intermittent porphyria, adenylosuccinate lyase deficiency, Adrenoleu-kodystrophy, Alexander disease, alkaptonuria, alpha-1 antitrypsin deficiency, Alstrom syndrome, Alzheimer's disease (type 1, 2, 3, and 4), Amelogenesis Imperfecta, amyotrophic lateral sclerosis, Amyotrophic lateral sclerosis type 2, Amyotrophic lateral sclerosis type 4, amyotrophic lateral sclerosis type 4, androgen insensitivity syndrome, Anemia, Angelman syndrome, Apert syndrome, ataxia-telangiectasia, Beare-Stevenson cutis gyrata syndrome, Benjamin syndrome, beta thalassemia, biotimidase deficiency, Birt-Hogg-Dube syndrome, bladder cancer, Bloom syndrome, Bone diseases, breast cancer, Camptomelic dysplasia, Canavan disease, Cancer, Celiac Disease, Chronic Granulomatous Disorder (CGD), Charcot-Marie-Tooth disease, Charcot-Marie-Tooth disease Type 1, Charcot-Marie-Tooth disease Type 4, Charcot-Marie-Tooth disease Type 2, Charcot-Marie-Tooth disease Type 4, Cockayne syndrome, Coffin-Lowry syndrome, collagenopathy types II and XI, Colorectal Cancer, Congenital absence of the vas deferens, congenital bilateral absence of vas deferens, congenital diabetes, congenital erythropoietic porphyria, Congenital heart disease, congenital hypothyroidism, Connective tissue disease, Cowden syndrome, Cri du chat syndrome, Crohn's dis-ease, fibrostenosing, Crouzon syndrome, Crouzonodermoskeletal syndrome, cystic fibrosis, De Grouchy Syndrome, Degenerative nerve diseases, Dent's disease, developmental disabilities, Di-George syndrome, Distal spinal muscular atrophy type V, Down syndrome, Dwarfism,

Ehlers-Danlos syndrome, Ehlers-Danlos syndrome arthrochalasia type, Ehlers-Danlos syndrome classical type, Ehlers-Danlos syndrome dermatosparaxis type, Ehlers-Danlos syndrome kyphoscoliosis type, vascular type, erythropoietic protoporphyria, Fabry's disease, Facial injuries and disorders, factor V Leiden thrombophilia, familial adenomatous polyposis, familial dysautonomia, fanconi anemia, FG syndrome, fragile X syndrome, Friedreich ataxia, Friedreich's ataxia, G6PD deficiency, galactosemia, Gaucher's disease (type 1, 2, and 3), Genetic brain disorders, Glycine encephalopathy, Haemochromatosis type 2, Haemochromatosis type 4, Harlequin Ichthyosis, Head and brain malformations, Hearing disorders and deafness, Hearing problems in children, hemochromatosis (neonatal, type 2 and type 3), hemophilia, hepatoerythropoietic porphyria, hereditary coproporphyria, Hereditary Multiple Exostoses, hereditary neuropathy with liability to pressure palsies, hereditary non-polyposis colorectal cancer, homocystinuria, Huntington's disease, Hutchinson Gilford Progeria Syndrome, hyperoxaluria, primary, hyperphenylalaninemia, hypochondrogenesis, hypochondroplasia, idic15, incontinentia pigmenti, Infantile Gaucher disease, infantile-onset ascending hereditary spastic paralysis, Infertility, Jackson-Weiss syndrome, Joubert syndrome, Juvenile Primary Lateral Sclerosis, Kennedy disease, Klinefelter syndrome, Kniest dysplasia, Krabbe disease, Learning disability, Lesch-Nyhan syndrome, Leukodystrophies, Li-Fraumeni syndrome, lipoprotein lipase deficiency, familial, Male genital disorders, Marfan syndrome, McCune-Albright syndrome, McLeod syndrome, Mediterranean fever, familial, Menkes disease, Menkes syndrome, Metabolic disorders, methemoglobinemia beta-globin type, Methemoglobinemia congenital methaemoglobinaemia, methylmalonic acidemia, Micro syndrome, Microcephaly, Movement disorders, Mowat-Wilson syndrome, Mucopolysaccharidosis (MPS I), Muenke syndrome, Muscular dystrophy, Muscular dystrophy, Duchenne and Becker type, muscular dystrophy, Duchenne and Becker types, myotonic dystrophy, Myotonic dystrophy type 1 and type 2, Neonatal hemochromatosis, neurofibromatosis, neurofibromatosis 1, neurofibromatosis 2, Neurofibromatosis type I, neurofibromatosis type II, Neurologic diseases, Neuromuscular disorders, Niemann-Pick disease, Nonketotic hyperglycinemia, nonsyndromic deafness,

Nonsyndromic deafness autosomal recessive, Noonan syn-drome, osteogenesis imperfecta (type I and type III), otospondylomegaepiphyseal dysplasia, pantothenate kinase-associated neurodegeneration, Patau Syndrome (Trisomy 13), Pendred syndrome, Peutz-Jeghers syndrome, Pfeiffer syndrome, phenylketonuria, porphyria, porphyria cutanea tarda, Prader-Willi syndrome, primary pulmonary hypertension, prion disease, Progeria, propionic acidemia, protein C deficiency, protein S deficiency, pseudo-Gaucher disease, pseudoxanthoma elasticum, Retinal disorders, retinoblastoma, retinoblastoma FA—Friedreich ataxia, Rett syndrome, Rubinstein-Taybi syndrome, Sandhoff disease, sensory and autonomic neuropathy type III, sickle cell anemia, skeletal muscle regeneration, Skin pigmentation disorders, Smith Lemli Opitz Syn-drome, Speech and communication disorders, spinal muscular atrophy, spinal-bulbar muscular atrophy, spinocerebellar ataxia, spondyloepimetaphyseal dysplasia, Strudwick type, spondyloepiphyseal dysplasia congenita, Stickler syndrome, Stickler syndrome COL2A1, Tay-Sachs disease, tetrahydrobiopterin deficiency, thanatophoric dysplasia, thiamine-responsive megaloblastic anemia with diabetes mellitus and sensorineural deafness, Thyroid disease, Tourette's Syndrome, Treacher Collins syndrome, triple X syndrome, tuberous sclerosis, Turner syndrome, Usher syndrome, variegate porphyria, von Hippel-Lindau disease, Waardenburg syndrome, Weissenbacher-Zweymüller syndrome, Wilson disease, Wolf-Hirschhorn syndrome, Xeroderma Pigmentosum, X-linked severe combined immunodeficiency, X-linked sideroblastic anemia, or X-linked spinal-bulbar muscle atrophy.

~~[00133]~~[00134] As used herein, a second therapy can include chemotherapy, radiation, bone marrow transplantation, immunotherapy, hormone therapy, cryotherapy, surgical procedure (such as tumor resection) or any combination thereof. A second therapy can include administration of a pharmaceutical composition, such as a small molecule. A second therapy can include administration of a pharmaceutical composition, such as one or more antiviral drugs, for example, interferon, oseltamivir, ribavirin, daclatasvir, sofosbuvir, velpatasvir, voxilapresvir, remdesivir, indomethacin, or any combination thereof. A second therapy can include administration of a pharmaceutical composition, such as one or more antibiotics. A second

therapy can comprise administration of a muscle relaxant, an anti-depressant, a steroid, an opioid, a cannabis-based therapeutic, acetaminophen, a non-steroidal anti-inflammatory, a neuropathic agent, a cannabis, a progestin, a progesterone, or any combination thereof. A neuropathic agent may comprise gabapentin. A non-steroidal anti-inflammatory can comprise naproxen, ibuprofen, a COX-2 inhibitor, or any combination thereof. A second therapy can comprise administration of a biologic agent, cellular therapy, regenerative medicine therapy, a tissue engineering approach, a stem cell transplantation or any combination thereof. A second therapy can comprise a medical procedure. A medical procedure can comprise an epidural injection (such as a steroid injection), acupuncture, exercise, physical therapy, an ultrasound, a surgical therapy, a chiropractic manipulation, an osteopathic manipulation, a chemonucleolysis, or any combination thereof. A second therapy can comprise use of a breathing assist device or a ventilator. A second therapy can comprise administration of a regenerative therapy or an immunotherapy such as a protein, a stem cell, a cord blood cell, an umbilical cord tissue, a tissue, or any combination thereof. A second therapy can comprise a biosimilar.

~~[00134]~~[00135] The term "fragment," as used herein, can be a portion of a sequence, a subset that can be shorter than a full-length sequence. A fragment can be a portion of a gene. A fragment can be a portion of a peptide or protein. A fragment can be a portion of an amino acid sequence. A fragment can be a portion of an oligonucleotide sequence. A fragment can be less than about: 20, 30, 40, 50 amino acids in length. A fragment can be less than about: 2, 5, 10, 20, 30, 40, 50 oligonucleotides in length.

~~[00135]~~[00136] Compositions and methods as described herein include methods of identifying mutations or modifications to a guide strand that may improve therapeutic efficacy through improved knockdown (at least partially or completely) of one or more targets. Sequence modifications to a passenger strand are also described herein. Chemical modifications to one or more both strands are also described herein. Constructs or mimics as described herein may comprise one or more sequence alterations in a guide strand that may curb target recognition toward a preferred mRNA target among a plurality of mRNA targets. Such constructs or mimics

may enhance stability, at least partially reduce or eliminate an immune stimulation, improve a pharmacological activity, retain one or more poly-targeting effect, or any combination thereof.

~~[00136]~~[00137] Compositions and methods as described herein can include miR mimics (such as miR-30, miR-29, miR-26, miR-27, miR-101, miR-145, miR-205, miR-338, and miR-375 mimics) having improved stability, safety, and/or activity as compared to a comparable miR (such as miR-30, miR-29, miR-26, miR-27, miR-101, miR-145, miR-205, miR-338, and miR-375).

~~[00137]~~[00138] Mimics can be identified using intelligent design, testing of one or more chemical modification patterns, sequence mutation in passenger strands that can improve mimic complementarity or alter mimic duplex structure, and sequence mutation to the guide strand that can yield benefits in activity. In some cases, a sequence mutation in the guide strand can move beyond use of natural guide sequence to use of mimics. For example, sequence alterations can tailor guide strand activity toward preferred downstream targets, such as clinical targets.

~~[00138]~~[00139] Because miRNAs are grouped in families based on sequence similarity, mutant sequences may be ‘non-natural’ or ‘artificial’ miRNA family members.

~~[00139]~~[00140] The miR-30 family of microRNAs (miRNAs) can include 5 family members in humans (i.e. miR-30a, miR-30b, miR-30c-1, miR-30c-2, miR-30d, and miR-30e). This family can possess tumor suppressor activity in several types of cancers and suppression of fibrosis, scarring or both. For example, miR-30 downregulation can be linked to poor outcome in recurrent head and neck cancer patients. As such, the miR-30 family is an ideal candidate for miRNA replacement therapy. However, developing miR-30 mimics into novel drug candidates can include overcoming pharmacological barriers for therapeutic application such as: (i) inherent metabolic instability being readily degraded by a variety of nucleases found in biological fluids; (ii) contain sequence patterns (e.g. CpG motifs) and structures that may be natural ligands for cell receptors (i.e. TLR family, RIG-I-like receptors, and other RNA sensors) that trigger the innate immune response that can lead to toxicities *in vivo;* (iii) poor pharmacology in regards to potency

and/or efficacy as natural miRNA sequences may not inherently optimized for mimetics; (iv) delivery *in vivo* to diseased or target tissues; (v) or any combination thereof.

~~[00140]~~[00141] The miR-29 family of microRNAs (miRNAs) can include 4 family members in humans (i.e. miR-29a, miR-29b-1, miR-29b-2, and miR-29c). This family can possess tumor suppressor activity in several types of cancers, antiviral activity, and suppression of fibrosis, scarring or both. For example, miR-29 overexpression can be linked to reduce Hepatitis C Viral abundance in cell culture. As such, the miR-29 family is an ideal candidate for miRNA replacement therapy. However, developing miR-29 mimics into novel drug candidates can include overcoming pharmacological barriers for therapeutic application such as: (i) inherent metabolic instability being readily degraded by a variety of nucleases found in biological fluids; (ii) contain sequence patterns (e.g. CpG motifs) and structures that may be natural ligands for cell receptors (i.e. TLR family, RIG-I-like receptors, and other RNA sensors) that trigger the innate immune response that can lead to toxicities *in vivo;* (iii) poor pharmacology in regards to potency and/or efficacy as natural miRNA sequences may not inherently optimized for mimetics; (iv) delivery *in vivo* to diseased or target tissues; (v) or any combination thereof.

~~[00141]~~[00142] In addition, high-degree of chemical modification and/or implementing conventional modification patterns based on siRNA design can often negatively impact miRNA mimic activity by reducing their pleiotropic effects of silencing multiple transcripts. Chemical modifications can alter sequence recognition of otherwise natural downstream targets. While desirable for improving siRNA specificity towards its intended target by reducing its “miRNA-like” off-target effect, it can be undesirable for miRNA mimetics that are developed to deliberately target multiple transcripts.

~~[00142]~~[00143] An oligonucleotide can comprise a sugar modification. An oligonucleotide can comprise a plurality of sugar modifications. A sugar modification can comprise a glucose or derivative thereof. A sugar modification can comprise a ribose or deoxyribose. A sugar modification can comprise a monosaccharide, a disaccharide, a trisaccharide or any combination thereof.

~~[00143]~~[00144] An oligonucleotide can comprise a chemical modification. An oligonucleotide can comprise a plurality of chemical modifications. An oligonucleotide can comprise a plurality of chemical modifications within a portion of an oligonucleotide, such as a terminal end. A chemical modification can comprise a methyl group, a fluoro group, a methoxyethyl group, an ethyl group, an amide group, an ester group, more than one of any of these, or any combination thereof. A chemical modification can comprise 1-methyl-adenosine, 1-methyl-guanosine, 1-methyl-inosine, 2,2-dimethyl-guanosine, 2,6-diaminopurine, 2'-amino-2'-deoxyadenosine, 2 '-amino-2'-deoxycytidine, 2'-amino-2'-deoxyguanosine, 2 '-amino-2'-deoxyuridine, 2-amino-6-chloropurineriboside, 2-aminopurine-riboside, 2'-araadenosine, 2'-aracytidine, 2'-arauridine, 2'-azido-2'-deoxyadenosine, 2'-azido-2'-deoxycytidine, 2'-azido-2 '-deoxyguanosine, 2'-azido-2'-deoxyuridine, 2-chloroadenosine, 2'-fluoro-2'-deoxyadenosine, 2 '-fluoro-2'-deoxycytidine, 2'-fluoro-2'-deoxyguanosine, 2'-fluoro-2'-deoxyuridine, 2'-fluorothymidine, 2-methyl-adenosine, 2-methyl-guanosine, 2-methyl-thio-N6-isopenenyl-adenosine, 2'-O-methyl-2-aminoadenosine, 2'-O-methyl-2'-deoxyadenosine, 2 '-0-methyl-2'-deoxycytidine, 2 '-0-methyl-2'-deoxyguanosine, 2'-0-methyl-2'-deoxyuridine, 2'-O-methyl-5-methyluridine, 2'-O-methylinosine, 2'-O-methylpseudouridine, 2-thiocytidine, 2-thio-cytidine, 3-methyl-cytidine, 4-acetyl-cytidine, 4-thiouridine, 5-(carboxyhydroxymethyl)-uridine, 5,6-dihydrouridine, 5-aminoallylcytidine, 5-aminoallyl-deoxyuridine, 5-bromouridine, 5-carboxymethylaminomethyl-2-thio-uracil, 5-carboxymethylamonomethyl-uracil, 5-chloro-ara-cytosine, 5-fluoro-uridine, 5-iodouridine, 5-methoxycarbonylmethyl-uridine, 5-methoxy-uridine, 5-methyl-2-thio-uridine, 6-Azacytidine, 6-azauridine, 6-chloro-7-deaza-guanosine, 6-chloropurineriboside, 6-mercapto-guanosine, 6-methyl-mercaptopurine-riboside, 7-deaza-2'-deoxy-guanosine, 7-deazaadenosine, 7-methyl-guanosine, 8-azaadenosine, 8-bromo-adenosine, 8-bromo-guanosine, 8-mercapto-guanosine, 8-oxoguanosine, benzimidazole-riboside, beta-D-mannosyl-queosine, dihydro-uridine, inosine, N1-methyladenosine, N6-([6-ami nohexyl] carbamoylmethyl)-adenosine, N6-isopentenyl-adenosine, N6-methyl-adenosine, N7-methyl-xanthosine, N-uracil-5-oxyacetic acid methyl ester,

puromycin, queosine, uracil-5-oxyacetic acid, uracil-5-oxyacetic acid methyl ester, wybutoxosine, xanthosine, xylo-adenosine, or any combination thereof.

~~[00144]~~[00145] In some cases, the engineered oligonucleotide can comprise a chemical modification, such as a chemical modification to a base or a sugar of the engineered oligonucleotide, relative to a natural base or sugar. In some cases, the engineered oligonucleotide can comprise more than one chemical modification, such as a plurality of chemical modifications. A portion of bases or a portion of sugars of the engineered oligonucleotide can comprise one or more chemical modifications. In some cases, about: 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more of bases or sugars in an engineered oligonucleotide can be chemically modified.

~~[00145]~~[00146] In some cases, a ribonucleotide (or in some cases a deoxynucleotide), can be modified, such as the base component, the sugar (ribose) component, the phosphate component forming the backbone of the engineered oligonucleotide, or any combination thereof, by a chemical modification as described herein.

~~[00146]~~[00147] In some cases, an engineered oligonucleotide can be engineered or modified to increase a specificity for an RNA sequence among a plurality of RNA sequences. An engineered oligonucleotide can be modified to significantly increase a specificity for an RNA sequence among a plurality of RNA sequences. Increased specificity can be compared to a comparable oligonucleotide that may not be engineered or can be compared to a comparable oligonucleotide that may be engineered or modified in a different way. A specificity may be increased by at least about: 2%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more as compared to a comparable oligonucleotide. An engineered oligonucleotide can be engineered or modified to increase a specificity for a first RNA sequence as compared to a second RNA sequence

~~[00147]~~[00148] In some cases, an engineered oligonucleotide can be selective for an RNA sequence encoding a gene, such as a gene implicated in a disease or condition as described herein, such as an oncogene. In some cases, the engineered oligonucleotide can be selective for

an RNA sequence encoding an oncogene, among a plurality of RNA sequences. In some cases, an engineered oligonucleotide can comprise an increased specificity for an RNA sequence encoding a gene, such as an oncogene, among a plurality of RNA sequences. In some cases, an engineered oligonucleotide can be selective for an RNA sequence encoding ITGA6, SERPINE1, EGFR, or any combination thereof, among a plurality of RNA sequences.

~~[00148]~~[00149] A chemically modified nucleotide as used herein can be guanosine, uridine, adenosine, thymidine or cytosine including, without implying any limitation, any natively occurring or non-natively occurring guanosine, uridine, adenosine, thymidine or cytidine that has been altered chemically, for example by acetylation, methylation, hydroxylation, etc., including 1-methyl-adenosine, 1-methyl-guanosine, 1-methyl-inosine, 2,2-dimethyl-guanosine, 2,6-diaminopurine, 2'-amino-2'-deoxyadenosine, 2 '-amino-2'-deoxycytidine, 2'-amino-2'-deoxyguanosine, 2 '-amino-2'-deoxyuridine, 2-amino-6-chloropurineriboside, 2-aminopurine-riboside, 2'-araadenosine, 2'-aracytidine, 2'-arauridine, 2'-azido-2'-deoxyadenosine, 2'-azido-2'-deoxycytidine, 2'-azido-2 '-deoxyguanosine, 2'-azido-2'-deoxyuridine, 2-chloroadenosine, 2'-fluoro-2'-deoxyadenosine, 2'-fluoro-2'-deoxycytidine, 2'-fluoro-2'-deoxyguanosine, 2'-fluoro-2'-deoxyuridine, 2'-fluorothymidine, 2-methyl-adenosine, 2-methyl-guanosine, 2-methyl-thio-N6-isopenenyl-adenosine, 2’-O-methyl-2-aminoadenosine, 2’-O-methyl-2'-deoxyadenosine, 2’-O-methyl-2'-deoxycytidine, 2’-O-methyl-2'-deoxyguanosine, 2’-O-methyl-2'-deoxyuridine, 2’-O-methyl-5-methyluridine, 2'-O-methylinosine, 2’-O-methylpseudouridine, 2-thiocytidine, 2-thio-cytidine, 3-methyl-cytidine, 4-acetyl-cytidine, 4-thiouridine, 5-(carboxyhydroxymethyl)-uridine, 5,6-dihydrouridine, 5-aminoallylcytidine, 5-aminoallyl-deoxyuridine, 5-bromouridine, 5-carboxymethylaminomethyl-2-thio-uracil, 5-carboxymethylamonomethyl-uracil, 5-chloro-ara-cytosine, 5-fluoro-uridine, 5-iodouridine, 5-methoxycarbonylmethyl-uridine, 5-methoxy-uridine, 5-methyl-2-thio-uridine, 6-Azacytidine, 6-azauridine, 6-chloro-7-deaza-guanosine, 6-chloropurineriboside, 6-mercapto-guanosine, 6-methyl-mercaptopurine-riboside, 7-deaza-2'-deoxy-guanosine, 7-deazaadenosine, 7-methyl-guanosine, 8-azaadenosine, 8-bromo-adenosine, 8-bromo-guanosine, 8-mercapto-guanosine, 8-oxoguanosine, benzimidazole-riboside, beta-D-

mannosyl-queosine, dihydro-uridine, inosine, N1-methyladenosine, N6-([6-ami nohexyl] carbamoylmethyl)-adenosine, N6-isopentenyl-adenosine, N6-methyl-adenosine, N7-methyl-xanthosine, N-uracil-5-oxyacetic acid methyl ester, puromycin, queosine, uracil-5-oxyacetic acid, uracil-5-oxyacetic acid methyl ester, wybutoxosine, xanthosine, or xylo-adenosine. The preparation of such variants is known to the person skilled in the art, for example from US patents US 4,373,071, US 4,401 ,796, US 4,415,732, US 4,458,066, US 4,500,707, US 4,668,777, US 4,973,679, US 5,047,524, US 5,132,418, US 5,153,319, US 5,262,530 or 5,700,642.

~~[00149]~~[00150] In some cases, the engineered nucleotide can comprise a chemically modified nucleotide such as 2-amino-6-chloropurineriboside-5'-triphosphate, 2-aminopurine-riboside-5'-triphosphate, 2 -aminoadenosine-5'-triphosphate, 2 '-amino-2'-deoxycytidine-triphosphate, 2-thiocytidine-5'-triphosphate, 2-thiouridine-5'-triphosphate, 2'-fluorothymidine-5'-triphosphate, 2'-O-methyl-inosine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5-ami noallylcytidine-5'-triphosphate, 5-ami noallyluridine-5'-triphosphate, 5-bromocytidine-5'-triphosphate, 5-bromouridine-5'-triphosphate, 5-bromo-2'-deoxycytidine-5'-triphosphate, 5-bromo-2'-deoxyuridine-5'-triphosphate, 5-iodocytidine-5'-triphosphate, 5-iodo-2'-deoxycytidine-5'-triphosphate, 5-iodouridine-5'-triphosphate, 5-iodo-2 '-deoxyuridine-5'-triphosphate, 5-methylcytidine-5'-triphosphate, 5-methyluridine-5'-triphosphate, 5-propynyl-2'-deoxycytidine-5'-triphosphate, 5-propynyl-2 '-deoxyuridine-5'-triphosphate, 6-azacytidine-5'-triphosphate, 6-azauridine-5'-triphosphate, 6-chloropurineriboside-5'-triphosphate, 7-deazaadenosine-5'-triphosphate, 7-deazaguanosine-5'-triphosphate, 8-azaadenosine-5'-triphosphate, 8-azidoadenosine-5'-triphosphate, benzimidazole-riboside-5'-triphosphate, N1-methyladenosine-5'-triphosphate, N1-methylguanosine-5'-triphosphate, N6-methyladenosine-5'-triphosphate, 06-methylguanosine-5'-triphosphate, pseudouridine-5'-triphosphate, puromycin-5'-triphosphate, xanthosine-5'-triphosphate, or any combination thereof.

~~[00150]~~[00151] In some cases, the engineered oligonucleotide can comprise a chemically modified nucleotide such as pyridin-4-one ribonucleoside, 5-aza-uridine, 2-thio-5-aza-uridine, 2-

thiouridine, 4-thio-pseudouridine, 2-thio-pseudouridine, 5-hydroxyuridine, 3-methyluridine, 5-carboxymethyl-uridine, 1-carboxymethyl-pseudouridine, 5-propynyl-uridine, 1-propynyl-pseudouridine, 5-taurinomethyluridine, 1-taurinomethyl-pseudouridine, 5-taurinomethyl-2-thio-uridine, 1-taurinomethyl-4-thio-uridine, 5-methyl-uridine, 1-methyl-pseudouridine, 4-thio-1-methyl-pseudouridine, 2-thio-1-methyl-pseudouridine, 1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-1-deaza-pseudouridine, dihydrouridine, dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-dihydropseudouridine, 2-methoxyuridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, 4-methoxy-2-thio-pseudouridine, or any combination thereof.

~~[00151]~~[00152] In some cases, the engineered oligonucleotide can comprise a chemically modified nucleotide such as 5-aza-cytidine, pseudoisocytidine, 3-methyl-cytidine, N4-acetylcytidine, 5-formylcytidine, N4-methylcytidine, 5-hydroxymethylcytidine, 1-methyl-pseudoisocytidine, pyrrolo-cytidine, pyrrolo-pseudoisocytidine, 2-thio-cytidine, 2-thio-5-methyl-cytidine, 4-thio-pseudoisocytidine, 4-thio-1-methyl-pseudoisocytidine, 4-thio-1-methyl-1-deaza-pseudoisocytidine, 1-methyl-1-deaza-pseudoisocytidine, zebularine, 5-aza-zebularine, 5-methyl-zebularine, 5-aza-2-thio-zebularine, 2-thio-zebularine, 2-methoxy-cytidine, 2-methoxy-5-methyl-cytidine, 4-methoxy-pseudoisocytidine, 4-methoxy-1-methyl-pseudoisocytidine, or any combination thereof.

~~[00152]~~[00153] In some cases, the engineered oligonucleotide can comprise a chemically modified nucleotide such as 2-aminopurine, 2, 6-diaminopurine, 7-deaza-adenine, 7-deaza-8-aza-adenine, 7-deaza-2-aminopurine, 7-deaza-8-aza-2-aminopurine, 7-deaza-2, 6-diaminopurine, 7-deaza-8-aza-2, 6-diaminopurine, 1-methyladenosine, N6-methyladenosine, N6-isopentenyladenosine, N6-(cis-hydroxyisopentenyl)adenosine, 2-methylthio-N6-(cis-hydroxyisopentenyl) adenosine, N6-glycinylcarbamoyladenosine, N6-threonylcarbamoyladenosine, 2-methylthio-N6-threonyl carbamoyladenosine, N6,N6-dimethyladenosine, 7-methyladenine, 2-methylthio-adenine, 2-methoxy-adenine, or any combination thereof.

~~[00153]~~[00154] In some cases, the engineered oligonucleotide can comprise a chemically modified nucleotide such as inosine, 1-methyl-inosine, wyosine, wybutosine, 7-deaza-guanosine, 7-deaza-8-aza-guanosine, 6-thio-guanosine, 6-thio-7-deaza-guanosine, 6-thio-7-deaza-8-aza-guanosine, 7-methyl-guanosine, 6-thio-7-methyl-guanosine, 7-methylinosine, 6-methoxy-guanosine, 1-methylguanosine, N2-methylguanosine, N2,N2-dimethylguanosine, 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, 1-methyl-6-thio-guanosine, N2-methyl-6-thio-guanosine, N2,N2-dimethyl-6-thio-guanosine, or any combination thereof.

~~[00154]~~[00155] In some cases, the engineered oligonucleotide can comprise a chemically modified nucleotide such as 6-aza-cytidine, 2-thio-cytidine, alpha-thio-cytidine, pseudo-iso-cytidine, 5-aminoallyl-uridine, 5-iodo-uridine, N1-methyl-pseudouridine, 5,6-dihydrouridine, alpha-thio-uridine, 4-thio-uridine, 6-aza-uridine, 5-hydroxy-uridine, deoxy-thymidine, 5-methyl-uridine, pyrrolo-cytidine, inosine, alpha-thio-guanosine, 6-methyl-guanosine, 5-methyl-cytdine, 8-oxo-guanosine, 7-deaza-guanosine, N1-methyl-adenosine, 2-amino-6-chloro-purine, N6-methyl-2-amino-purine, pseudo-iso-cytidine, 6-chloro-purine, N6-methyl-adenosine, alpha-thio-adenosine, 8-azido-adenosine, 7-deaza-adenosine, or any combination thereof.

~~[00155]~~[00156] In some cases, the engineered oligonucleotide can comprise a chemically modified nucleotide, which can be chemically modified at the 2' position. The chemically modified oligonucleotide can comprise a substituent at the 2' carbon atom, wherein the substituent can comprise a halogen, an alkoxy group, a hydrogen, an aryloxy group, an amino group or an aminoalkoxy group, such as a 2'-hydrogen (2'-deoxy), 2’-O-methyl, 2’-O-methoxyethyl, 2'-fluoro, 2’ Methoxyethyl, 2′-fluoro, Locked Nucleic acid, or any combination thereof.

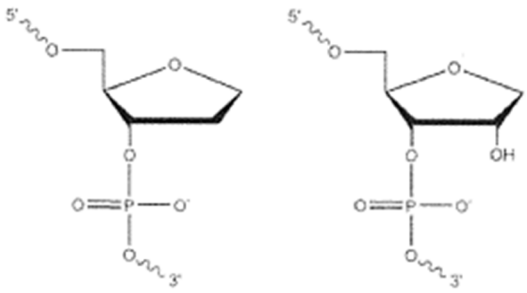
~~[00156]~~[00157] Another chemical modification (such as one involving the 2' position of a nucleotide) can be a locked nucleic acid (LNA) nucleotide, an ethylene bridged nucleic acid (ENA) nucleotide, an (S)-constrained ethyl cEt nucleotide, a bridged nucleic acid (BNA) or any combination thereof. A backbone modification can lock the sugar of the modified nucleotide into a preferred northern conformation. In some case, a presence of that type of modification in the

target sequence of the engineered oligonucleotide can allow for stronger and faster binding of the targeting sequence to the target site.

~~[00157]~~[00158] In some cases, the engineered oligonucleotide can comprise at least one chemically modified nucleotide, wherein the phosphate backbone, which can be incorporated into the engineered oligonucleotide, can be modified. One or more phosphate groups of the backbone can be modified, for example, by replacing one or more of the oxygen atoms with a different substituent. Further, the modified nucleotide can include a full replacement of an unmodified phosphate moiety with a modified phosphate as described herein. Examples of modified phosphate groups can include a phosphorothioate, a methylphosphonate, a phosphoroselenate, a borano phosphate, a borano phosphate ester, a hydrogen phosphonate, a phosphoroamidate, an alkyl phosphonate, an aryl phosphonate or a phosphotriester. The phosphate linker can also be modified by the replacement of a linking oxygen with nitrogen (bridged phosphoroamidates), sulfur (bridged phosphorothioates) and carbon (bridged methylene-phosphonates).

~~[00158]~~[00159] In some cases, the engineered oligonucleotide can comprise a sugar modification. The sugar modification can comprise a conjugate, such as a linker. In some cases, the engineered oligonucleotide can comprise one or more linker groups. The engineered oligonucleotide can be linked to an antibody, a protein, a lipid, an aptamer, a small molecule, a drug, or any combination thereof. A linker can form a covalent bond. The engineered oligonucleotide can be linked to one or more engineered oligonucleotides, such as a second engineered oligonucleotide via a linker. In some cases, the linker may be a cleavable linker. In some cases, a linker can comprise an azide linker. An engineered oligonucleotide can comprise a base of a nucleotide that is glycosylated with a glycan. In some cases, the engineered oligonucleotide can comprise an abasic site, such as a nucleotide lacking an organic base. In some cases, the abasic nucleotide can comprise a chemical modification as described herein, such as at the 2' position of the ribose. In some cases, the 2' C atom of the ribose can be substituted with a substituent such as a halogen, an alkoxy group, a hydrogen, an aryloxy group, an amino

group or an aminoalkoxy group, in some cases from 2'-hydrogen (2'-deoxy), 2'-O-methyl, 2'-O-methoxyethyl or 2'-fluoro. In some cases, an abasic site nucleotide can comprise structures 1 A or 1 B:



~~[00159]~~[00160] dSpacer (1A) rSpacer (1 B)

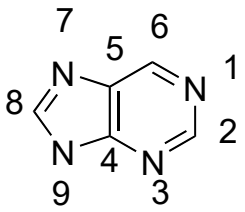
~~[00160]~~[00161] In some cases, the engineered oligonucleotide can be modified by the addition of a '5'-CAP' structure. A 5'-cap can be an entity, such as a modified nucleotide entity, which can 'cap' the 5'-end of a mature miRNA. A 5'-cap can typically be formed by a modified nucleotide, particularly by a derivative of a guanine nucleotide. In some cases, the 5'-cap can be linked to the 5'-terminus of the engineered oligonucleotide via a 5'-51-triphosphate linkage. A 5'-cap can be methylated, e.g. m7GpppN, wherein N can be the terminal 5' nucleotide of the nucleic acid carrying the 5'-cap, such as the 5'-end of an RNA. A 5'-cap structure can include glyceryl, inverted deoxy abasic residue (moiety), 4', 5' methylene nucleotide, 1-(beta-D-erythrofuranosyl) nucleotide, 4'-thio nucleotide, carbocyclic nucleotide, 1 ,5-anhydrohexitol nucleotide, L-nucleotides, alpha-nucleotide, modified base nucleotide, threo-pentofuranosyl nucleotide, acyclic 3',4'-seco nucleotide, acyclic 3,4-dihydroxybutyl nucleotide, acyclic 3,5 di hydroxy pentyl nucleotide, 3'-3'-inverted nucleotide moiety, 3'-3'-inverted abasic moiety, 3'-2'-inverted nucleotide moiety, 3'-2'-inverted abasic moiety, 1 ,4-butanediol phosphate, 3'-phosphoramidate, hexylphosphate, aminohexyl phosphate, 3'-phosphate, 3'phosphorothioate, phosphorodithioate, or bridging or non-bridging methylphosphonate moiety. In some cases, a modified 5'-CAP structure can comprise a CAP1 (methylation of the ribose of the adjacent nucleotide of m7G), CAP2 (methylation of the ribose of the 2nd nucleotide downstream of the m7G), CAP3 (methylation of the ribose of the 3rd nucleotide downstream of the m7G), CAP4 (methylation of the ribose of the

4th nucleotide downstream of the m7G), ARCA (anti-reverse CAP analogue, modified ARCA (e.g. phosphothioate modified ARCA), inosine, N1-methyl-guanosine, 2'-fluoro-guanosine, 7-deaza-guanosine, 8-oxo-guanosine, 2-amino-guanosine, LNA-guanosine, or 2-azido-guanosine.

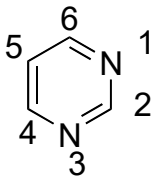
~~[00161]~~[00162] The term “epigenetic marker” as used herein, can be any covalent modification of a nucleic acid base. In some cases, a covalent modification can comprise adding a methyl group, a hydroxymethyl group, a carbon atom, an oxygen atom, or any combination thereof to one or more bases of a nucleic acid sequence. In some cases, a covalent modification can comprise changing an oxidation state of a molecule associated with a nucleic acid sequence, such as an oxygen atom, or a combination thereof. A covalent modification can occur at any base, such as a cytosine, a thymine, a uracil, an adenine, a guanine, or any combination thereof. In some cases, an epigenetic modification can comprise an oxidation or a reduction. A nucleic acid sequence can comprise one or more epigenetically modified bases. An epigenetically modified base can comprise any base, such as a cytosine, a uracil, a thymine, adenine, or a guanine. An epigenetically modified base can comprise a methylated base, a hydroxymethylated base, a formylated base, or a carboxylic acid containing base or a salt thereof. An epigenetically modified base can comprise a 5-methylated base, such as a 5-methylated cytosine (5-mC). An epigenetically modified base can comprise a 5-hydroxymethylated base, such as a 5-hydroxymethylated cytosine (5-hmC). An epigenetically modified base can comprise a 5-formylated base, such as a 5-formylated cytosine (5-fC). An epigenetically modified base can comprise a 5-carboxylated base or a salt thereof, such as a 5-carboxylated cytosine (5-caC). In some cases, an epigenetically modified base can comprise a methyltransferase-directed transfer of an activated group (mTAG).

~~[00162]~~[00163] An epigenetically modified base can comprise one or more bases or a purine (such as Structure 1) or one or more bases of a pyrimidine (such as Structure 2). An epigenetic modification may occur at one or more of any positions. For example, an epigenetic modification can occur at one or more positions of a purine, including positions 1, 2, 3, 4, 5, 6, 7, 8, 9, as

shown in Structure 1. In some cases, an epigenetic modification can occur at one or more positions of a pyrimidine, including positions 1, 2, 3, 4, 5, 6, as shown in Structure 2.



Structure 1



Structure 2

~~[00163]~~[00164] A nucleic acid sequence may comprise an epigenetically modified base. A nucleic acid sequence may comprise a plurality of epigenetically modified bases. A nucleic acid sequence may comprise an epigenetically modified base positioned within a CG site, a CpG island, or a combination thereof. A nucleic acid sequence may comprise different epigenetically modified bases, such as a methylated base, a hydroxymethylated base, a formylated base, a carboxylic acid containing base or a salt thereof, a plurality of any of these, or any combination thereof.

In some cases, an engineered oligonucleotide or salt thereof, when chemically modified, can be of formula: Guide Pattern 1, Guide Pattern 2, or Guide Pattern 3 as shown in Table 7.

Table 7 – Chemical modification patterns

Pattern	**Sequence (5′-3′)**
Guide Pattern 1	$(N)_a(mN)_b(N)_cNN$
Guide Pattern 2	$(N)_a(mN)_b(N)_csfNsmN$
Guide Pattern 3	$(fNmN)_h(mN)_i(fNmN)_jsfNsmN$
Passenger Pattern 1	$CAP–mNmNmN(N)_kmNmNmN$

N can be any natural or non-natural nucleotide; mN can be a 2'-O-methyl-modified uracil, guanine, adenine, or cytosine; s can be a phosphothionate-modified backbone; fN can be 2'fluoro-modified uracil, guanine, adenine, or cytosine; CAP can be 5'-terminal methyl group (5'-OMethyl) or alkylamino group such as amino-carbon 6 chain (5'-Amino C6); a can be from 8-10; b can be from 7-10; c can be from 2-4; h can be 5-7; i can be 0 or 1; j can be 3-4; and k can be 12-19.

~~[00164]~~[00165] An engineered oligonucleotide or salt thereof, when chemically modified, can have at least 90% sequence identity to any one of SEQ ID NOs: 52-89, 127-154, 184-201, 205-222, 225-233, 235-243, 264-443, 445-453, 455-463, 620, 644-825, 835-837, and 846-899.

~~[00165]~~[00166] In some cases, a vector can be used for miR delivery, in an *in vitro* setting, *in vivo* setting, or any combination thereof. In some cases, the vector can be targeted to but may not be limited to a mammal, or a specific organ, or a specific cell, or any combination thereof. The vector can comprise any composition described herein. In some cases, the vector can comprise more than one composition, such as a miR-30 family construct and a second miR-29 family construct, or a miR-30 family construct and a second miR-30 family construct, or a miR-29 family construct and a second miR-29 family construct, or any combination thereof. In some cases, the vector can be comprised of a liposome, a nanoparticle or any combination thereof. The liposome can include but may not be limited to unilamellar liposome, multilamellar liposome, archaeosome, niosome, novasome, cryptosome, emulsome, vesosome, or a derivative of any of these, or any combination thereof. The nanoparticle can include but may not be limited to biopolymeric nanoparticle, alginate nanoparticle, xanthan gum nanoparticle, cellulose nanoparticle, dendrimer, polymeric micelle, polyplexed, inorganic nanoparticle, nanocrystal, metallic nanoparticle, quantum dot, protein nanoparticle, polysaccharide nanoparticle, or a derivative of any of these, or any combination thereof. In some cases, the vector can be an RNA viral vector which can include but may not be limited to a retrovirus, lentivirus, coronavirus, alphavirus, flavivirus, rhabdovirus, morbillivirus, picornavirus, coxsackievirus, or picornavirus or portions of any of these, or fragments of any of these, or any combination thereof. In some cases, the vector can be a DNA viral vector which can include but may not be limited to an adeno-associated viral (AAV) vector, adenovirus, hybrid adenoviral system, hepadnavirus, parvovirus,

papillomavirus, polyomavirus, herpesvirus, poxvirus, a portion of any of these, or a fragment of any of these, or any combination thereof.

~~[00166]~~[00167] Compositions and methods are described herein can include miR mimics. Such miR mimics can contain one or more sequence modifications, one or more chemical modifications, or a combination thereof that can: enhance stability of the miR mimic; substantially reduce or eliminate immune stimulation (such as via the innate immune response); improve pharmacological activity of the miR mimic; retain poly-targeting effects of the miR mimic; or any combination thereof. Engineered miR family members comprising sequence alterations in the guide strand can bias target recognition toward two or more clinical targets.

~~[00167]~~[00168] As used herein, a “biosimilar” or a “biosimilar product” can refer to a biological product that is licensed based on a showing that it is substantially similar to an FDA-approved biological product, known as a reference product, and has no clinically meaningful differences in terms of safety and effectiveness from the reference product. Only minor differences in clinically inactive components may be allowable in biosimilar products. A “biosimilar” of an approved reference product/biological drug refers to a biologic product that is similar to the reference product based upon data derived from (a) analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; (b) animal studies (including the assessment of toxicity); and/or (c) a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product. In some embodiments, the biosimilar biological product and reference product utilize the same mechanism or mechanisms of action for the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling, but only to the extent the mechanism or mechanisms of action are known for the reference product. In some embodiments, the condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been

previously approved for the reference product. In some embodiments, the route of administration, the dosage form, and/or the strength of the biological product are the same as those of the reference product. In some embodiments, the facility in which the biological product is manufactured, processed, packed, or held may meet standards designed to assure that the biological product continues to be safe, pure, and potent. The reference product may be approved in at least one of the U.S., Europe, or Japan. In some embodiments, a response rate of human subjects administered the biosimilar product can be 50%-150% of the response rate of human subjects administered the reference product. For example, the response rate of human subjects administered the biosimilar product can be 50%-100%, 50%-110%, 50%-120%, 50%-130%, 50%-140%, 50%-150%, 60%-100%, 60%-110%, 60%-120%, 60%-130%, 60%-140%, 60%-150%, 70%-100%, 70%-110%, 70%-120%, 70%-130%, 70%-140%, 70%-150%, 80%-100%, 80%-110%, 80%-120%, 80%-130%, 80%-140%, 80%-150%, 90%-100%, 90%-110%, 90%-120%, 90%-130%, 90%-140%, 90%-150%, 100%-110%, 100%-120%, 100%-130%, 100%-140%, 100%-150%, 110%-120%, 110%-130%, 110%-140%, 110%-150%, 120%-130%, 120%-140%, 120%-150%, 130%-140%, 130%-150%, or 140%-150% of the response rate of human subjects administered the reference product. In some embodiments, a biosimilar product and a reference product can utilize the same mechanism or mechanisms of action for the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling, but only to extent the mechanism or mechanisms are known for the reference product. To obtain approval for biosimilar drugs, studies and data of structure, function, animal toxicity, pharmacokinetics, pharmacodynamics, immunogenicity, and clinical safety and efficacy may be needed. A biosimilar may also be known as a follow-on biologic or a subsequent entry biologic. In some embodiments, a biosimilar product may be substantially similar to the reference product notwithstanding minor different in clinically inactive components.

~~[00168]~~[00169] As used herein, a “interchangeable biological product” may refer to a biosimilar of an FDA-approved reference product and may meet additional standards for interchangeability. In some embodiments, an interchangeable biological product can, for example, produce the same

clinical result as the reference product in any given subject. In some embodiments, an interchangeable product may contain the same amount of the same active ingredients, may possess comparable pharmacokinetic properties, may have the same clinically significant characteristics, and may be administered in the same way as the reference compound. In some embodiments, an interchangeable product can be a biosimilar product that meets additional standards for interchangeability. In some embodiments, an interchangeable product can produce the same clinical result as a reference product in all the reference product's licensed conditions of use. In some embodiments, an interchangeable product can be substituted for the reference product by a pharmacist without the intervention of the health care provider who prescribed the reference product. In some embodiments, when administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch. In some embodiments, an interchangeable product can be a regulatory agency approved product. In some embodiments, a response rate of human subjects administered the interchangeable product can be 80%-120% of the response rate of human subjects administered the reference product. For example, the response rate of human subjects administered the interchangeable product can be 80%-100%, 80%-110%, 80%-120%, 90%-100%, 90%-110%, 90%-120%, 100%-110%, 100%-120%, or 110%-120 of the response rate of human subjects administered the reference product.

~~[00169]~~[00170] In some cases, at least a portion of the RNA sequence can be encoded by an oncogene. The oncogene can comprise ABL1, ABL2, AKT1, AKT2, AKT3, ATF1, BCL11A, BCL2, BCL3, BCL6, BCR, BRAF, CARD11, CBLB, CBLC, CCND1, CCND2, CCND3, CDX2, CTNNB1, DDB2, BBIT3, BBX6, DEK, EGFR, ELK4, ERBB2, ERBB3, E2F1, 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, SERPINE1, SMO, SS18, TCL1A, TET2, TFG, TLX1, TPR, USP6, or any combination thereof. In some cases, the oncogene can comprise ITGA6, BCL2, DEK, PLAG1, SERPINE1, MYCN, LMO2, PIM1, EGFR, IRS1, NT5E, EGFR, GLDC, SOCS1, STAT1, LOX, PDGFRB, WNT5A, CD80, CCNA1, THBS2, IGF1R, AFAP1L2, CTHRC1, MET, FAP, SERPINE1, IL1A, GJA1, MYBL2, CDK6, ATG9A, SETDB1or any combination thereof. In some cases, an engineered oligonucleotide or salt thereof as described herein can be selective for one or more particular RNA sequences among a plurality of RNA sequences. For example, an engineered oligonucleotide or salt thereof as described herein can be selective for one or more of ABL1, ABL2, AKT1, AKT2, ATF1, BCL11A, BCL2, BCL3, BCL6, BCR, BRAF, CARD11, CBLB, CBLC, CCND1, CCND2, CCND3, CDX2, CTNNB1, DDB2, BBIT3, BBX6, DEK, EGFR, ELK4, ERBB2, 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, SERPINE1, SMO, SS18, TCL1A, TET2, TFG, TLX1, TPR, USP6, relative to a plurality of other RNA sequences.

~~[00170]~~[00171] A portion of an RNA sequence can be at least about: 70%, 75%, 80%, 85%, 90%, 95% of the bases of an RNA sequence.

~~[00171]~~[00172] In some cases, the disease or condition can comprise fibrosis. In some cases, at least a portion of the RNA sequence can be 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. In some cases, at least a portion of the RNA sequence can be encoded by COL1A1, COL11A1, COL2A1, COL5A3, COL5A2, COL4A4, COL21A1, COL7A1, COL9A1, COL19A1, COL5A1, COL22A1, COL8A1, COL4A2, COL6A2, COL24A1, COL4A3, COL4A6, COL25A1, COL16A1, COL15A1, or any combination thereof. In some cases, at least a portion of the RNA sequence can be encoded by

the platelet-derived growth factor gene, such as PDGFB, PDGFC, or PDGFRB. In some cases, at least a portion of the RNA sequence can be encoded by the TGF-β signaling gene (such as WISP1 or TGFB2). In some cases, at least a portion of the RNA sequence can be encoded by the collagen remodeling gene (such as LOXL2). In some cases, at least a portion of the RNA sequence can be encoded by the extracellular matrix remodeling gene (such as COL1A1, COL11A1, COL2A1, COL5A3, COL5A2, COL4A4, COL21A1, COL7A1, COL9A1, COL19A1, COL5A1, COL22A1, COL8A1, COL4A2, COL6A2, COL24A1, COL4A3, COL4A6, COL25A1, COL16A1, COL15A1, LOXL2, or Elastin). In some cases, at least a portion of the RNA sequence can be encoded by the Wnt signaling gene (such as WISP1). In some cases, at least a portion of the RNA sequence can be encoded by the HDGF signaling gene (such as HDGF). A portion can be at least about: 60%, 70%, 80%, 90%, 95% of the bases on the RNA sequence.

~~[00172]~~[00173] In some cases, the engineered oligonucleotide or salt thereof can be from about 5 to about 50 nucleotides in length. In some cases, the engineered oligonucleotide or salt thereof can be from about 5 to about 40 nucleotides in length. In some cases, the engineered oligonucleotide or salt thereof can be from about 5 to about 30 nucleotides in length. In some cases, the engineered oligonucleotide or salt thereof can be from about 5 to about 25 nucleotides in length. In some cases, the engineered oligonucleotide or salt thereof can be from about 5 to about 60 nucleotides in length. In some cases, the engineered oligonucleotide or salt thereof can be from about 5 to about 80 nucleotides in length. In some cases, the engineered oligonucleotide or salt thereof can be from about 5 to about 100 nucleotides in length. In some cases, the engineered oligonucleotide or salt thereof can be from about 5 to about 200 nucleotides in length.

~~[00173]~~[00174] In some cases, the engineered oligonucleotide or salt thereof, when contacted with the mRNA sequence, can produce at least about: 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 3, 4, 5, 6, 7, 8, 9, 10 fold lower expression of a polypeptide encoded by the mRNA sequence, as compared to contacting an equivalent amount of the otherwise comparable oligonucleotide with

the mRNA sequence. Lower expression can be from about 1.2-fold to about 10-fold lower expression.

~~[00174]~~[00175] In some cases, the engineered oligonucleotide or salt thereof, when contacted with the mRNA sequence, can produce at least about: 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 3, 4, 5, 6, 7, 8, 9 ,10 fold lower activity of a polypeptide encoded by the mRNA sequence, as compared to contacting an equivalent amount of the otherwise comparable oligonucleotide with the mRNA sequence. Lower activity can be from about 1.2-fold to about 10-fold lower activity.

~~[00175]~~[00176] In some cases, at least about: 70%, 7%, 80%, 85%, 90%, 95% of an initial amount of the engineered oligonucleotide or salt thereof remains when the engineered oligonucleotide or salt thereof can be stored in a closed container placed in a room for a time period of at least about: 1 month, 2 months, 3 months, 4 months, 5 months, 6 months at about from about 21 to about 25 degrees Celsius (such as about: 21, 22, 23, 24, 25 degrees Celsius) with a relative atmospheric humidity of from about 45% to about 55% (such as about: 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%). In some cases, the time period can be from about 1 month to about 1 year. In some cases, the time period can be from about 1 month to about 2 year. In some cases, the time period can be from about 1 month to about 6 months. In some cases, the time period can be from about 1 month to about 3 year. In some cases, the time period can be from about 1 month to about 9 months.

~~[00176]~~[00177] The disease or condition can comprise a viral infection such as a SARS virus infection, a Covid-19 viral infection, or an HCV Genotype 1 infection. In some cases, at least a portion of the RNA sequence can be encoded in a coronavirus genome (e.g. a SARS-CoV, a SARS-CoV2, a MERS-CoV, or a CoV-HKU1 genome). The RNA sequence can comprise at least about: 70%, 75%, 80%, 85%, 90%, 95% sequence identity to a sequence recited in SEQ ID NOS: 500-531, 829-831 (Table 6), SEQ ID NOS: 474-499, 826-828 (Table 6), SEQ ID NOS: 532-554 (Table 6), or SEQ ID NOS: 555-586 (Table 6). In some cases, an RNA sequence can comprise at least about: 70%, 75%, 80%, 85%, 90%, 95% sequence identity to SEQ ID NO: 476, SEQ ID NO: 481, or SEQ ID NO: 495. The RNA sequence can comprise at least about: 5, 10, 15,

20 contiguous bases having at least about: 70%, 75%, 80%, 85%, 90%, 95% sequence identity to SEQ ID NO: 476, SEQ ID NO: 481, or SEQ ID NO: 495. In some cases, at least a portion of the RNA sequence can be encoded in an HCV Genotype 1 genome. The RNA sequence can comprise at least about: 70%, 75%, 80%, 85%, 90%, 95% sequence identity to SEQ ID NO: 587, SEQ ID NO: 588, or SEQ ID NO: 589. The RNA sequence can comprise at least about: 5, 10, 15, 20 contiguous bases having at least about: 70%, 75%, 80%, 85%, 90%, 95% sequence identity to SEQ ID NO: 587, SEQ ID NO: 588, or SEQ ID NO: 589. In some cases, at least a portion of the RNA sequence is encoded in a SARS-CoV-2 virus genome. The RNA sequence can comprise at least about: 70%, 75%, 80%, 85%, 90%, 95% sequence identity to SEQ ID NO: 500, SEQ ID NO: 513, or SEQ ID NO: 518. The RNA sequence can comprise at least about: 5, 10, 15, 20 contiguous bases having at least about: 70%, 75%, 80%, 85%, 90%, 95% sequence identity to SEQ ID NO: 500, SEQ ID NO: 513, or SEQ ID NO: 518.

~~[00177]~~[00178] An engineered oligonucleotide or salt thereof can comprise at least about: 70%, 75%, 80%, 85%, 90%, 95% or more 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, or any combination thereof. An engineered oligonucleotide or salt thereof can comprise at least about 5, 10, 15, 20 contiguous bases having at least about: 70%, 75%, 80%, 85%, 90%, 95% or more 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, or any combination thereof.

~~[00178]~~[00179] A change in polypeptide expression, such as a fold lower or fold greater expression, can be determined by methods as described herein. For example, the engineered oligonucleotide or salt thereof can be contacted with an mRNA sequence and compared to contacting an equivalent amount of an miR-29 or miR-30 oligonucleotide naturally present in a cell. The change in expression can be determined by: (a) transfecting the engineered oligonucleotide into a first isolated cell comprising the mRNA sequence, (b) transfecting the

miR-29 or miR-30 oligonucleotide into a second isolated cell comprising the mRNA sequence, and (c) measuring an amount of the polypeptide expressed in the first isolated cell and the isolated second cell.

~~[00179]~~[00180] A nucleic acid construct can comprise a first strand comprising the engineered oligonucleotide and a second strand comprising a sequence complementary to at least a portion of the engineered oligonucleotide. The second strand may be complementary to at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more of the first strand. The second strand may be complementary to at least about: 5, 10, 15, or 20 contiguous bases of the first strand. A nucleic acid construct may comprise an end overhang, such as a 5' end or a 3' end. The first strand, the second strand or a combination thereof may comprise one or more chemical modifications. At least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% of bases of a first strand, a second strand, or a combination thereof may comprise a chemical modification. The first strand, the second strand or a combination thereof may comprise one or more sugar modifications. At least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% of bases of a first strand, a second strand, or a combination thereof may comprise a sugar modification. A sugar modification can comprise a glycosylated base. In some cases, a base of a nucleotide can be glycosylated with a glycan. The first strand, the second strand or a combination thereof may comprise a combination of bases having a chemical modification and a sugar modification.

~~[00180]~~[00181] In some cases, an engineered passenger oligonucleotide as described herein can comprise at least about: 70%, 75%, 80%, 85%, 90%, 95% or more sequence identity to any one of SEQ ID NOs: 6-11, 15-18, 21-23, 26-27, 29, 31, 33, 35, 37, 46-51, 90-99, 155-183, 202-204, 223-224, 234, 244, 444, 454, 464, 466, 838-839, and 900, or any combination thereof. An engineered passenger oligonucleotide as described herein can comprise at least about 5, 10, 15, 20 contiguous bases having at least about: 70%, 75%, 80%, 85%, 90%, 95% or more sequence identity to any one of SEQ ID NOs: 6-11, 15-18, 21-23, 26-27, 29, 31, 33, 35, 37, 46-51, 90-99, 155-183, 202-204, 223-224, 234, 244, 444, 454, 464, 466, 838-839, and 900, or any combination thereof.

~~[00181]~~[00182] In some cases, a second strand can comprise a chemically modified base of a nucleotide. In some cases, a subset of bases of the second strand can be chemically modified, such as from about 1% to about 5% of bases, from about 1% to about 10% of bases, from about 1% to about 20% of bases, from about 1% to about 30% of bases, from about 1% to about 40% of bases, from about 1% to about 50% of bases, from about 1% to about 60% of bases, from about 1% to about 70% of bases, from about 1% to about 80% of bases, or from about 1% to about 90% of bases, or more.

~~[00182]~~[00183] A second strand as described herein can be chemically modified in the same manner as described herein for the engineered oligonucleotide. In some cases, a second strand, when chemically modified, can have at least 90% sequence identity to any one of SEQ ID NOs: 51, 95-99.

~~[00183]~~[00184] A vector can be employed to deliver the engineered oligonucleotide, the nucleic acid construct, or any combination thereof. A vector can comprise DNA, such as double stranded DNA or single stranded DNA. A vector can comprise RNA. In some cases, the RNA can comprise a base modification. The vector can comprise a recombinant vector. The vector can be a vector that is modified from a naturally occurring vector. The vector can comprise at least a portion of a non-naturally occurring vector. Any vector can be utilized. In some cases, the vector can comprise a viral vector, a liposome, a nanoparticle, an exosome, an extracellular vesicle, or any combination thereof. In some cases, a viral vector can comprise an adenoviral vector, an adeno-associated viral vector (AAV), a lentiviral vector, a retroviral vector, a portion of any of these, or any combination thereof. In some cases, a nanoparticle vector can comprise a polymeric-based nanoparticle, an aminolipid based nanoparticle, a metallic nanoparticle (such as gold-based nanoparticle), a portion of any of these, or any combination thereof. In some cases, a vector can comprise an AAV vector. A vector can be modified to include a modified VP1 protein (such as an AAV vector modified to include a VP1 protein). An AAV can comprise a serotype – such as an AAV1 serotype, an AAV2 serotype, AAV3 serotype, an AAV4 serotype, AAV5

serotype, an AAV6 serotype, AAV7 serotype, an AAV8 serotype, an AAV9 serotype, a derivative of any of these, or any combination thereof.

~~[00184]~~[00185] A pharmaceutical composition can comprise the engineered oligonucleotide, the nucleic acid construct, the vector, or any combination thereof. The pharmaceutical composition can further comprise a pharmaceutically acceptable excipient, diluent or carrier. The pharmaceutical composition can be formulated in a unit dose form. The pharmaceutical composition can be formulated with a single active ingredient. The pharmaceutical composition can be encapsulated. The pharmaceutical composition can be formulated as a liquid or as a semi-solid, such as a gel, or a solid. The pharmaceutical composition can be formulated at a solution. The pharmaceutical composition can be formulated as an injectable. The pharmaceutical composition can be formulated as a subdermal implant. The pharmaceutical composition can be implantable. The pharmaceutical composition can be formulated for oral delivery.

~~[00185]~~[00186] A subject in need thereof may be treated for a disease or condition. A treatment may be a pre-treatment, a prophylactic treatment, or a preventive treatment. Treatment may include administration to the subject in need thereof the engineered oligonucleotide, a nucleic acid construct, a vector, or a pharmaceutical composition as described herein. Administration can include delivery via one or more delivery routes, such as oral, otic, ocular, rectal or any combination thereof. Administration can include delivery by an intravenous injection, an intramuscular injection, an intrathecal injection, an intraorbital injection, a subcutaneous injection, or any combination thereof. Treatment may include more than one engineered oligonucleotide delivered in a single dose. Delivery can be concurrent delivery, such as delivery more than one engineered oligonucleotide in a single injection or in two separate injections at the same time. Delivery can be sequential, such as delivery of a first dose and a second dose that can be separated by a period of time, such as minutes, hours, days, weeks, or months.

~~[00186]~~[00187] Treatment can include a second therapy or a co-therapy. In cases of treatment of cancer, a second therapy can include radiation, chemotherapy, an immunotherapy, surgery, or any combination thereof. In cases of treatment of a viral infection, a second therapy can include

an immunotherapy, an antiviral, or any combination thereof. In cases of treatment of fibrosis, a second therapy can include a lifestyle change, an organ transplant, an oxygen therapy, an organ rehabilitation, a pharmaceutical composition, or any combination thereof. Administration of a second therapy can be concurrent or sequential, such as separated by a period of time such as minutes, hours, days, weeks, or months.

~~[00187]~~[00188] In some cases, a subject may not have been previously diagnosed with a disease or condition. In some cases, a subject may have been diagnosed with a disease or condition. In some cases, a subject may not have received a definitive diagnosis of a disease or condition. In some cases, a subject may have previously had a disease or condition. A subject may be in remission. A subject may be at risk of developing a disease or condition (such as based at least in part on a previous condition, a lifestyle factor, a genetic variant, or any combination thereof). A subject may have received a diagnostic test. A diagnostic test can include an imaging procedure, a blood count analysis, a tissue pathology analysis, a biomarker analysis, or any combination thereof. In some cases, the disease or condition may be fibrosis or a related condition. In some cases, the disease or condition may be a viral infection, such as a SARS-CoV infection, a SARS-CoV2 infection, a MERS-CoV infection, a CoV-HKU1 infection, an HIV infection, an HCV infection, or any combination thereof. In some cases, the disease or condition may be cancer, such as a head cancer, a neck cancer, skin cancer, a cervical cancer, a prostate cancer, or any combination thereof.

~~[00188]~~[00189] Methods can include *in vivo* or *in vitro* delivery methods. Methods can include contacting a cell, such as a cell *in vivo* with the engineered oligonucleotide, the nucleic acid construct, the vector, or the pharmaceutical composition as described herein. Methods can include contacting a cell, such as an isolated and purified cell (such as a cell *in vitro*) with the engineered oligonucleotide, the nucleic acid construct, the vector, or the pharmaceutical composition as described herein. Methods can include contacting a tissue, such as an *in vivo* tissue or an isolated *in vitro* tissue, with the engineered oligonucleotide, the nucleic acid construct, the vector, or the pharmaceutical composition as described herein.

~~[00189]~~[00190] A kit can include the engineered oligonucleotide in a container, the nucleic acid construct in a container, the vector in a container, the pharmaceutical composition in a container. A kit can include more than one engineered oligonucleotide in a container, more than one vector in a container, more than one nucleic acid construct in a container, or more than one pharmaceutical composition in a container. A kit can include a plurality of containers, each container comprising one or more engineered oligonucleotides, or nucleic acid constructs, or vectors, or pharmaceutical compositions. A kit can include an excipient or a diluent or a buffer or a liquid or gel-like medium for storage of the engineered oligonucleotide, the nucleic acid construct, the vector, or the pharmaceutical composition. A kit can include an excipient or a diluent or a buffer or a liquid or gel-like medium for *in vivo* delivery to a subject of the engineered oligonucleotide, the nucleic acid construct, the vector, or the pharmaceutical composition. An excipient or diluent or buffer or liquid or gel-like medium can be included in the container housing the engineered oligonucleotide (or nucleic acid construct or vector or pharmaceutical composition) or housed in a separate container. A kit can include a delivery vehicle, such as a syringe or needle. A kit can include one or more reagents for a downstream analysis.

~~[00190]~~[00191] Referring to **FIG. 1A-B**, this figure shows natural miR-30 guide strand and passenger strand sequences and examples of engineered family members. **FIG. 1A** shows the sequences of all the natural miR-30 family members found in human (i.e. miR-30a-e-5p) which can have tumor suppressor activity in HNSCC. Sequence variation between the different family members as compared to miR-30a-5p are highlighted in light grey. A guanidine base at position 13 (highlighted in dark gray) represents a non-natural sequence addition comprising a subset of engineered family members that can have benefits over natural sequence for drug development. We have implemented this sequence modification in a subset of oligonucleotides. **FIG. 1B** shows the sequence of the mature miR-30a-3p passenger strand found in human miR-30a duplex. Listed are examples of non-natural passenger strand sequence (SEQ ID NO: 6 and 46 through 51) which can be used in combination with the guide strands to create, in part, the library of miR-30a mimic

duplexes. Changes in sequence from miR-30a-3p are highlighted in grey. The engineered sequence modifications can be implemented to alter duplex structure and biochemical characteristics including stability to nucleases and potency.

~~[00191]~~[00192] Referring to **FIG. 2A-C,** this figure shows a schematic visualization of guide strand interactions with cognate target sites in 3'UTRs of oncogenic mRNAs. **FIG. 2A** shows free energy (ΔG) and hybridization between natural miR-30a-5p sequence and target sites in the 3'UTRs of ITGA6, SERPINE1, and EGFR transcripts can be predicted using the software RNA hybrid 2.2. **FIG. 2B** shows free energy (ΔG) and hybridization between engineered family G007-30 (SEQ ID NO: 39) containing the 'G' insertion at position 13 and the ITGA6, SERPINE1, and EGFR target sites. Note the lower predicted free energy and greater complementarity can infer improved target recognition. **FIG. 2C** shows that a mimic containing the same 'G' insertion at position 13 as found in G007-30 can demonstrate improved knockdown of select oncogenic targets. M30-021 and M30-037 duplexes are composed of guide strands G039-30 (SEQ ID NO: 68) and G011-30 (SEQ ID NO: 55) respectively and contain the natural miR-30a sequence with certain chemical modifications. , M30-040 is composed of engineered guide strand G032-30 (SEQ ID NO: 65) and M30-048 is composed of guide strand G132-30 (SEQ ID NO: 88), both of which have the G007-30 'G' insertion but with different chemical modification patterns. UM-SCC-47 cells were plated in 6-well plates and transfected with 15 nM of the indicated engineered miR-30 mimics for 72 hrs. Following treatment, total RNA was collected from the wells and RT-qPCR was performed to determine expression of ITGA6, SERPINE1, and EGFR. HPRT1 served as an endogenous normalization control and expression levels were normalized to negative control (Neg Con) transfections. In each case, M30-040, with the 'G' insertion, demonstrated greater knockdown of targeted oncogenes than M30-021 and M30-037 (natural guide strand sequence) and demonstrated as good or greater knockdown of targeted oncogenes than M30-048, which also has the 'G' insertion.

~~[00192]~~[00193] Referring to **FIG. 3**, this figure shows a schematic visualization of miR-30-5p target sites in the MTDH 3'UTR. Shown is an illustration of the MTDH mRNA including its

coding domain and three experimentally-validated miR-30-5p target sites (indicated in grey) within its 3'UTR. Hybridization between natural miR-30a-5p and the MTDH target sites, as well as calculated free energy (ΔG) for miR-30-5p and all the indicated engineered guide strands were calculated using the software RNAhybrid 2.2 (https://bibiserv.cebitec.uni-bielefeld.de/rnahybrid). Net sum of free energy across all three target sites (NET) and their averaged ΔG (Avg.) is also indicated. Note all artificial guide strands have lower calculated net and averaged free energy for hybridization than natural miR-30-5p family members inferring improved target recognition.

~~[00193]~~[00194] Referring to **Table 8**, this table shows calculated free energy requirements for target recognition of natural and mimic miR-30 family guide strands to 3' UTR sites in EGFR, IGF1R, MET and IRS1 gene transcripts. miR-30 mimic exemplary guide strand constructs are indicated include G007-30 (SEQ ID NO: 39) and G064-30 (SEQ ID NO: 43) that have predicted improved base pairing and lower G targeting of these oncogenes.

Table 8: Calculated Free Energy Requirements for Target Recognition of Mimic Guide Strands to miR-30 Downstream Transcript

		Free energy (ΔG)* [kcal/mol]			
SEQ ID NO:	**Guide Strand**	**EGFR**	**IGF1R**	**MET**	**IRS1**
1	miR-30a-5p	-15.0	-16.4	-10.6	-19.8
2	miR-30b-5p	-13.6	-17.0	-11.6	-13.6
3	miR-30c-5b	-11.8	-17.0	-11.6	-13.6
4	miR-30d-5p	-14.8	-14.9	-10.6	-19.8
5	miR-30e-5p	-15.8	-16.4	-11.6	-19.8
628	G079-30	-15.5	-16.5	-10.6	-21.0
629	G080-30	-15.2	-15.3	-10.6	-14.0
630	G081-30	-14.2	-15.3	-10.6	-14.0
631	G082-30	-13.6	-15.3	-10.6	-13.0
632	G083-30	-12.3	-15.3	-10.6	-13.0
633	G084-30	-13.7	-13.9	-10.8	-12.1
634	G085-30	-11.8	-13.9	-10.8	-12.1
635	G086-30	-13.6	-13.9	-10.6	-12.1
636	G087-30	-11.8	-13.9	-10.6	-12.1
39	G007-30	-18.1	-17.4	-10.6	-21.1
624	G075-30	-14.1	-18.0	-14.1	-17.9
44	G065-30	-13.0	-18.0	-14.1	-17.8
40	G061-30	-16.4	-14.5	-10.6	-19.4
41	G062-30	-17.1	-17.4	-12.4	-21.1
42	G063-30	-16.2	-16.4	-11.0	-19.4
637	G088-30	-18.5	-16.7	-10.6	-16.1
638	G089-30	-13.0	-17.2	-10.6	-17.3

639	G090-30	-17.3	-18.2	-10.6	-18.8
640	G091-30	-13.4	-15.6	-11.1	-21.6
626	G077-30	-19.6	-17.2	-10.6	-18.7
627	G078-30	-19.8	-16.7	-10.6	-18.3
641	G092-30	-16.1	-17.3	-10.6	-21.4
642	G093-30	-19.3	-17.5	-10.6	-21.0

*Free energy (ΔG) was calculated using RNAhybrid 2.2 between the indicated mimic guide strand sequences and target sites in the 3'UTRs of EGFR (SEQ ID NO:469), IGF1R (SEQ ID NO: 832), MET (SEQ ID NO: 833), and IRS2 (SEQ ID NO: 834) gene transcripts. Lower predicted free energy (ΔG) infers improved target recognition.

~~[00194]~~[00195] Referring to **FIG. 4A-D**, this figure shows that engineered oligonucleotides hybridized to form novel miR-30-5p mimics can have equivalent or improved anti-tumor activity in cancer cell lines. **FIG. 4A** shows UM-SCC-1, UM-SCC-47, and UM-SCC-109 cells were plated in 96-well plates and were transfected with 15 nM mimics using RNAimax agent 6 hours after plating for 5 days. Following treatment, cell viability was assessed by XTT assay. All data represent the mean ± SEM relative to cells treated in absence of mimic (designated as 100% viability). All mimics can have unique patterns of chemical modifications and can have one of the modified passenger strands. Mimics are separated based on guide sequence including either miR-30a-5p (Native) or miR-G-30-5p derivatives (Engineered). Anti-tumor activity for each mimic can be statistically ($P<0.05$) an improvement in reducing cell viability or equivalent to natural miR-30a duplex in each cell line. **FIG. 4B** shows luciferase activity following treatments in a subline of UM-SCC-1 (UM-SCC-1^{luc}) genetically engineered to overexpress a luciferase reporter containing cancer-relevant miR-30 target sites within its 3' untranslated region (UTR). UM-SCC-1^{luc} cells were plated in 96-well plates and transfected with 15 nM mimics using RNAimax agent 6 hrs after plating for 3 days before cell lysis and luciferase assay. **FIG. 4C** displays the anti-tumor activity of native miR-30a and exemplar engineered mimics, M30-043 and M30-046, in additional cell lines with different genetic backgrounds. Indicated cancer cell lines were plated in 96-well plates and were transfected with 25 nM mimics using RNAimax agent 6 hrs after plating for 5 days. Following treatment, cell viability was assessed by XTT

assay. Statistical significance (P<0.01) compared to Neg Con treatment is indicated. **FIG. 4D** displays further anti-tumor activity of a panel of engineered miR-30 mimics in additional cancel cell lines with different histology and genetic backgrounds. Indicated cancer cell lines were plated in 96-well plates and were transfected with 25 nM mimics using RNAimax agent 6 hrs after plating for 5 days. Following treatment, cell viability was assessed by XTT assay. Statistical significance (P<0.01) compared to Neg Con treatment is indicated. All data represent the mean ± SEM from a minimum three independent experiments.

~~[00195]~~[00196] Referring to **FIG. 5A-B,** this figure shows chemical modifications and structural modifications of engineered mimic duplexes can improve guide strand and duplex stability to biological nucleases. **FIG. 5A** shows an example of Urea-PAGE resolving a nucleic acid marker (M) and sample comprising mimic duplex, guide strand, and degraded fragments (≤n-1). **FIG. 5B** shows engineered 10 uM miR-30-5p mimics were incubated in 10% human sera at 37˚C for the indicated lengths of time. Duplex stability at each time point was visualized by denaturing Urea-PAGE. An exceptional example displays that removal of the single nucleotide internal bulge in M30-040 stabilized the M30-044 mimic duplex to biological nucleases out to 7 days (168 hrs).

~~[00196]~~[00197] Referring to **FIG. 6A-B,** this figure shows that modification of mimic sequence and structure can improve stability. **FIG. 6A** shows engineered mimics; M30-025, M30-040, and M30-044; which have the identical highly stable engineered guide strand, G032-30 (SEQ ID NO: 65) in duplex with passenger strands with sequence and chemical modifications which alter the mimic structure. Indicated is the design schematic towards M30-044 incorporating design features that can further enhance mimic stability. Bases in bold contain 2'-O-methyl modifications, lower case bases have 2'-flouro substitutions, 'ps' signifies phosphothioate backbone and (Amino C6) indicates addition of an amino-carbon 6 chain. **FIG. 6B** shows mimics were incubated in 10% human sera at 37˚C for the indicated lengths of time. Duplex stability at each time point was visualized by denaturing Urea-PAGE. Mimics with enhanced stability can be preferred for use with conjugation-based delivery systems in which the mimic can be directly

exposed to nucleases in biological fluids and the delivery does not provide any additional shielding benefit. M30-040 displays superior anti-tumor activity compared to M30-025 or M30-044 as previously demonstrated in **FIG. 4B**.

~~[00197]~~[00198] Referring to **FIG. 7A-C,** this figure shows the effect of sequence changes on the mimic structure and activity. **FIG. 7A** displays the sequences of mimics; M30-033, M30-034, and M30-040. All guide strands have similar chemical modifications (not shown). The same is true for the passenger strands. M30-033 and M30-034 are comprised of the highly stable guide strand G042-30 (SEQ ID NO: 69) which contains the natural miR-30a-5p guide sequence. M30-040 is comprised of G032-30 (SEQ ID NO: 65) which has identical chemical modifications to G042-30 but has an inserted 'G' at position 13 (highlighted in grey). M30-033 retains a similar structure as M30-040 (i.e. internal bulge) and M30-034 has the same passenger strand as M30-040. **FIG. 7B** shows a panel of 6 HNSCC cell lines that were transfected with M30-033, M30-034, M30-040, or a negative control (Neg Con) at 15 nM for 5 days as described above. Cell viability was assessed by XTT assay. Mock treatments were transfected in the absence of mimic. All data represent the mean ± SEM from three independent experiments. Statistical improvement ($P<0.01$) in M30-040 reduction in cell viability compared to M30-033 (*) and M30-043 (#) were determined by a two-way t-test. **FIG. 7C** shows luciferase activity following 15 nM treatments of UM-SCC-1^{luc} genetically engineered to overexpress a luciferase reporter containing miR-30 target sites within its 3'UTR. All data represent the mean ± SEM from three independent experiments. Collectively, M30-040 demonstrates a greater reduction in cell viability and luciferase knockdown activity.

~~[00198]~~[00199] Referring to **FIG. 8A-B,** this figure shows anti-tumor activity of miR-30 mimic, M30-040, is dependent on guide strand incorporation into RNA-induced Silencing Complex (RISC). **FIG. 8A** shows the structure of two modifications that can be made to the 5' terminus of the guide strand. In this experiment, two variants of M30-040 were synthesized with either a 5'-terminal methyl group (5'-OMethyl) or amino-carbon 6 chain (5'-Amino C6) modification of the guide strand, referred to as mimics 5'OMe M30-040 and 5'Amino C6 M30-040, respectively.

Chemical modification of the 5'-hydroxyl terminus in guide strands can attenuate activity at least in context to siRNA duplexes by blocking intracellular phosphorylation and subsequent recognition by the RISC effector. **FIG. 8B** shows UM-SCC-1 and A431 cancer cells treated with each mimic at 15 nM and cell viability was assessed by XTT assay on day 5 as described above. Both 5'-terminal modifications interfere with anti-cancer cell activity of M30-040 *in vitro.*

~~[00199]~~[00200] Referring to **FIG. 9A-C,** this figure shows an example development path of an engineered miR-30 mimic with improved activity. In **FIG. 9A**, the sequence and structure of mimics M30-037 and M30-043 are composed of guide strands G011-30 (SEQ ID NO: 55) and G129-30 (SEQ ID NO: 86) respectively and contain the natural miR-30a sequence with the chemical modifications as shown. Sequence and structures are also displayed for engineered mimics M30-046 and M30-048 which are composed of guide strand G130-30 (SEQ ID NO: 87) and G132-30 (SEQ ID NO: 88) respectively and contain an engineered sequence. Its chemical modification pattern was designed to retain poly-targeting activity of downstream transcripts. Indicated is the design schematic towards M30-048 incorporating an accumulation of features leading to improved activity, including a 3' terminal modification pattern and mimic bulge structure. Bases in bold contain 2'-O-Methyl modifications, lower case bases have 2'-fluoro substitutions, 'ps' signifies phosphothioate backbone and (Amino C6) indicates addition of an amino-carbon 6 chain. **FIG. 9B** displays anti-tumor activity in a panel of cancer cell lines transfected with the indicated mimics or a negative control (Neg Con) at 15 nM for 5 days. Cell viability was assessed by XTT assay. Mock treatments were transfected in the absence of mimic. All data represent the mean ± SEM of at least three independent experiments. **FIG. 9C** displays luciferase activity following 15 nM treatments of UM-SCC-1^{luc} as described above. All data represent the mean ± SEM from three independent experiments.

~~[00200]~~[00201] Referring to **FIG. 10A-B, FIG. 10A** displays improved anticancer activity and silencing of engineered mimic M30-043 which is composed of guide strand G129-30 (SEQ ID NO: 86) which is a miR-30 mimic containing the natural miR-30a sequence with chemical modifications. Compared to unmodified, natural miR-30a, M30-043 has improved activity on

cell viability at 7.5 nM in a panel of 7 HNSCC cell lines *in vitro.* Statistical significance ($P<0.05$) compared to miR-30a treatment is indicated. **FIG. 10B** shows luciferase activity following 15 nM treatments in a subline of UM-SCC-1 (UM-SCC-1^{luc}) genetically engineered to overexpress a luciferase reporter containing miR-30 target sites within its 3'UTR. Mock samples were transfected in the absence of API. All data represent the mean ± SEM from three independent experiments.

~~[00201]~~[00202] Referring to **FIG. 11A-B,** this figure displays reductions in innate immunostimulation for engineered miR-30 mimics. Human Peripheral Blood Mononuclear Cells (PBMCs)(~2-6 x 10^5 cells) were plated in round bottom 96 well plates and transfected at 133 nM concentrations of the indicated mimics for 48 hours with RNAiMAX reagent. Levels of TNF-α (**FIG. 11A**) and IFN-α (**FIG. 11B**) in supernatant media were quantified by ELISA. Poly (dA:dT) oligonucleotide served as a positive control for immunostimultation. Transfection with a non-chemically modified RNA duplex (Non-mod) demonstrated potential of mimic immunostimulation. Cells treated in the absence of mimic served to establish baseline.

~~[00202]~~[00203] Referring to **FIG. 12A-D,** this figure displays sensitization of cancer cells to approved treatments, cisplatin and cetuximab, when treated with engineered mimic, M30-040, in combination *in vitro.* **FIG. 12A** shows UM-SCC-1 and -46 cancer cells were cultured in the presence of escalating micro-doses of cisplatin for ≥3 months to create sublines resistant to cisplatin. Dose response curves evaluating cytotoxicity demonstrated enhanced resistance to cisplatin compared to parental cell lines. **FIG. 12B** shows parental and cisplatin-resistant cell lines were transfected with 15 nM M30-040 or nonspecific control mimic (Neg Con) for 5 days as described above. Relative cell number was quantified by XTT. Data is normalized to mock transfection treatments. **FIG. 12C** shows combination treatment of parental UM-SCC-1 and -46 cells transfected with M30-040 at 15 nM for 48 h and then subsequently treated with cisplatin at their respective IC50 concentrations (Cis IC50). Relative cell number was quantified by XTT at day 5 post-transfection. **FIG. 12D** shows another cancer cell line, UM-SCC-47, were transfected

with 15 nM M30-040 for 48 h and subsequently treated with the indicated concentrations of cetuximab. M30-040 pre-treatment may have sensitized UM-SCC-47 cells to cetuximab.

~~[00203]~~[00204] Referring to **FIG. 13A-C,** this figure shows anti-tumor activity in orthotopic HNSCC tumors. **FIG. 13A** shows female SCID mice were implanted with UM-SCC-1^{Luc} subline in floor-of-mouth on the left side of their oral cavity. 14 days after tumor implantation, bioluminescence was monitored in live animals using *In Vivo* Imaging System (IVIS) by dosing with D-luciferin at 150 mg/kg via IP injection. Animals were treated by intravenous injection (IV) with 3 doses BIW at 3 mg/kg with NOV340 (PMID: 24832107) LNP-formulated mimics M30-037 and M30-040 or Empty NOV340 LNP control. Images show tumor bioluminescence from a pair of anesthetized animals in each treatment group at day 0 prior to first dose and day 13 of the study. **FIG. 13B** shows bioluminescence was quantified for each animal at the indicated time points and mean radiance ± SEM was plotted to generate tumor growth curves. Indicated are the 3 sequential BIW doses of formulated mimic. **FIG. 13C** female SCID mice were implanted with UM-SCC-109 tumors on the right flank, grown to ~150 mm3, and subsequently treated by intravenous injection (IV) at 3 mg/kg with NOV340 formulated M30-040 or Empty NOV340 LNP control for 6 doses on a BIW schedule. Tumor growth curves were plotted by calculating tumor volume at each time point. A significant growth delay was observed with M30-040 treatment.

~~[00204]~~[00205] Referring to **FIG. 14A-B**, this figure shows local tumor treatment with engineered mimic M30-048. **FIG. 14A** shows Female SCID mice were implanted with UM-SCC-1^{Luc} subline in floor-of-mouth on the left side of their oral cavity. 14 days after tumor implantation, bioluminescence was monitored in live animals using In Vivo Imaging System (IVIS) by dosing with D-luciferin at 150 mg/kg via IP injection. Engineered mimic, M30-048, or a Negative control mimic (Neg. Con.) was formulated into an Atelocollagen gel using the AteloGene® local kit (koken). Animals were treated with a single treatment of 1.5 mg/kg or 3 mg/kg of M30-048 or 3 mg/kg of Neg. Con mimic and silencing of luciferase was monitored for

96 hrs. **FIG. 14B** displays quantitation of luciferase signal which is completely silenced by 96 hours at both doses.

~~[00205]~~[00206] Referring to **FIG. 15,** this figure shows natural miR-29 guide strand sequences and examples of engineered family members. Shown are the sequences of the natural miR-29 family members found in human (i.e. miR-29a-c-3p). Sequence variation between the different family members as compared to miR-29c-3p are highlighted in grey. Examples of non-natural sequences comprising subsets of engineered family members can include (i) combining the natural differences between miR-29a-3p and miR-29b-3p into hybrid sequences (Hybrid); (ii) A-to-G and/or U-to-G base mutations at positions 14 and/or 15, respectively (Mutation); (iii) guanidine base insertion at position 15 (Insert.); and (iv) sequences combining mutation with the base insertion into miR-29b-3p (Mut. + Insert.) or hybrid sequence (Hybrid + Mut. + Insert.). Non-natural sequence changes are highlighted in light grey. Trimming the 3' end by 1-2 nt is also indicated to comprise additional variants.

~~[00206]~~[00207] Referring to **FIG. 16**, this figure shows a schematic visualization of a human host cell gene that is an epigenetic modifier and is involved cancer and reactivation of latent HIV virus .Shown is an illustration of the TET1 mRNA including its coding domain and three experimentally-validated miR-29 target sites (indicated in grey) within its 3'UTR. Hybridization between natural miR-29b-3p and the TET1 target sites, as well as calculated free energy (ΔG) for miR-29-3p and the indicated artificial guide strands were calculated using the software RNAhybrid 2.2 (https://bibiserv.cebitec.uni-bielefeld.de/rnahybrid). Net sum of free energy across all three target sites (NET) and their averaged ΔG (Avg.) is also indicated. Note all artificial guide strands can have lower calculated net and averaged free energy for hybridization than natural miR-29b-3p inferring improved target recognition. As with the NEF example depicted in **FIG. 22**, the engineered miR-29 guide strands depicted in **FIG. 16** can be used to bind and inhibit an mRNA expressing a TET1 host protein with a lower predicted free energy (ΔG), a greater specificity, and greater complementarity, than corresponding natural miRNA sequences lacking the modifications described herein. Since TET1 is important in many

disorders included Cancer and viral infections, this demonstrates that the engineered miR-29 guide strands may have improved properties as therapeutic agents by improving targeting of TET1.

~~[00207]~~[00208] Referring to **FIG. 17** this figure shows miR-29 mimics can have equivalent or greater knockdown activity compared to native miR-29b-1. Luciferase activity of a stable subline of HEK cells () genetically engineered to overexpress a luciferase reporter containing a miR-29 target site within its 3'UTR. HEK^{luc} cells were plated in 96-well plates and transfected with 15 nM mimics using RNAimax agent 6 hrs after plating for 3 days before cell lysis and luciferase assay. Mock treatments were transfected in the absence of mimic. All data represent mean ± SEM from three independent experiments 72 hours after transfection.

~~[00208]~~[00209] Referring to **FIG. 18A-B,** this figure shows passenger strand modification impacts mimic stability in absence of chemical modifications to the guide strand. **FIG. 18A** shows sequence comparison of native miR-29b-1 duplex to mimics M29-004 and M29-012 in which their passenger strands (top strand) contain three terminal 2'O-methyl nucleotides (bold) on both ends with an amino-carbon 6 chain (Amino C6) 5'-cap. Duplex complementarity was enhanced via sequence alterations in M29-012. In some cases, chemical modifications can be performed to any of the guide strands. **FIG. 18B** shows that reduction in duplex bulges in combination with the chemical modification pattern of the passenger strand contributes to improving duplex stability in absence of additional chemical modification of the guide strand. 5 µM of miR-29b-1 and the miR-29 mimics were incubated in 10% human sera at 37˚C for the indicated lengths of time. Duplex stability was visualized at the indicated time points by denaturing Urea-PAGE.

~~[00209]~~[00210] Referring to **FIG**. **19A-B**, this figure shows chemical modifications can improve miR-29 mimic stability. **FIG**. **19A** shows sequence and structure of exemplar engineered miR-29 mimics with chemical modifications to stabilize them to human nucleases. **FIG. 19B** shows miR-29 mimics were incubated in 10% human sera at 37˚C for the indicated lengths of time. Duplex stability at each time point was visualized by denaturing Urea-PAGE. Time points without bands

or with prominent smearing are either missing samples time points or user loading error, respectively.

~~[00210]~~[00211] Referring to **FIG. 20A-C,** this figure shows passenger strand modification that can improve native miR-29a-3p and miR-29b-3p knockdown activity. **FIG. 20A** shows sequence comparison of native miR-29a duplex with mimics M29-023 and M29-002, which differ by passenger strand composition. All three duplexes contain unmodified, natural miR-29a-3p guide strand sequence. Bases in bold contain 2'-O-methyl. Amino-carbon 6 chain (Amino C6) modification of the 5' terminus for the indicated passenger strands is also shown. **FIG. 20B** shows sequence comparison of native miR-29b duplex with mimics M29-007 and M29-008. All three duplexes contain the same unmodified, natural miR-29b-3p guide strand sequence. **FIG. 20C** shows luciferase activity following treatments of stable subline of HEK cells (HEK^{luc}) genetically engineered to overexpress a luciferase reporter containing a miR-29 target site within its 3'UTR with 15 nM native miR-29a, native miR-29b, and miR-29 mimics. All data represent the mean ± SEM from three independent experiments where cells were assayed 72 hours post-transfection. The knockdown activity of mimics containing either native miR-29a-3p (29a-3p) or miR-29b-3p (29b-3p) can be improved over natural miR-29a and miR-29b duplexes by hybridizing guide strands with modified passenger strands.

~~[00211]~~[00212] Referring to **FIG. 21,** this figure displays reductions in innate immunostimulation for engineered miR-29 mimics. Human Peripheral Blood Mononuclear Cells (PBMCs)(~2 x 10^5 cells) were plated in round bottom 96 well plates and transfected at 133 nM concentrations of the indicated mimics for 48 hours with RNAiMAX reagent.. Levels of IFN-α and TNF-α in supernatant were quantified by ELISA. Poly(dA:dT) oligonucleotide and non-modified RNA duplex with known strong stimulatory effects (Pos Con) served as positive controls for immunostimulation. Transfection with non-chemically modified miR-29a and miR-29b duplexes (Non-mod) served as comparative controls for the indicated example mimics containing chemical modifications. Cells treated in in absence of mimic served to establish baseline.

~~[00212]~~[00213] Referring to **FIG. 22A-B,** this figure shows a schematic visualization of an HIV viral RNA transcript that codes for a viral protein (NEF) and can be an antiviral target for HIV. **FIG. 22A** shows free energy (ΔG) and hybridization between natural miR-29b-3p with its cognate target site in the viral transcript of NEF was calculated using the software RNAhybrid 2.2 (https://bibiserv.cebitec.uni-bielefeld.de/rnahybrid). For example, artificial miR-29 guide strands consisting of hybrid sequence (G003-29) and/or other non-natural changes (G004-29, G020-29, G027-29, and G031-29) can have lower predicted free energy (ΔG) and greater complementarity inferring improved target recognition. Improved target recognition, as demonstrated herein, can result in a decrease in a Gibbs Free Energy of binding of an engineered oligonucleotide for a target RNA, can result in an increase specificity of the engineered oligonucleotide for the target RNA, among a plurality of other RNA sequences, or a combination of these features. Accordingly, the engineered miR-29 guide strands depicted in **FIG. 22A** can be used to bind and inhibit an mRNA expressing a NEF viral protein with a lower predicted free energy (ΔG), a greater specificity, and greater complementarity, than corresponding natural miRNA sequences lacking the modifications described herein. Thus, the engineered miR-29 guide strands can display a potent anti-viral activity against HIV viruses or other virus displaying a NEF viral protein as demonstrated in **FIG. 22B**. FIG. 22C shows $3*10^4$ CD4+ human t-cells were transfected with 100 nM of either control, M29-012 or M29-028 mimic. 24 hours post-transfection cells were infected with pNL4-HIV, which contains a GFP reporter cloned nest to the NEF gene. Relative GFP expression, measured 36 hours post-infection by flow cytometry, was significantly reduced in cells pre-treated with M29-012 and M29-028.

~~[00213]~~[00214] Referring to **FIG. 23A-C**, this figure shows knockdown of mRNAs related to HIV replication and latency by miR-29a-3p, miR-29b-3p, M29-002, M29-023, and M29-028. $1x10^5$ Jurkat t-cells were plated in 1 mL of media in 6 well plates and immediately treated with 100 nM control, natural miR-29a, natural miR-29b, or miR-29 mimics for 72 hours formulated into transfection agent. Cells were collected and total RNA was purified by directzol kits. Following reverse transcription relative expression of miR-29 target genes Tet3 (**FIG. 23A**),

Cyclin T1 (**FIG. 23B**), and DNMT3A (**FIG. 23C**) was assessed by quantitative RT-PCR. Values represent the mean of three biological replicates and error bars represent SEM. * denotes p-value <0.05 by 2 tailed student's T-test. In all cases the engineered mimics of miR-29 have improved knockdown of targeted mRNA than the natural miRNAs.

~~[00214]~~[00215] Referring to **FIG. 24A-B,** this figure shows calculated free energy requirements for target recognition of mimic miR-29 (**FIG. 24A**) and miR-30 (**FIG. 24B**) family guide strands to SARS viral transcript. miR-29 mimic exemplary guide strand constructs are indicated. miR-29 guide sequences, for example SEQ. ID. NO. 12 or SEQ. ID. NO. 103, and miR-30 guide sequences, for example SEQ. ID. NO. 86 or SEQ. ID. NO. 88, can have antiviral activity against the SARS virus.

~~[00215]~~[00216] Referring to **FIG. 25A-C,** this figure shows calculated free energy requirements for target recognition of mimic miR-29 (**FIG. 25A**) and miR-30 (**FIG. 25B**) family guide strands to SARS-CoV-2 viral transcript. Hybridization and binding free energy (ΔG) between select guide strands and three predicted targets were calculated using the software RNAhybrid 2.2 (https://bibiserv.cebitec.uni-bielefeld.de/rnahybrid). Net sum of free energy across all three target sites (NET) and their averaged ΔG (Avg.) is also indicated. **FIG 25C** demonstrates the protective effects of exemplar engineered miR-29 (M29-028) and miR-30 mimics against (M30-043 and M30-48) SARS-CoV-2- induced cell death. $5x10^3$ Vero cells were plated in 29 well plates and 6hrs after plating transfected with 25 nM control, , M29-028, M30-043 or M30-048 mimics and then infected with SARS-CoV-2 (MOI 0.03) 24 hours later. After another 72 hours, cells were assayed for viral-induced cytopathic effect using viral toxglo assay (Promega). Pre-treatment with either M29-028, M30-43 or M30-048 resulted in ~30-40% less viral-induced cell death. miR-29 guide sequences, for example SEQ. ID. NO. 102 or SEQ. ID. NO. 109, and miR-30 guide sequences, for example SEQ. ID. NO. 86 or SEQ. ID. NO. 88, can have antiviral activity against the SARS-CoV-2 virus.

~~[00216]~~[00217] Referring to **FIG. 26,** this figure shows calculated free energy requirements for target recognition of mimic miR-29 family guide strands to HCV Genotype 1 transcript. miR-29

mimic exemplary guide strand constructs are indicated. miR-29 guide sequences, for example SEQ. ID. NOs. 12, 13, 102, 103, 112, 115, 119, 117, 105, 110, 109, 100, can have antiviral activity against the HCV Genotype 1.

~~[00217]~~[00218] The antiviral properties of the miR-29, miR-30, or miR-26 families can also be conserved amongst other RNA-based viruses that contain target sites within their genome or depend on similar host gene transcripts (e.g. TET1, TET2, TET3, etc.). Based on seed sequence complementarity, 26 and 32 candidate target sites in the genomic transcripts of SARS and SARS-CoV-2 coronavirus, respectively. Calculated free energy (ΔG) for three example targeted sites indicate that many of the artificial family member can have improved binding potential over native miR-29a-3p, miR-29b-3p, or miR-30a-5p in both SARS (**FIG. 24**) and SARS-CoV-2 (**FIG. 25**) genomic transcript. Similarly, artificial family members also demonstrated improved calculated binding across three candidate target sites in Hepatitis C virus (HCV) genome (**FIG. 26**). The mimics, including artificial family members, may have broad acting antiviral properties at treating or preventing infection of RNA-based viruses.

~~[00218]~~[00219] SEQ ID NOS: 500-531, 829-831 (Table 6) shows miR-29 target sequences in a COVID-19 Coronavirus (SARS-CoV-2) genomic RNA. For example, target sequences in the COVID-19 genome indicated by SEQ. ID. NO. 500 or SEQ. ID. NO. 502 can be targeted by one or more constructs as described herein, such as one or more miR-29 constructs.

~~[00219]~~[00220] SEQ ID NOS: 474-499, 826-828 (Table 6) shows miR-29 target sequences in a SARS Coronavirus (SARS-CoV) genomic RNA. For example, target sequences in the SARS genome indicated by SEQ. ID. NO. 474 or SEQ. ID. NO. 475 can be targeted by one or more constructs as described herein, such as one or more miR-29 constructs.

~~[00220]~~[00221] SEQ ID NOS: 532-554 (Table 6) shows miR-29 target sequences in a MERS Coronavirus (MERS-CoV) genomic RNA. For example, target sequences in the MERS genome indicated by SEQ. ID. NO. 535 or SEQ. ID. NO. 537 can be targeted by one or more constructs as described herein, such as one or more miR-29 constructs.

~~[00221]~~[00222] SEQ ID NOS: 555-586 (Table 6) shows miR-29 target sequences in a HKU1 Coronavirus (CoV-HKU1) genomic RNA. For example, target sequences in the HKU1 genome indicated by SEQ. ID. NO. 556 or SEQ. ID. NO. 566 can be targeted by one or more constructs as described herein, such as one or more miR-29 constructs.

~~[00222]~~[00223] Referring to **Table 9** and **FIG. 27**, this figure shows engineered artificial anti-cancer miRNA mimic E1-001 which has no similar natural ncRNA. The Guide strand of E1-001, G001-E1, is engineered to target single and multiple sites in the 3' UTRs of several oncogenic mRNAs. **Table 9** shows calculated free energy requirements for target recognition of G001-E1 guide strand to the targeted sites in the oncogenic mRNAs. Hybridization and binding free energy (ΔG) were calculated using the software RNAhybrid 2.2 (https://bibiserv.cebitec.uni-bielefeld.de/rnahybrid). **FIG. 27** displays activity of engineered artificial miRNA E1-001 in normal non-cancerous cells including fibroblasts, retinal pigment epithelial cell line (RPE-1) or human oral keratinocytes (HOK) cells. Treatments were also performed on various cancer cell lines with different genetic backgrounds. Indicated cell lines were plated in 96-well plates and transfected with 7.5 nM E1-001 using RNAimax agent 6 hrs after plating for 5 days. Following treatment cell viability was assessed by XTT assay. Statistical significance ($P<0.01$) compared to Neg Con miRNA treatment is indicated. All Data represent the mean ± SEM from a minimum three independent experiments. Cancer cell lines are significantly more sensitive than non-cancerous cells.

Table 9: Calculated binding free energy between ENG-miR-1 guide strand and various targets.

SEQ ID NO:	Target	ΔG	SEQ ID NO:	Target	ΔG
594	CSNK1G1 site 1	-17.4	608	RAB11FIP1 site 4	-18
595	CSNK1G1 site 2	-19.1	608	RBJ site 1	-19.6
596	CSNK1G1 site 3	-20.5	609	RBJ site 2	-18
597	CSNK1G1 site 4	-21.7	610	SERBP1 site 1	-17.4
598	CSNK1G1 site 5	-21.3	611	SERBP1 site 2	-18
599	CSNK1G1 site 6	-20.1	612	CTBP1	-18.8
600	ARHGAP26 site 1	-20.3	613	CRKL	-24.7
601	ARHGAP26 site 2	-21.8	614	ITGA3	-24.2

602	ARHGAP26 site 3	-17.6	615	ITGAV	-18.4
603	ARHGAP26 site 4	-20.1	616	LAMC1	-17.1
604	ARHGAP26 site 5	-18.1	617	G6PC2	-19.9
605	RAB11FIP1 site 1	-27.3	618	PPP2R5E	-17.5
606	RAB11FIP1 site 2	-17.2	619	KLF17	-23.9
607	RAB11FIP1 site 3	-17.2			

~~[00223]~~[00224] Referring to **Table 10**, this table shows engineered miR-205 guide strands and predicted free energy of binding for cancer-relevant RNAs in the 3' UTRs of ZEB1 (SEQ ID NO: 590), E2F1 (SEQ ID NO: 591), HER3 (SEQ ID NO: 592), and SHIP2 (SEQ ID NO: 593) gene transcripts. Lower predicted free energy (ΔG) infers improved target recognition. Target HER3 (PMID: 19276373) is an oncogene stimulating cancer grown while SHIP2 (PMID: 19033458) is a tumor suppressor inhibiting cancer growth. Exemplar Engineered guide strands G016-205 (SEQ ID NO: 260) and G011-205 (SEQ ID NO: 255) and predicted to have stronger targeting of HER3 and weaker targeting of SHIP2.

Table 10. Calculated Free Energy Requirements for Target Recognition of Mimic Guide Strands to miR-205 Downstream Transcript

		Free energy (ΔG)* [kcal/mol]			
SEQ ID NO:	**Guide Strand**	**ZEB1**	**E2F1**	**HER3**	**SHIP2**
32	miR-205-5p	-20.6	-29.3	-28	-30.2
840	G200-205	-22	-24.9	-27.5	-27.5
841	G201-205	-19.4	-24.9	-26.8	-29.3
262	G018-205	-19.1	-29.3	-30.4	-30.2
260	G016-205	-20.6	-32.7	-31.8	-24.6
247	G003-205	-19.9	-24.9	-32.6	-27.5
254	G010-205	-18.4	-24.9	-31.1	-29.3
245	G001-205	-22	-28.3	-31.3	-23.4
253	G009-205	19.4	-28.3	-30.6	-23.4
263	G019-205	-19.1	-32.7	-34.4	-27.2
248	G004-205	-19.9	-28.3	-36.6	-25.4
255	G011-205	-18.4	-28.3	-34.9	-25.4
842	G202-205	-22.6	-25.5	-30.7	-31.4
843	G203-205	-20.1	-25.5	-31.8	-31.4
259	G015-205	-20.6	-33.9	-34.7	-27
249	G005-205	-22.4	-30.1	-36.7	-27.5

256	G012-205	-20.1	-30.1	-37.8	-27.5
250	G006-205	-22.6	-28.9	-34.5	-25.3
257	G013-205	-20.1	-28.9	-35.6	-25.3
246	G002-205	-21.1	-23.1	-28	-28.8
844	G204-205	-21.2	-23	-26.5	-28.9
845	G205-205	-21.4	-25.5	-33.4	-31.4
261	G017-205	-19.6	-30.9	-34.7	-27.7
251	G007-205	-20.4	-30.1	-39.6	-27.5
258	G014-205	-17.6	-30.1	-36.9	-27.5
252	G008-205	-21.4	-28.9	-37.4	-25.3

*Free energy (ΔG) was calculated using RNAhybrid 2.2 between the indicated mimic guide strand sequences and target sites in the 3'UTRs of ZEB1 (SEQ ID NO: 590), E2F1 (SEQ ID NO: 591), HER3 (SEQ ID NO: 592), and SHIP2 (SEQ ID NO: 593) gene transcripts. Lower predicted free energy (ΔG) infers improved target recognition.

~~[00224]~~[00225] Referring to **Table 11,** this table shows miR-29 mimic target genes that may linked to tissue scarring and fibrosis. Analyses of candidate downstream target genes within the human genome identified enrichment for a number genes that can participate in tissue scarring and fibrosis including most members within the collagen superfamily. The miR-29 mimics may have further therapeutic potential in fibrotic/scarring pathologies.

Table 11 – miR-29 Mimic Target Genes Linked to Tissue Scarring and Fibrosis

Target Genes	Gene Ontology	Reference (PMID)
COL1A1, COL11A1, COL2A1, COL5A3, COL5A2, COL4A4, COL21A1, COL7A1, COL9A1, COL19A1, COL5A1, COL22A1, COL8A1, COL4A2, COL6A2, COL24A1, COL4A3, COL4A6, COL25A1, COL16A1, COL15A1	Collagen Super Family; Extracellular Matrix Remodeling	25785236; 31231509; 22772564
PDGFB, PDGFC, PDGFRB	Platelet-Derived Growth Factors (PDGF) Signaling	29155002; 28983598; 27816607; 25678385
WISP1	TGF-b/Wnt Signaling	26867691
LOXL2	Collagen/Extracellular Matrix Remodeling	30986934; 28073888; 23821193
Elastin	Extracellular Matrix Remodeling	10761639; 30944168
TGFB2	Transforming growth factor beta (TGF-b) Signaling	26704519; 31992593; 31939600; 29615587
HDGF	Hepatoma-derived growth factor (HDGF) Signaling	19913322

~~[00225]~~[00226] Referring to **FIG. 28**, this figure shows simultaneous knockdown of DUX4 and DBET RNA transcripts in FSHD patient myoblasts by multi-targeted antisense oligonucleotides (ASOs). AS-DX-10 only targets the DUX4 transcript, while AS-DX-25, -37, and -55 target both DUX4 and DBET transcripts. Immortalized 15Abic myoblast cells were plated in 12-well plates and the next day transfected with control or targeted ASOs at 50 nM using the transfection agent RNAiMAX. One day after plating differentiation media was added to induce myoblast formation and DUX4 expression. 72 hrs after transfection cells were lysed and total RNA was collected from the wells and RT-qPCR was performed to determine expression of DUX4 or DBET transcripts. ASOs AS-DX-25, -37, and -55 knockdown both DUX4 and DBET transcripts while AS-DX-10 only knocks down DUX4.

~~[00226]~~[00227] In some cases, as shown in **FIG. 30**, a sample **202** containing a genetic material can be obtained from a subject **201**, such as a human subject. A sample **202** can be subjected to one or more methods as described herein, such as performing an assay. In some cases, an assay can comprise sequencing (such as nanopore sequencing), genotyping, hybridization, amplification, labeling, or any combination thereof. One or more results from a method can be input into a processor **204**. One or more input parameters such as a sample identification, subject identification, sample type, a reference, or other information can be input into a processor **204**. One or more metrics from an assay can be input into a processor **204** such that the processor can produce a result, such as a diagnosis of degenerative disc disease or a recommendation for a treatment. A processor can send a result, an input parameter, a metric, a reference, or any combination thereof to a display **205**, such as a visual display or graphical user interface. A processor **204** can (i) send a result, an input parameter, a metric, or any combination thereof to a server **207**, (ii) receive a result, an input parameter, a metric, or any combination thereof from a server **207**, (iii) or a combination thereof.

Computer control systems

~~[00227]~~[00228] The present disclosure provides computer control systems that are programmed to implement methods of the disclosure. **FIG. 29** shows a computer system 101 that is

programmed or otherwise configured to predict or confirm efficacy of various constructs for therapeutic effect, such as in cancer therapeutics or anti-viral therapeutics. The computer system 101 can regulate various aspects of the present disclosure, such as, for example, modeling or identifying constructs for various therapeutic targets, modeling efficacy or stability of constructs, or any combination thereof. The computer system 101 can be an electronic device of a user or a computer system that is remotely located with respect to the electronic device. The electronic device can be a mobile electronic device.

~~[00228]~~[00229] The computer system 101 includes a central processing unit (CPU, also "processor" and "computer processor" herein) 105, which can be a single core or multi core processor, or a plurality of processors for parallel processing. The computer system 101 also includes memory or memory location 110 (e.g., random-access memory, read-only memory, flash memory), electronic storage unit 115 (e.g., hard disk), communication interface 120 (e.g., network adapter) for communicating with one or more other systems, and peripheral devices 125, such as cache, other memory, data storage and/or electronic display adapters. The memory 110, storage unit 115, interface 120 and peripheral devices 125 are in communication with the CPU 105 through a communication bus (solid lines), such as a motherboard. The storage unit 115 can be a data storage unit (or data repository) for storing data. The computer system 101 can be operatively coupled to a computer network ("network") 130 with the aid of the communication interface 120. The network 130 can be the Internet, an internet and/or extranet, or an intranet and/or extranet that is in communication with the Internet. The network 130 in some cases is a telecommunication and/or data network. The network 130 can include one or more computer servers, which can enable distributed computing, such as cloud computing. The network 130, in some cases with the aid of the computer system 101, can implement a peer-to-peer network, which can enable devices coupled to the computer system 101 to behave as a client or a server.

~~[00229]~~[00230] The CPU 105 can execute a sequence of machine-readable instructions, which can be embodied in a program or software. The instructions can be stored in a memory location, such as the memory 110. The instructions can be directed to the CPU 105, which can

subsequently program or otherwise configure the CPU 105 to implement methods of the present disclosure. Examples of operations performed by the CPU 105 can include fetch, decode, execute, and writeback.

~~[00230]~~[00231] The CPU 105 can be part of a circuit, such as an integrated circuit. One or more other components of the system 101 can be included in the circuit. In some cases, the circuit is an application specific integrated circuit (ASIC).

~~[00231]~~[00232] The storage unit 115 can store files, such as drivers, libraries and saved programs. The storage unit 115 can store user data, e.g., user preferences and user programs. The computer system 101 in some cases can include one or more additional data storage units that are external to the computer system 101, such as located on a remote server that is in communication with the computer system 101 through an intranet or the Internet.

~~[00232]~~[00233] The computer system 101 can communicate with one or more remote computer systems through the network 130. For instance, the computer system 101 can communicate with a remote computer system of a user. Examples of remote computer systems include personal computers (e.g., portable PC), slate or tablet PC's (e.g., Apple® iPad, Samsung® Galaxy Tab), telephones, Smart phones (e.g., Apple® iPhone, Android-enabled device, Blackberry®), or personal digital assistants. The user can access the computer system 101 via the network 130.

~~[00233]~~[00234] Methods as described herein can be implemented by way of machine (e.g., computer processor) executable code stored on an electronic storage location of the computer system 101, such as, for example, on the memory 110 or electronic storage unit 115. The machine executable or machine-readable code can be provided in the form of software. During use, the code can be executed by the processor 105. In some cases, the code can be retrieved from the storage unit 1115 and stored on the memory 110 for ready access by the processor 105. In some situations, the electronic storage unit 115 can be precluded, and machine-executable instructions are stored on memory 110.

~~[00234]~~[00235] The code can be pre-compiled and configured for use with a machine having a processer adapted to execute the code or can be compiled during runtime. The code can be

supplied in a programming language that can be selected to enable the code to execute in a pre-compiled or as-compiled fashion.

~~[00235]~~[00236] Aspects of the systems and methods provided herein, such as the computer system 101, can be embodied in programming. Various aspects of the technology can be thought of as "products" or "articles of manufacture" typically in the form of machine (or processor) executable code and/or associated data that is carried on or embodied in a type of machine readable medium. Machine-executable code can be stored on an electronic storage unit, such as memory (e.g., read-only memory, random-access memory, flash memory) or a hard disk. "Storage" type media can include any or all of the tangible memory of the computers, processors or the like, or associated modules thereof, such as various semiconductor memories, tape drives, disk drives and the like, which can provide non-transitory storage at any time for the software programming. All or portions of the software can at times be communicated through the Internet or various other telecommunication networks. Such communications, for example, can enable loading of the software from one computer or processor into another, for example, from a management server or host computer into the computer platform of an application server. Thus, another type of media that can bear the software elements includes optical, electrical and electromagnetic waves, such as used across physical interfaces between local devices, through wired and optical landline networks and over various air-links. The physical elements that carry such waves, such as wired or wireless links, optical links or the like, also can be considered as media bearing the software. As used herein, unless restricted to non-transitory, tangible "storage" media, terms such as computer or machine "readable medium" refer to any medium that participates in providing instructions to a processor for execution.

~~[00236]~~[00237] Hence, a machine readable medium, such as computer-executable code, can take many forms, including but not limited to, a tangible storage medium, a carrier wave medium or physical transmission medium. Non-volatile storage media include, for example, optical or magnetic disks, such as any of the storage devices in any computer(s) or the like, such as can be used to implement the databases, etc. shown in the drawings. Volatile storage media include

dynamic memory, such as main memory of such a computer platform. Tangible transmission media include coaxial cables; copper wire and fiber optics, including the wires that comprise a bus within a computer system. Carrier-wave transmission media can take the form of electric or electromagnetic signals, or acoustic or light waves such as those generated during radio frequency (RF) and infrared (IR) data communications. Common forms of computer-readable media therefore include for example: a floppy disk, a flexible disk, hard disk, magnetic tape, any other magnetic medium, a CD-ROM, DVD or DVD-ROM, any other optical medium, punch cards paper tape, any other physical storage medium with patterns of holes, a RAM, a ROM, a PROM and EPROM, a FLASH-EPROM, any other memory chip or cartridge, a carrier wave transporting data or instructions, cables or links transporting such a carrier wave, or any other medium from which a computer can read programming code and/or data. Many of these forms of computer readable media can be involved in carrying one or more sequences of one or more instructions to a processor for execution.

~~[00237]~~[00238] The computer system 101 can include or be in communication with an electronic display 135 that comprises a user interface (UI) 140 for providing, for example, one or more results (immediate results or archived results from a previous method), one or more user inputs, a reference value or derivative thereof from a library or database, or any combination thereof. Examples of UI's include, without limitation, a graphical user interface (GUI) and web-based user interface.

~~[00238]~~[00239] Methods and systems of the present disclosure can be implemented by way of one or more algorithms. An algorithm can be implemented by way of software upon execution by the central processing unit 105. The algorithm can, for example, determine optimized constructs via supervised learning to optimize therapeutic efficacy, stability, or other attribute of one or more constructs.

~~[00239]~~[00240] While exemplary embodiments have been shown and described herein, such embodiments are by way of example only. Numerous variations, changes, and substitutions can

be performed on the exemplary embodiments. It should be understood that various alternatives to the embodiments described herein may be employed.

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 mircro 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 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.

11. The engineered oligonucleotide or salt thereof of claim 10, 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.

12. The engineered oligonucleotide or salt thereof of any one of claims 10 or 11, 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.

13. The engineered oligonucleotide or salt thereof of any one of claims 10-12, 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: 283, SEQ ID NO: 284, SEQ ID NO: 285, SEQ ID NO: 286, SEQ ID NO: 287, SEQ ID NO: 288, SEQ ID NO: 289, SEQ ID NO: 290, SEQ ID NO: 291, SEQ ID NO: 292, SEQ ID NO: 293, SEQ ID NO: 294, SEQ ID NO: 295, SEQ ID NO: 296, SEQ ID NO: 297, SEQ ID NO: 298, SEQ ID NO: 299, SEQ ID NO: 300, SEQ ID NO: 301, SEQ ID NO: 302, SEQ ID NO: 303, SEQ ID NO: 304, SEQ ID NO: 305, SEQ ID NO: 306, SEQ ID NO: 307, SEQ ID NO: 308, SEQ ID NO: 309, SEQ ID NO: 310, SEQ ID NO: 311, SEQ ID NO: 312, SEQ ID NO: 313, SEQ ID NO: 314, SEQ ID NO: 315, SEQ ID NO: 316,

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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.

14. The engineered oligonucleotide or salt thereof of claim 10, wherein the engineered oligonucleotide sequence comprises the sugar, base, or backbone modification.

15. The engineered oligonucleotide or salt thereof of claim 14, wherein the modification comprises a linker.

16. The engineered oligonucleotide or salt thereof of claim 15, wherein the linker is a covalent linker.

17. The engineered oligonucleotide or salt thereof of claim 15, wherein the linker is a cleavable linker.

18. The engineered oligonucleotide or salt thereof of claim 15-17, wherein the linker is further modified to comprise a conjugate.

19. The engineered oligonucleotide or salt thereof of claim 18, wherein the conjugate is an antibody, a naturally occurring ligand, a small molecule, or a peptide.

20. The engineered oligonucleotide or salt thereof of any one of claims 1-19, wherein the first or the second RNA at least partially comprises an mRNA sequence.

21. The engineered oligonucleotide or salt thereof of any one of claims 1-20, wherein the disease or condition comprises a neuromuscular disorder including a muscular dystrophy or a myopathy.

22. The engineered oligonucleotide or salt thereof of claim 21, 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.

23. The engineered oligonucleotide or salt there of claims 21-22 wherein the disease or condition is caused by an inherited or spontaneous autosomal dominant mutation.

24. The engineered oligonucleotide or salt thereof of any one of claims 21-23, 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.

25. The engineered oligonucleotide or salt thereof of claims 21-24, 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.

26. 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.

27. 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 1-26.

28. A nucleic acid construct comprising: (a) a first strand comprising the engineered oligonucleotide or salt thereof of any one of claims 1-26 and (b) a second strand comprising an engineered passenger oligonucleotide or salt thereof of claim 27 with a sequence complementary to at least a portion of the first strand.

29. A vector that comprises the engineered oligonucleotide or salt thereof of any one of claims 1-26 or the nucleic acid construct of claim 28.

30. The vector of claim 29, wherein the vector is present in a liposome, a nanoparticle, or any combination thereof.

31. A pharmaceutical composition comprising: (a) the engineered oligonucleotide or salt thereof of any one of claims 1-26, the nucleic acid construct of claim 28, or the vector of any one of claims 29-30; and (b) a pharmaceutically acceptable excipient, diluent, or carrier.

32. Use of the engineered oligonucleotide or salt thereof of any one of claims 1-26, the nucleic acid construct of claim 28, the vector of any one of claims 29-30, or the pharmaceutical composition of claim 31 in the manufacture of a medicament for the treatment of a disease or condition.

33. The use of claim 32, wherein the disease or condition is muscular dystrophy.

34. A method comprising: contacting the engineered oligonucleotide or salt thereof of any one of claims 1-26, the nucleic acid construct of claim 28, or the vector of any one of claims 29-30, with an isolated cell or an isolated tissue.

35. A kit that comprises a container and the engineered oligonucleotide or salt thereof of any one of claims 1-26, the nucleic acid construct of claim 28, the vector of any one of claims 29-30, or the pharmaceutical composition of claim 31.

36. The engineered oligonucleotide or salt thereof of any one of claims 1-26, the nucleic acid construct of claim 28, the vector of any one of claims 29-30, or the pharmaceutical composition of claim 31 for use in therapy.

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 mircro 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:

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

$(N)_a(mN)_b(N)_csfNsmN$; 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.

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: 283, SEQ ID NO: 284, SEQ ID NO: 285, SEQ ID NO: 286, SEQ ID NO: 287, SEQ ID NO: 288, SEQ ID NO: 289, SEQ ID NO: 290, SEQ ID NO: 291, SEQ ID NO: 292, SEQ ID NO: 293, SEQ ID NO: 294, SEQ ID NO: 295, SEQ ID NO: 296, SEQ ID NO: 297, SEQ ID NO: 298, SEQ ID NO: 299, SEQ ID NO: 300, SEQ ID NO: 301, SEQ ID NO:

~~302, SEQ ID NO: 303, SEQ ID NO: 304, SEQ ID NO: 305, SEQ ID NO: 306, SEQ ID NO: 307, SEQ ID NO: 308, SEQ ID NO: 309, SEQ ID NO: 310, SEQ ID NO: 311, SEQ ID NO: 312, SEQ ID NO: 313, SEQ ID NO: 314, SEQ ID NO: 315, SEQ ID NO: 316, SEQ ID NO: 317, SEQ ID NO: 318, SEQ ID NO: 319, SEQ ID NO: 320, SEQ ID NO: 321, SEQ ID NO: 322, SEQ ID NO: 323, SEQ ID NO: 324, SEQ ID NO: 325, SEQ ID NO: 326, SEQ ID NO: 327, SEQ ID NO: 328, SEQ ID NO: 329, SEQ ID NO: 330, SEQ ID NO: 331, SEQ ID NO: 332, SEQ ID NO: 333, SEQ ID NO: 334, SEQ ID NO: 335, SEQ ID NO: 336, SEQ ID NO: 337, SEQ ID NO: 338, SEQ ID NO: 339, SEQ ID NO: 340, SEQ ID NO: 341, SEQ ID NO: 342, SEQ ID NO: 343, SEQ ID NO: 344, SEQ ID NO: 345, SEQ ID NO: 346, SEQ ID NO: 347, SEQ ID NO: 348, SEQ ID NO: 349, SEQ ID NO: 350, SEQ ID NO: 351, SEQ ID NO: 352, SEQ ID NO: 353, SEQ ID NO: 354, SEQ ID NO: 355, SEQ ID NO: 356, SEQ ID NO: 357, SEQ ID NO: 358, SEQ ID NO: 359, SEQ ID NO: 360, SEQ ID NO: 361, SEQ ID NO: 362, SEQ ID NO: 363, SEQ ID NO: 364, SEQ ID NO: 365, SEQ ID NO: 366, SEQ ID NO: 367, SEQ ID NO: 368, SEQ ID NO: 369, SEQ ID NO: 370, SEQ ID NO: 371, SEQ ID NO: 372, SEQ ID NO: 373, SEQ ID NO: 374, SEQ ID NO: 375, SEQ ID NO: 376, SEQ ID NO: 377, SEQ ID NO: 378, SEQ ID NO: 379, SEQ ID NO: 380, SEQ ID NO: 381, SEQ ID NO: 382, SEQ ID NO: 383, SEQ ID NO: 384, SEQ ID NO: 385, SEQ ID NO: 386, SEQ ID NO: 387, SEQ ID NO: 388, SEQ ID NO: 389, SEQ ID NO: 390, SEQ ID NO: 391, SEQ ID NO: 392, SEQ ID NO: 393, SEQ ID NO: 394, SEQ ID NO: 395, SEQ ID NO: 396, SEQ ID NO: 397, SEQ ID NO: 398, SEQ ID NO: 399, SEQ ID NO: 400, SEQ ID NO: 401, SEQ ID NO: 402, SEQ ID NO: 403, SEQ ID NO: 404, SEQ ID NO: 405, SEQ ID NO: 406, SEQ ID NO: 407, SEQ ID NO: 408, SEQ ID NO: 409, SEQ ID NO: 410, SEQ ID NO: 411, SEQ ID NO: 412, SEQ ID NO: 413, SEQ ID NO: 414, SEQ ID NO: 415, SEQ ID NO: 416, SEQ ID NO: 417, SEQ ID NO: 418, SEQ ID NO: 419, SEQ ID NO: 420, SEQ ID NO: 421, SEQ ID NO: 422, SEQ ID NO: 423, SEQ ID NO: 424, SEQ ID NO: 425, SEQ ID NO: 426, SEQ ID NO: 427, SEQ ID NO: 428, SEQ ID NO: 429, SEQ ID NO: 430, SEQ ID NO: 431, SEQ ID NO: 432, SEQ ID NO: 433, SEQ ID NO: 434, SEQ ID NO: 435, SEQ ID NO: 436, SEQ ID NO: 437, SEQ ID NO: 438, SEQ ID NO: 439, SEQ ID NO: 440, SEQ ID NO: 441, SEQ ID NO: 442, SEQ ID NO: 443, SEQ ID NO: 445, SEQ ID NO: 446, SEQ ID NO: 447, SEQ ID NO: 448, SEQ ID NO: 449, SEQ ID NO: 450, SEQ ID NO: 451, SEQ ID NO: 452, SEQ ID NO: 453, SEQ ID NO: 455, SEQ ID NO: 456, SEQ ID NO: 457, SEQ ID NO: 458, SEQ ID NO: 459, SEQ ID NO: 460, SEQ ID NO: 461, SEQ ID NO: 462, SEQ ID NO: 463, SEQ ID NO: 620, SEQ ID NO: 644, SEQ ID NO: 645, SEQ ID NO: 646, SEQ ID NO: 647, SEQ ID NO: 648, SEQ ID NO: 649,~~

~~SEQ ID NO: 650, SEQ ID NO: 651, SEQ ID NO: 652, SEQ ID NO: 653, SEQ ID NO: 654, SEQ ID NO: 655, SEQ ID NO: 656, SEQ ID NO: 657, SEQ ID NO: 658, SEQ ID NO: 659, SEQ ID NO: 660, SEQ ID NO: 661, SEQ ID NO: 662, SEQ ID NO: 663, SEQ ID NO: 664, SEQ ID NO: 665, SEQ ID NO: 666, SEQ ID NO: 667, SEQ ID NO: 668, SEQ ID NO: 669, SEQ ID NO: 670, SEQ ID NO: 671, SEQ ID NO: 672, SEQ ID NO: 673, SEQ ID NO: 674, SEQ ID NO: 675, SEQ ID NO: 676, SEQ ID NO: 677, SEQ ID NO: 678, SEQ ID NO: 679, SEQ ID NO: 680, SEQ ID NO: 681, SEQ ID NO: 682, SEQ ID NO: 683, SEQ ID NO: 684, SEQ ID NO: 685, SEQ ID NO: 686, SEQ ID NO: 687, SEQ ID NO: 688, SEQ ID NO: 689, SEQ ID NO: 690, SEQ ID NO: 691, SEQ ID NO: 692, SEQ ID NO: 693, SEQ ID NO: 694, SEQ ID NO: 695, SEQ ID NO: 696, SEQ ID NO: 697, SEQ ID NO: 698, SEQ ID NO: 699, SEQ ID NO: 700, SEQ ID NO: 701, SEQ ID NO: 702, SEQ ID NO: 703, SEQ ID NO: 704, SEQ ID NO: 705, SEQ ID NO: 706, SEQ ID NO: 707, SEQ ID NO: 708, SEQ ID NO: 709, SEQ ID NO: 710, SEQ ID NO: 711, SEQ ID NO: 712, SEQ ID NO: 713, SEQ ID NO: 714, SEQ ID NO: 715, SEQ ID NO: 716, SEQ ID NO: 717, SEQ ID NO: 718, SEQ ID NO: 719, SEQ ID NO: 720, SEQ ID NO: 721, SEQ ID NO: 722, SEQ ID NO: 723, SEQ ID NO: 724, SEQ ID NO: 725, SEQ ID NO: 726, SEQ ID NO: 727, SEQ ID NO: 728, SEQ ID NO: 729, SEQ ID NO: 730, SEQ ID NO: 731, SEQ ID NO: 732, SEQ ID NO: 733, SEQ ID NO: 734, SEQ ID NO: 735, SEQ ID NO: 736, SEQ ID NO: 737, SEQ ID NO: 738, SEQ ID NO: 739, SEQ ID NO: 740, SEQ ID NO: 741, SEQ ID NO: 742, SEQ ID NO: 743, SEQ ID NO: 744, SEQ ID NO: 745, SEQ ID NO: 746, SEQ ID NO: 747, SEQ ID NO: 748, SEQ ID NO: 749, SEQ ID NO: 750, SEQ ID NO: 751, SEQ ID NO: 752, SEQ ID NO: 753, SEQ ID NO: 754, SEQ ID NO: 755, SEQ ID NO: 756, SEQ ID NO: 757, SEQ ID NO: 758, SEQ ID NO: 759, SEQ ID NO: 760, SEQ ID NO: 761, SEQ ID NO: 762, SEQ ID NO: 763, SEQ ID NO: 764, SEQ ID NO: 765, SEQ ID NO: 766, SEQ ID NO: 767, SEQ ID NO: 768, SEQ ID NO: 769, SEQ ID NO: 770, SEQ ID NO: 771, SEQ ID NO: 772, SEQ ID NO: 773, SEQ ID NO: 774, SEQ ID NO: 775, SEQ ID NO: 776, SEQ ID NO: 777, SEQ ID NO: 778, SEQ ID NO: 779, SEQ ID NO: 780, SEQ ID NO: 781, SEQ ID NO: 782, SEQ ID NO: 783, SEQ ID NO: 784, SEQ ID NO: 785, SEQ ID NO: 786, SEQ ID NO: 787, SEQ ID NO: 788, SEQ ID NO: 789, SEQ ID NO: 790, SEQ ID NO: 791, SEQ ID NO: 792, SEQ ID NO: 793, SEQ ID NO: 794, SEQ ID NO: 795, SEQ ID NO: 796, SEQ 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:~~

~~a. transfecting the engineered oligonucleotide or salt thereof into a first isolated mammalian cell comprising the mRNA sequence,~~

~~b. transfecting the ncRNA into a second isolated mammalian cell comprising the mRNA sequence, and~~

~~c. 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:~~

~~a. transfecting the engineered oligonucleotide or salt thereof into a first isolated mammalian cell comprising the mRNA sequence,~~

~~b. transfecting the ncRNA into a second isolated mammalian cell comprising the mRNA sequence, and~~

~~c. 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, BBIT3, 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 there 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)$_k$mNmNmN; 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 1-76 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.~~