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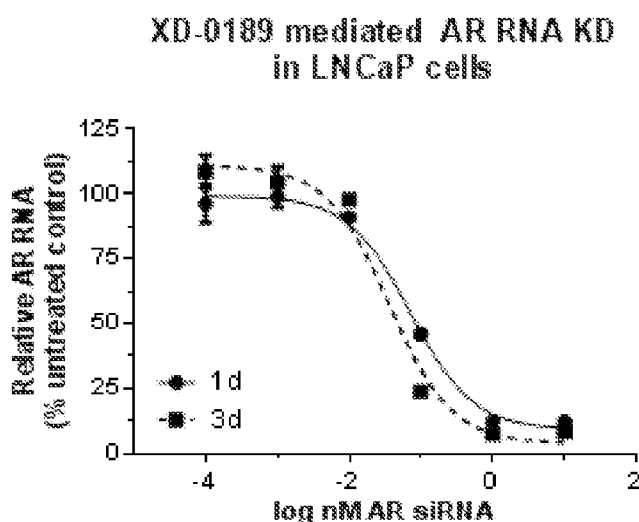
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[Continued on next page]

(54) **Title:** ANDROGEN RECEPTOR NUCLEIC ACIDS AND USES THEREOF

Fig. 1A



(57) **Abstract:** Disclosed herein are molecules and pharmaceutical compositions that mediate RNA interference against androgen receptor. Also described herein include methods for treating a disease or disorder that comprises a molecule or a pharmaceutical composition that mediate RNA interference against androgen receptor.

**Declarations under Rule 4.17:**

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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- *with international search report (Art. 21(3))*
- *with sequence listing part of description (Rule 5.2(a))*

ANDROGEN RECEPTOR NUCLEIC ACIDS AND USES THEREOF**CROSS-REFERENCE**

[0001] This application claims the benefit of U.S. Provisional Application No. 62/317,116, filed April 1, 2016, which application is incorporated herein by reference.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on March 27, 2017, is named 45532-710_601_SL.txt and is 87,114 bytes in size.

BACKGROUND OF THE DISCLOSURE

[0003] Gene suppression by RNA-induced gene silencing provides several levels of control: transcription inactivation, small interfering RNA (siRNA)-induced mRNA degradation, and siRNA-induced transcriptional attenuation. In some instances, RNA interference (RNAi) provides long lasting effect over multiple cell divisions. As such, RNAi represents a viable method useful for drug target validation, gene function analysis, pathway analysis, and disease therapeutics.

SUMMARY OF THE DISCLOSURE

[0004] Disclosed herein, in certain embodiments, are molecules and pharmaceutical compositions for modulating RNA function and/or gene expression in a cell.

[0005] Disclosed herein, in certain embodiments, is a polynucleic acid molecule that mediates RNA interference against androgen receptor, wherein the polynucleic acid molecule comprises at least one 2' modified nucleotide, at least one modified internucleotide linkage, or at least one inverted abasic moiety.

[0006] In some embodiments, the at least one 2' modified nucleotide comprises 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl, 2'-deoxy, T-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), T-O-dimethylaminoethyloxyethyl (2'-O-DMAEOE), or 2'-O-N-methylacetamido (2'-O-NMA) modified nucleotide. In some embodiments, the at least one 2' modified nucleotide comprises locked nucleic acid (LNA) or ethylene nucleic acid (ENA). In some embodiments, the at least one inverted basic moiety is at at least one terminus. In some embodiments, the at least one modified internucleotide linkage comprises a phosphorothioate linkage or a phosphorodithioate linkage.

[0007] In some embodiments, the polynucleic acid molecule is at least from about 10 to about 30 nucleotides in length. In some embodiments, the polynucleic acid molecule is at least one of: from about 15 to about 30, from about 18 to about 25, from about 18 to about 24, from about 19 to about 23, or from about 20 to about 22 nucleotides in length. In some embodiments, the polynucleic acid molecule is at least about 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleotides in length.

[0008] In some embodiments, the polynucleic acid molecule comprises at least one of: from about 5% to about 100% modification, from about 10% to about 100% modification, from about 20% to about 100% modification, from about 30% to about 100% modification, from about 40% to about 100% modification, from about 50% to about 100% modification, from about 60% to about 100% modification, from about 70% to about 100% modification, from about 80% to about 100% modification, and from about 90% to about 100% modification.

[0009] In some embodiments, the polynucleic acid molecule comprises at least one of: from about 10% to about 90% modification, from about 20% to about 90% modification, from about 30% to about 90% modification, from about 40% to about 90% modification, from about 50% to about 90% modification, from about 60% to about 90% modification, from about 70% to about 90% modification, and from about 80% to about 100% modification.

[0010] In some embodiments, the polynucleic acid molecule comprises at least one of: from about 10% to about 80% modification, from about 20% to about 80% modification, from about 30% to about 80% modification, from about 40% to about 80% modification, from about 50% to about 80% modification, from about 60% to about 80% modification, and from about 70% to about 80% modification.

[0011] In some embodiments, the polynucleic acid molecule comprises at least one of: from about 10% to about 70% modification, from about 20% to about 70% modification, from about 30% to about 70% modification, from about 40% to about 70% modification, from about 50% to about 70% modification, and from about 60% to about 70% modification.

[0012] In some embodiments, the polynucleic acid molecule comprises at least one of: from about 10% to about 60% modification, from about 20% to about 60% modification, from about 30% to about 60% modification, from about 40% to about 60% modification, and from about 50% to about 60% modification.

[0013] In some embodiments, the polynucleic acid molecule comprises at least one of: from about 10% to about 50% modification, from about 20% to about 50% modification, from about 30% to about 50% modification, and from about 40% to about 50% modification.

[0014] In some embodiments, the polynucleic acid molecule comprises at least one of: from about 10% to about 40% modification, from about 20% to about 40% modification, and from about 30% to about 40% modification.

[0015] In some embodiments, the polynucleic acid molecule comprises at least one of: from about 10% to about 30% modification, and from about 20% to about 30% modification.

[0016] In some embodiments, the polynucleic acid molecule comprises from about 10% to about 20% modification.

[0017] In some embodiments, the polynucleic acid molecule comprises from about 15% to about 90%, from about 20% to about 80%, from about 30% to about 70%, or from about 40% to about 60% modifications.

[0018] In some embodiments, the polynucleic acid molecule comprises at least about 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 99% modification.

[0019] In some embodiments, the polynucleic acid molecule comprises at least about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, or more modifications.

[0020] In some embodiments, the polynucleic acid molecule comprises at least about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, or more modified nucleotides.

[0021] In some embodiments, the polynucleic acid molecule comprises a sequence that hybridizes to a target sequence selected from SEQ ID NOs: 1-50.

[0022] In some embodiments, the polynucleic acid molecule comprises a single strand.

[0023] In some embodiments, the polynucleic acid molecule comprises two or more strands.

[0024] In some embodiments, the polynucleic acid molecule comprises a first polynucleotide and a second polynucleotide hybridized to the first polynucleotide to form a double-stranded polynucleic acid molecule.

[0025] In some embodiments, the second polynucleotide comprises at least one modification.

[0026] In some embodiments, the first polynucleotide and the second polynucleotide are RNA molecules. In some embodiments, the first polynucleotide and the second polynucleotide are siRNA molecules.

[0027] In some embodiments, the first polynucleotide comprises a sequence having at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NOs: 51-290. In some embodiments, the first polynucleotide consists of a sequence selected from SEQ ID NOs: 51-290. In some embodiments, the second polynucleotide comprises a

sequence having at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NOs: 51-290. In some embodiments, the second polynucleotide consists of a sequence selected from SEQ ID NOs: 51-290.

[0028] Disclosed herein, in certain embodiments, is a pharmaceutical composition comprising: a) a molecule disclosed above; and b) a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is formulated as a nanoparticle formulation. In some embodiments, the pharmaceutical composition is formulated for parenteral, oral, intranasal, buccal, rectal, or transdermal administration.

[0029] Disclosed herein, in certain embodiments, is a method of treating a disease or disorder in a patient in need thereof, comprising administering to the patient a composition comprising a molecule disclosed above. In some embodiments, the disease or disorder is a cancer. In some embodiments, the cancer is a solid tumor. In some embodiments, the cancer is a hematologic malignancy. In some embodiments, the cancer comprises an androgen receptor-associated cancer. In some embodiments, the cancer comprises bladder cancer, breast cancer, colorectal cancer, endometrial cancer, esophageal cancer, glioblastoma multiforme, head and neck cancer, kidney cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, or thyroid cancer. In some embodiments, the cancer comprises acute myeloid leukemia, CLL, DLBCL, or multiple myeloma.

[0030] Disclosed herein, in certain embodiments, is a method of inhibiting the expression of an androgen receptor gene in a primary cell of a patient, comprising administering a molecule disclosed above to the primary cell. In some embodiments, the method is an *in vivo* method. In some embodiments, the patient is a human.

[0031] Disclosed herein, in certain embodiments, is a kit comprising a molecule disclosed above.

BRIEF DESCRIPTION OF THE DRAWINGS

[0032] Various aspects of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0033] Fig. 1A-Fig. 1C illustrate relative AR or PSA RNA levels after transfection with siRNA in LNCaP cells.

[0034] Fig. 2A-Fig. 2C illustrate AR (Fig. 2A), PSA (Fig. 2B) or PSMA (Fig. 2C) mRNA levels after transfection with siRNA XD-01829 (also referred to as XD-0189).

[0035] Fig. 3 illustrates androgen receptor knock-down in 22RV1 and LNCaP cell lines with siRNA XD-01817 and XD-01829.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0036] Androgen receptor (AR) (also known as NR3C4, nuclear receptor subfamily 3, group C, gene 4) belongs to the steroid hormone group of nuclear receptor superfamily along with related members: estrogen receptor (ER), glucocorticoid receptor (GR), progesterone receptor (PR), and mineralocorticoid receptor (MR). Androgens, or steroid hormones, modulate protein synthesis and tissue remodeling through the androgen receptor. The AR protein is a ligand-inducible zinc finger transcription factor that regulates target gene expression. The presence of mutations in the *AR* gene has been observed in several types of cancers (e.g., prostate cancer, breast cancer, bladder cancer, or esophageal cancer), and in some instances, has been linked to metastatic progression.

[0037] Disclosed herein, in certain embodiments, are polynucleic acid molecules and pharmaceutical compositions that modulate the expression of the *AR* gene. In some instances, the polynucleic acid molecules and pharmaceutical compositions modulate the expression of wild type *AR* gene. In other instances, the polynucleic acid molecules and pharmaceutical compositions modulate the expression of mutant *AR*.

[0038] In some embodiments, the polynucleic acid molecules and pharmaceutical compositions are used for the treatment of a disease or disorder (e.g., cancer or an androgen receptor-associated disease or disorder). In additional embodiments, the polynucleic acid molecules and pharmaceutical compositions are used for inhibiting the expression of *AR* gene in a primary cell of a patient in need thereof.

[0039] In additional cases, also included herein are kits that comprise one or more of polynucleic acid molecules and pharmaceutical compositions described herein.

Polynucleic Acid Molecule

[0040] In some embodiments, a polynucleic acid molecule described herein modulates the expression of the *AR* gene (GenBank: AH002607.1). In some embodiments, *AR* DNA or RNA is wild type or comprises one or more mutations and/or splice variants. In some instances, *AR* DNA or RNA comprises one or more mutations. In some instances, *AR* DNA or RNA comprises one or more splice variants selected from AR splice variants including, but not limited to, AR1/2/2b, ARV2, ARV3, ARV4, AR1/2/3/2b, ARV5, ARV6, ARV7, ARV9, ARV10, ARV11, ARV12, ARV13, ARV14, ARV15, ARV16, and ARV(v567es). In some instances, the polynucleic acid molecule hybridizes to a target region of *AR* DNA or RNA comprising a mutation (e.g., a substitution, a deletion, or an addition) or a splice variant.

[0041] In some embodiments, *AR* DNA or RNA comprises one or more mutations. In some embodiments, *AR* DNA or RNA comprises one or more mutations within one or more exons. In some instances, the one or more exons comprise exon 1, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, or exon 8. In some embodiments, *AR* DNA or RNA comprises one or more mutations within exon 1, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, exon 8, or a combination thereof. In some instances, *AR* DNA or RNA comprises one or more mutations at positions corresponding to amino acid residues 2, 14, 16, 29, 45, 54, 57, 64, 106, 112, 176, 180, 184, 194, 198, 204, 214, 221, 222, 233, 243, 252, 255, 266, 269, 287, 288, 334, 335, 340, 363, 368, 369, 390, 403, 443, 491, 505, 513, 524, 524, 528, 533, 547, 548, 564, 567, 568, 574, 547, 559, 568, 571, 573, 575, 576, 577, 578, 579, 580, 581, 582, 585, 586, 587, 596, 597, 599, 601, 604, 607, 608, 609, 610, 611, 615, 616, 617, 619, 622, 629, 630, 638, 645, 647, 653, 662, 664, 670, 671, 672, 674, 677, 681, 682, 683, 684, 687, 688, 689, 690, 695, 700, 701, 702, 703, 705, 706, 707, 708, 710, 711, 712, 715, 717, 720, 721, 722, 723, 724, 725, 726, 727, 728, 730, 732, 733, 737, 739, 741, 742, 743, 744, 745, 746, 748, 749, 750, 751, 752, 754, 755, 756, 757, 758, 759, 762, 763, 764, 765, 766, 767, 768, 771, 772, 774, 777, 779, 786, 795, 780, 782, 784, 787, 788, 790, 791, 793, 794, 798, 802, 803, 804, 806, 807, 812, 813, 814, 819, 820, 821, 824, 827, 828, 830, 831, 834, 840, 841, 842, 846, 854, 855, 856, 863, 864, 866, 869, 870, 871, 874, 875, 877, 879, 880, 881, 886, 888, 889, 891, 892, 895, 896, 897, 898, 902, 903, 904, 907, 909, 910, 911, 913, 916, 919, or a combination thereof of the *AR* polypeptide. In some embodiments, *AR* DNA or RNA comprises one or more mutations at positions corresponding to amino acid residues selected from E2K, P14Q, K16N, V29M, S45T, L54S, L57Q, Q64R, Y106C, Q112H, S176S, K180R, L184P, Q194R, E198G, G204S, G214R, K221N, N222D, D233K, S243L, A252V, L255P, M266T, P269S, A287D, E288K, S334P, S335T, P340L, Y363N, L368V, A369P, P390R, P390S, P390L, A403V, Q443R, G491S, G505D, P513S, G524D, G524S, D528G, P533S, L547F, P548S, D564Y, S567F, G568W, L574P, L547F, C559Y, G568W, G568V, Y571C, Y571H, A573D, T575A, C576R, C576F, G577R, S578T, C579Y, C579F, K580R, V581F, F582Y, F582S, R585K, A586V, A587S, A596T, A596S, S597G, S597I, N599Y, C601F, D604Y, R607Q, R608K, K609N, D610T, C611Y, R615H, R615P, R615G, R616C, L616R, L616P, R617P, C619Y, A622V, R629W, R629Q, K630T, L638M, A645D, S647N, E653K, S662 (nonsense), I664N, Q670L, Q670R, P671H, I672T, L674P, L677P, E681L, P682T, G683A, V684I, V684A, A687V, G688Q, H689P, D690V, D695N, D695V, D695H, L700M, L701P, L701I, H701H, S702A, S703G, N705S, N705Y, E706 (nonsense), L707R, G708A, R710T, Q711E, L712F, V715M, K717Q, K720E, A721T, L722F, P723S, G724S, G724D, G724N, F725L, R726L, N727K, L728S, L728I, V730M, D732N, D732Y, D732E, Q733H, I737T, Y739D, W741R, M742V, M742I, G743R, G743V, L744F, M745T, V746M, A748D, A748V, A748T, M749V, M749I, G750S, G750D, W751R,

R752Q, F754V, F754L, T755A, N756S, N756D, V757A, N758T, S759F, S759P, L762F, Y763H, Y763C, F764L, A765T, A765V, P766A, P766S, D767E, L768P, L768M, N771H, E772G, E772A, R774H, R774C, K777T, R779W, R786Q, G795V, M780I, S782N, C784Y, M787V, R788S, L790F, S791P, E793D, F794S, Q798E, Q802R, G803L, F804L, C806Y, M807V, M807R, M807I, L812P, F813V, S814N, N819Q, G820A, L821V, Q824L, Q824R, F827L, F827V, D828H, L830V, L830P, R831Q, R831L, Y834C, R840C, R840H, I841S, I842T, R846G, R854K, R855C, R855H, F856L, L863R, D864N, D864E, D864G, V866L, V866M, V866E, I869M, A870G, A870V, R871G, H874Y, H874R, Q875K, T877S, T877A, D879T, D879G, L880Q, L881V, M886V, S888L, V889M, F891L, P892L, M895T, A896T, E897D, I898T, Q902R, V903M, P904S, P904H, L907F, G909R, G909E, K910R, V911L, P913S, F916L, Q919R, or a combination thereof of the AR polypeptide.

[0042] In some embodiments, a polynucleic acid molecule hybridizes to a target region of *AR* DNA or RNA comprising one or more mutations. In some embodiments the polynucleic acid hybridizes to one or more AR splice variants. In some embodiments the polynucleic acid hybridizes to *AR* DNA or RNA comprising one or more AR splice variants including but not limited to AR1/2/2b, ARV2, ARV3, ARV4, AR1/2/3/2b, ARV5, ARV6, ARV7, ARV9, ARV10, ARV11, ARV12, ARV13, ARV14, ARV15, ARV16, and ARV(v567es). In some embodiments, the polynucleic acid molecule hybridizes to a target region of *AR* DNA or RNA comprising one or more mutations within exon 1, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, exon 8, or a combination thereof. In some embodiments, the polynucleic acid molecule hybridizes to a target region of *AR* DNA or RNA comprising one or more mutations at positions corresponding to amino acid residues 2, 14, 16, 29, 45, 54, 57, 64, 106, 112, 176, 180, 184, 194, 198, 204, 214, 221, 222, 233, 243, 252, 255, 266, 269, 287, 288, 334, 335, 340, 363, 368, 369, 390, 403, 443, 491, 505, 513, 524, 524, 528, 533, 547, 548, 564, 567, 568, 574, 547, 559, 568, 571, 573, 575, 576, 577, 578, 579, 580, 581, 582, 585, 586, 587, 596, 597, 599, 601, 604, 607, 608, 609, 610, 611, 615, 616, 617, 619, 622, 629, 630, 638, 645, 647, 653, 662, 664, 670, 671, 672, 674, 677, 681, 682, 683, 684, 687, 688, 689, 690, 695, 700, 701, 702, 703, 705, 706, 707, 708, 710, 711, 712, 715, 717, 720, 721, 722, 723, 724, 725, 726, 727, 728, 730, 732, 733, 737, 739, 741, 742, 743, 744, 745, 746, 748, 749, 750, 751, 752, 754, 755, 756, 757, 758, 759, 762, 763, 764, 765, 766, 767, 768, 771, 772, 774, 777, 779, 786, 795, 780, 782, 784, 787, 788, 790, 791, 793, 794, 798, 802, 803, 804, 806, 807, 812, 813, 814, 819, 820, 821, 824, 827, 828, 830, 831, 834, 840, 841, 842, 846, 854, 855, 856, 863, 864, 866, 869, 870, 871, 874, 875, 877, 879, 880, 881, 886, 888, 889, 891, 892, 895, 896, 897, 898, 902, 903, 904, 907, 909, 910, 911, 913, 916, 919, or a combination thereof of the AR polypeptide. In some embodiments, the polynucleic acid molecule hybridizes to a target region of *AR* DNA or RNA

comprising one or more mutations selected from E2K, P14Q, K16N, V29M, S45T, L54S, L57Q, Q64R, Y106C, Q112H, S176S, K180R, L184P, Q194R, E198G, G204S, G214R, K221N, N222D, D233K, S243L, A252V, L255P, M266T, P269S, A287D, E288K, S334P, S335T, P340L, Y363N, L368V, A369P, P390R, P390S, P390L, A403V, Q443R, G491S, G505D, P513S, G524D, G524S, D528G, P533S, L547F, P548S, D564Y, S567F, G568W, L574P, L547F, C559Y, G568W, G568V, Y571C, Y571H, A573D, T575A, C576R, C576F, G577R, S578T, C579Y, C579F, K580R, V581F, F582Y, F582S, R585K, A586V, A587S, A596T, A596S, S597G, S597I, N599Y, C601F, D604Y, R607Q, R608K, K609N, D610T, C611Y, R615H, R615P, R615G, R616C, L616R, L616P, R617P, C619Y, A622V, R629W, R629Q, K630T, L638M, A645D, S647N, E653K, S662 (nonsense), I664N, Q670L, Q670R, P671H, I672T, L674P, L677P, E681L, P682T, G683A, V684I, V684A, A687V, G688Q, H689P, D690V, D695N, D695V, D695H, L700M, L701P, L701I, H701H, S702A, S703G, N705S, N705Y, E706 (nonsense), L707R, G708A, R710T, Q711E, L712F, V715M, K717Q, K720E, A721T, L722F, P723S, G724S, G724D, G724N, F725L, R726L, N727K, L728S, L728I, V730M, D732N, D732Y, D732E, Q733H, I737T, Y739D, W741R, M742V, M742I, G743R, G743V, L744F, M745T, V746M, A748D, A748V, A748T, M749V, M749I, G750S, G750D, W751R, R752Q, F754V, F754L, T755A, N756S, N756D, V757A, N758T, S759F, S759P, L762F, Y763H, Y763C, F764L, A765T, A765V, P766A, P766S, D767E, L768P, L768M, N771H, E772G, E772A, R774H, R774C, K777T, R779W, R786Q, G795V, M780I, S782N, C784Y, M787V, R788S, L790F, S791P, E793D, F794S, Q798E, Q802R, G803L, F804L, C806Y, M807V, M807R, M807I, L812P, F813V, S814N, N819Q, G820A, L821V, Q824L, Q824R, F827L, F827V, D828H, L830V, L830P, R831Q, R831L, Y834C, R840C, R840H, I841S, I842T, R846G, R854K, R855C, R855H, F856L, L863R, D864N, D864E, D864G, V866L, V866M, V866E, I869M, A870G, A870V, R871G, H874Y, H874R, Q875K, T877S, T877A, D879T, D879G, L880Q, L881V, M886V, S888L, V889M, F891L, P892L, M895T, A896T, E897D, I898T, Q902R, V903M, P904S, P904H, L907F, G909R, G909E, K910R, V911L, P913S, F916L, Q919R, or a combination thereof of the AR polypeptide.

[0043] In some embodiments, the polynucleic acid molecule comprises a sequence that hybridizes to a target sequence illustrated in Table 1. In some embodiments, the polynucleic acid molecule hybridizes to an AR target sequence selected from SEQ ID NOs: 1-50. In some cases, the polynucleic acid molecule hybridizes to an AR target sequence selected from SEQ ID NOs: 1-50 with less than 5 mismatched bases, with less than 4 mismatched bases, with less than 3 mismatched bases, with less than 2 mismatched bases, or with 1 mismatched base. In some cases, the polynucleic acid molecule hybridizes to an AR target sequence selected from SEQ ID NOs: 1-50 with less than 4 mismatched bases.

[0044] In some embodiments, a polynucleic acid molecule comprises a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a sequence listed in Table 2, Table 3, or Table 6A. In some embodiments, the polynucleic acid molecule comprises a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NOs: 51-290. In some embodiments, the polynucleic acid molecule comprises a sequence having at least 50% sequence identity to SEQ ID NOs: 51-290. In some embodiments, the polynucleic acid molecule comprises a sequence having at least 60% sequence identity to SEQ ID NOs: 51-290. In some embodiments, the polynucleic acid molecule comprises a sequence having at least 70% sequence identity to SEQ ID NOs: 51-290. In some embodiments, the polynucleic acid molecule comprises a sequence having at least 75% sequence identity to SEQ ID NOs: 51-290. In some embodiments, the polynucleic acid molecule comprises a sequence having at least 80% sequence identity to SEQ ID NOs: 51-290. In some embodiments, the polynucleic acid molecule comprises a sequence having at least 85% sequence identity to SEQ ID NOs: 51-290. In some embodiments, the polynucleic acid molecule comprises a sequence having at least 90% sequence identity to SEQ ID NOs: 51-290. In some embodiments, the polynucleic acid molecule comprises a sequence having at least 95% sequence identity to SEQ ID NOs: 51-290. In some embodiments, the polynucleic acid molecule comprises a sequence having at least 96% sequence identity to SEQ ID NOs: 51-290. In some embodiments, the polynucleic acid molecule comprises a sequence having at least 97% sequence identity to SEQ ID NOs: 51-290. In some embodiments, the polynucleic acid molecule comprises a sequence having at least 98% sequence identity to SEQ ID NOs: 51-290. In some embodiments, the polynucleic acid molecule comprises a sequence having at least 99% sequence identity to SEQ ID NOs: 51-290. In some embodiments, the polynucleic acid molecule consists of SEQ ID NOs: 51-290.

[0045] In some embodiments, a polynucleic acid molecule comprises a first polynucleotide and a second polynucleotide. In some instances, the first polynucleotide comprises a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NOs: 51-290. In some cases, the second polynucleotide comprises a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NOs: 51-290. In some cases, the polynucleic acid molecule comprises a first polynucleotide having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NOs: 51-290 and a second polynucleotide having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NOs: 51-290.

[0046] In some embodiments, a polynucleic acid molecule described herein comprises RNA or DNA. In some cases, the polynucleic acid molecule comprises RNA. In some instances, RNA comprises short interfering RNA (siRNA), short hairpin RNA (shRNA), microRNA (miRNA), double-stranded RNA (dsRNA), transfer RNA (tRNA), ribosomal RNA (rRNA), or heterogeneous nuclear RNA (hnRNA). In some instances, RNA comprises shRNA. In some instances, RNA comprises miRNA. In some instances, RNA comprises dsRNA. In some instances, RNA comprises tRNA. In some instances, RNA comprises rRNA. In some instances, RNA comprises hnRNA. In some instances, the RNA comprises siRNA. In some instances, the polynucleic acid molecule comprises siRNA.

[0047] In some embodiments, a polynucleic acid molecule is from about 10 to about 50 nucleotides in length. In some instances, the polynucleic acid molecule is from about 10 to about 30, from about 15 to about 30, from about 18 to about 25, from about 18 to about 24, from about 19 to about 23, or from about 20 to about 22 nucleotides in length.

[0048] In some embodiments, a polynucleic acid molecule is about 50 nucleotides in length. In some instances, the polynucleic acid molecule is about 45 nucleotides in length. In some instances, the polynucleic acid molecule is about 40 nucleotides in length. In some instances, the polynucleic acid molecule is about 35 nucleotides in length. In some instances, the polynucleic acid molecule is about 30 nucleotides in length. In some instances, the polynucleic acid molecule is about 25 nucleotides in length. In some instances, the polynucleic acid molecule is about 20 nucleotides in length. In some instances, the polynucleic acid molecule is about 19 nucleotides in length. In some instances, the polynucleic acid molecule is about 18 nucleotides in length. In some instances, the polynucleic acid molecule is about 17 nucleotides in length. In some instances, the polynucleic acid molecule is about 16 nucleotides in length. In some instances, the polynucleic acid molecule is about 15 nucleotides in length. In some instances, the polynucleic acid molecule is about 14 nucleotides in length. In some instances, the polynucleic acid molecule is about 13 nucleotides in length. In some instances, the polynucleic acid molecule is about 12 nucleotides in length. In some instances, the polynucleic acid molecule is about 11 nucleotides in length. In some instances, the polynucleic acid molecule is about 10 nucleotides in length. In some instances, the polynucleic acid molecule is from about 10 to about 50 nucleotides in length. In some instances, the polynucleic acid molecule is from about 10 to about 45 nucleotides in length. In some instances, the polynucleic acid molecule is from about 10 to about 40 nucleotides in length. In some instances, the polynucleic acid molecule is from about 10 to about 35 nucleotides in length. In some instances, the polynucleic acid molecule is from about 10 to about 30 nucleotides in length. In some instances, the polynucleic acid molecule is from about 10 to about 25 nucleotides in length.

In some instances, the polynucleic acid molecule is from about 10 to about 20 nucleotides in length. In some instances, the polynucleic acid molecule is from about 15 to about 25 nucleotides in length. In some instances, the polynucleic acid molecule is from about 15 to about 30 nucleotides in length. In some instances, the polynucleic acid molecule is from about 12 to about 30 nucleotides in length.

[0049] In some embodiments, a polynucleic acid molecule comprises a first polynucleotide. In some instances, the polynucleic acid molecule comprises a second polynucleotide. In some instances, the polynucleic acid molecule comprises a first polynucleotide and a second polynucleotide. In some instances, the first polynucleotide is a sense strand or passenger strand. In some instances, the second polynucleotide is an antisense strand or guide strand.

[0050] In some embodiments, a polynucleic acid molecule is a first polynucleotide. In some embodiments, the first polynucleotide is from about 10 to about 50 nucleotides in length. In some instances, the first polynucleotide is from about 10 to about 30, from about 15 to about 30, from about 18 to about 25, from about 18 to about 24, from about 19 to about 23, or from about 20 to about 22 nucleotides in length.

[0051] In some instances, a first polynucleotide is about 50 nucleotides in length. In some instances, the first polynucleotide is about 45 nucleotides in length. In some instances, the first polynucleotide is about 40 nucleotides in length. In some instances, the first polynucleotide is about 35 nucleotides in length. In some instances, the first polynucleotide is about 30 nucleotides in length. In some instances, the first polynucleotide is about 25 nucleotides in length. In some instances, the first polynucleotide is about 20 nucleotides in length. In some instances, the first polynucleotide is about 19 nucleotides in length. In some instances, the first polynucleotide is about 18 nucleotides in length. In some instances, the first polynucleotide is about 17 nucleotides in length. In some instances, the first polynucleotide is about 16 nucleotides in length. In some instances, the first polynucleotide is about 15 nucleotides in length. In some instances, the first polynucleotide is about 14 nucleotides in length. In some instances, the first polynucleotide is about 13 nucleotides in length. In some instances, the first polynucleotide is about 12 nucleotides in length. In some instances, the first polynucleotide is about 11 nucleotides in length. In some instances, the first polynucleotide is about 10 nucleotides in length. In some instances, the first polynucleotide is from about 10 to about 50 nucleotides in length. In some instances, the first polynucleotide is from about 10 to about 45 nucleotides in length. In some instances, the first polynucleotide is from about 10 to about 40 nucleotides in length. In some instances, the first polynucleotide is from about 10 to about 35 nucleotides in length. In some instances, the first polynucleotide is from about 10 to about 30 nucleotides in length. In some instances, the first polynucleotide is from about 10 to about 25 nucleotides in length. In some instances, the first

polynucleotide is from about 10 to about 20 nucleotides in length. In some instances, the first polynucleotide is from about 15 to about 25 nucleotides in length. In some instances, the first polynucleotide is from about 15 to about 30 nucleotides in length. In some instances, the first polynucleotide is from about 12 to about 30 nucleotides in length.

[0052] In some embodiments, a polynucleic acid molecule is a second polynucleotide. In some embodiments, the second polynucleotide is from about 10 to about 50 nucleotides in length. In some instances, the second polynucleotide is from about 10 to about 30, from about 15 to about 30, from about 18 to about 25, from about 18 to about 24, from about 19 to about 23, or from about 20 to about 22 nucleotides in length.

[0053] In some instances, a second polynucleotide is about 50 nucleotides in length. In some instances, the second polynucleotide is about 45 nucleotides in length. In some instances, the second polynucleotide is about 40 nucleotides in length. In some instances, the second polynucleotide is about 35 nucleotides in length. In some instances, the second polynucleotide is about 30 nucleotides in length. In some instances, the second polynucleotide is about 25 nucleotides in length. In some instances, the second polynucleotide is about 20 nucleotides in length. In some instances, the second polynucleotide is about 19 nucleotides in length. In some instances, the second polynucleotide is about 18 nucleotides in length. In some instances, the second polynucleotide is about 17 nucleotides in length. In some instances, the second polynucleotide is about 16 nucleotides in length. In some instances, the second polynucleotide is about 15 nucleotides in length. In some instances, the second polynucleotide is about 14 nucleotides in length. In some instances, the second polynucleotide is about 13 nucleotides in length. In some instances, the second polynucleotide is about 12 nucleotides in length. In some instances, the second polynucleotide is about 11 nucleotides in length. In some instances, the second polynucleotide is about 10 nucleotides in length. In some instances, the second polynucleotide is from about 10 to about 50 nucleotides in length. In some instances, the second polynucleotide is from about 10 to about 45 nucleotides in length. In some instances, the second polynucleotide is from about 10 to about 40 nucleotides in length. In some instances, the second polynucleotide is from about 10 to about 35 nucleotides in length. In some instances, the second polynucleotide is from about 10 to about 30 nucleotides in length. In some instances, the second polynucleotide is from about 10 to about 25 nucleotides in length. In some instances, the second polynucleotide is from about 10 to about 20 nucleotides in length. In some instances, the second polynucleotide is from about 15 to about 25 nucleotides in length. In some instances, the second polynucleotide is from about 15 to about 30 nucleotides in length. In some instances, the second polynucleotide is from about 12 to about 30 nucleotides in length.

[0054] In some embodiments, a polynucleic acid molecule comprises a first polynucleotide and a second polynucleotide. In some instances, the polynucleic acid molecule further comprises a blunt terminus, an overhang, or a combination thereof. In some instances, the blunt terminus is a 5' blunt terminus, a 3' blunt terminus, or both. In some cases, the overhang is a 5' overhang, 3' overhang, or both. In some cases, the overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 non-base pairing nucleotides. In some cases, the overhang comprises 1, 2, 3, 4, 5, or 6 non-base pairing nucleotides. In some cases, the overhang comprises 1, 2, 3, or 4 non-base pairing nucleotides. In some cases, the overhang comprises 1 non-base pairing nucleotide. In some cases, the overhang comprises 2 non-base pairing nucleotides. In some cases, the overhang comprises 3 non-base pairing nucleotides. In some cases, the overhang comprises 4 non-base pairing nucleotides.

[0055] In some embodiments, a sequence of the polynucleic acid molecule is at least 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99%, or 99.5% complementary to a target sequence described herein. In some embodiments, the sequence of the polynucleic acid molecule is at least 50% complementary to a target sequence described herein. In some embodiments, the sequence of the polynucleic acid molecule is at least 60% complementary to a target sequence described herein. In some embodiments, the sequence of the polynucleic acid molecule is at least 70% complementary to a target sequence described herein. In some embodiments, the sequence of the polynucleic acid molecule is at least 80% complementary to a target sequence described herein. In some embodiments, the sequence of the polynucleic acid molecule is at least 90% complementary to a target sequence described herein. In some embodiments, the sequence of the polynucleic acid molecule is at least 95% complementary to a target sequence described herein. In some instances, the sequence of the polynucleic acid molecule is 100% complementary to a target sequence described herein.

[0056] In some embodiments, the sequence of a polynucleic acid molecule has 5 or less mismatches to a target sequence described herein. In some embodiments, the sequence of the polynucleic acid molecule has 4 or less mismatches to a target sequence described herein. In some instances, the sequence of the polynucleic acid molecule has 3 or less mismatches to a target sequence described herein. In some cases, the sequence of the polynucleic acid molecule has 2 or less mismatches to a target sequence described herein. In some cases, the sequence of the polynucleic acid molecule has 1 or less mismatches to a target sequence described herein.

[0057] In some embodiments, the specificity of a polynucleic acid molecule that hybridizes to a target sequence described herein is a 95%, 98%, 99%, 99.5% or 100% sequence complementarity

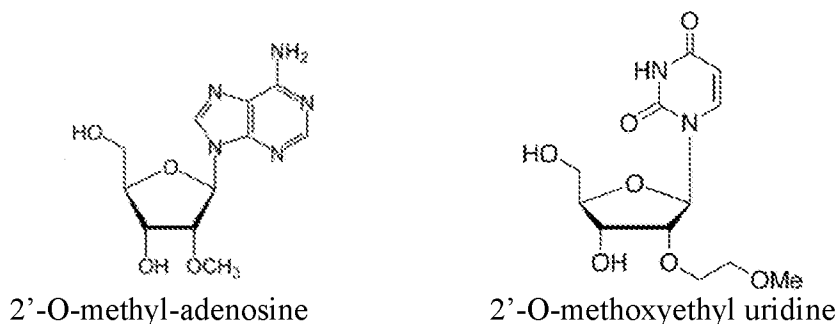
of the polynucleic acid molecule to a target sequence. In some instances, the hybridization is a high stringent hybridization condition.

[0058] In some embodiments, a polynucleic acid molecule has reduced off-target effect. In some instances, “off-target” or “off-target effects” refer to any instance in which a polynucleic acid polymer directed against a given target causes an unintended effect by interacting either directly or indirectly with another mRNA sequence, a DNA sequence or a cellular protein or other moiety. In some instances, an “off-target effect” occurs when there is a simultaneous degradation of other transcripts due to partial homology or complementarity between that other transcript and the sense and/or antisense strand of the polynucleic acid molecule.

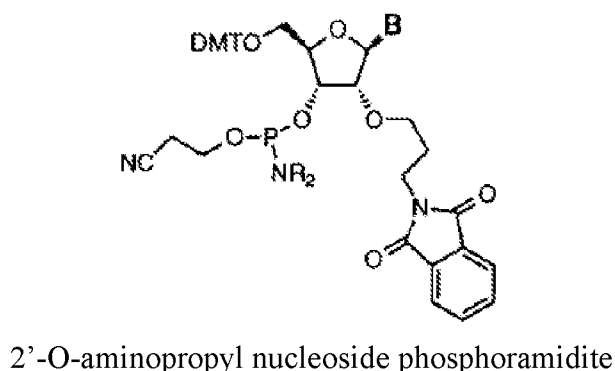
[0059] In some embodiments, a polynucleic acid molecule comprises natural, synthetic or artificial nucleotide analogues or bases. In some cases, the polynucleic acid molecule comprises combinations of DNA, RNA and/or nucleotide analogues. In some instances, the synthetic or artificial nucleotide analogues or bases comprise modifications at one or more of ribose moiety, phosphate moiety, nucleoside moiety, or a combination thereof.

[0060] In some embodiments, nucleotide analogues or artificial nucleotide base comprise a nucleic acid with a modification at a 2' hydroxyl group of the ribose moiety. In some instances, the modification includes an H, OR, R, halo, SH, SR, NH₂, NHR, NR₂, or CN, wherein R is an alkyl moiety. Exemplary alkyl moiety includes, but is not limited to, halogens, sulfurs, thiols, thioethers, thioesters, amines (primary, secondary, or tertiary), amides, ethers, esters, alcohols and oxygen. In some instances, the alkyl moiety further comprises a modification. In some instances, the modification comprises an azo group, a keto group, an aldehyde group, a carboxyl group, a nitro group, a nitroso group, a nitrile group, a heterocycle (e.g., imidazole, hydrazino or hydroxylamino) group, an isocyanate or cyanate group, or a sulfur containing group (e.g., sulfoxide, sulfone, sulfide, or disulfide). In some instances, the alkyl moiety further comprises a hetero substitution. In some instances, the carbon of the heterocyclic group is substituted by a nitrogen, oxygen or sulfur. In some instances, the heterocyclic substitution includes but is not limited to, morpholino, imidazole, and pyrrolidino.

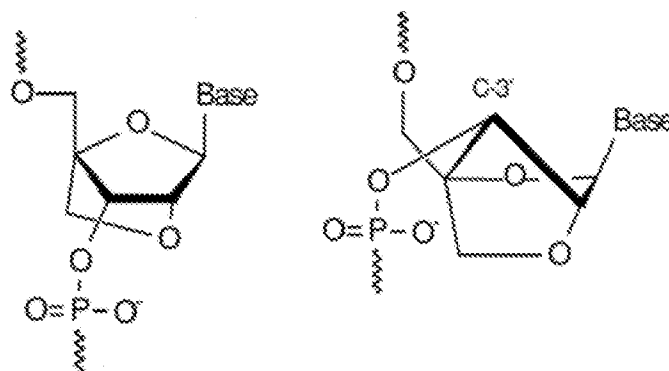
[0061] In some instances, the modification at the 2' hydroxyl group is a 2'-O-methyl modification or a 2'-O-methoxyethyl (2'-O-MOE) modification. In some cases, the 2'-O-methyl modification adds a methyl group to the 2' hydroxyl group of the ribose moiety whereas the 2'-O-methoxyethyl modification adds a methoxyethyl group to the 2' hydroxyl group of the ribose moiety. Exemplary chemical structures of a 2'-O-methyl modification of an adenosine molecule and 2'-O-methoxyethyl modification of a uridine are illustrated below.



[0062] In some instances, the modification at the 2' hydroxyl group is a 2'-O-aminopropyl modification in which an extended amine group comprising a propyl linker binds the amine group to the 2' oxygen. In some instances, this modification neutralizes the phosphate-derived overall negative charge of the oligonucleotide molecule by introducing one positive charge from the amine group per sugar and thereby improves cellular uptake properties due to its zwitterionic properties. An exemplary chemical structure of a 2'-O-aminopropyl nucleoside phosphoramidite is illustrated below.

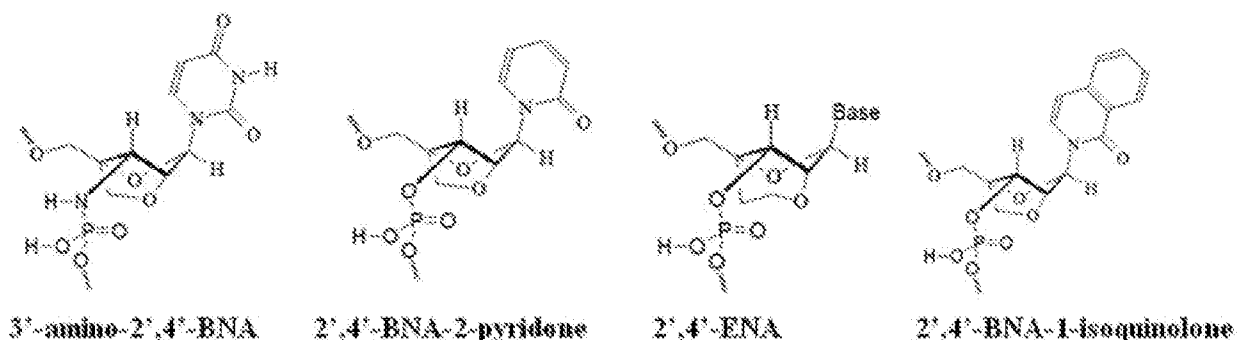


[0063] In some instances, the modification at the 2' hydroxyl group is a locked or bridged ribose modification (e.g., locked nucleic acid or LNA) in which the oxygen molecule bound at the 2' carbon is linked to the 4' carbon by a methylene group, thus forming a 2'-C,4'-C-oxy-methylene-linked bicyclic ribonucleotide monomer. Exemplary representations of the chemical structure of LNA are illustrated below. The representation shown to the left highlights the chemical connectivities of an LNA monomer. The representation shown to the right highlights the locked 3'-endo (³E) conformation of the furanose ring of an LNA monomer.



LNA (Locked Nucleic Acids)

[0064] In some instances, the modification at the 2' hydroxyl group comprises ethylene nucleic acids (ENA) such as for example 2'-4'-ethylene-bridged nucleic acid, which locks the sugar conformation into a C_{3'}'-endo sugar pucker conformation. ENA are part of the bridged nucleic acids class of modified nucleic acids that also comprises LNA. Exemplary chemical structures of the ENA and bridged nucleic acids are illustrated below.



3'-amino-2',4'-BNA

2',4'-BNA-2-pyridone

2',4'-ENA

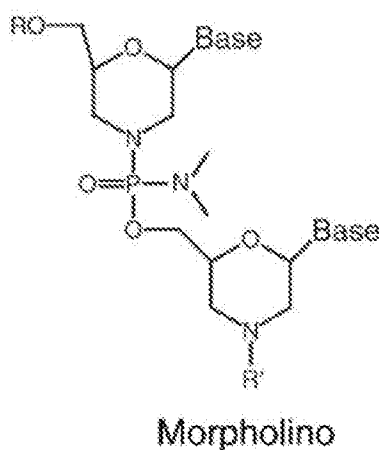
2',4'-BNA-1-isoquinolone

[0065] In some embodiments, additional modifications at the 2' hydroxyl group include 2'-deoxy, T-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), T-O- dimethylaminoethoxyethyl (2'-O-DMAEOE), or 2'-O-N-methylacetamido (2'-O-NMA).

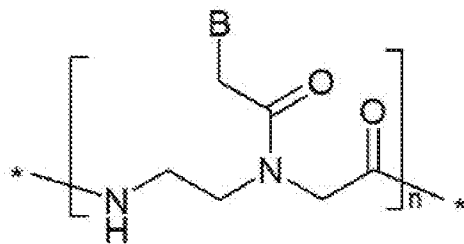
[0066] In some embodiments, nucleotide analogues comprise modified bases such as, but not limited to, 5-propynyluridine, 5-propynylcytidine, 6-methyladenine, 6-methylguanine, N, N, -dimethyladenine, 2-propyladenine, 2-propylguanine, 2-aminoadenine, 1-methylinosine, 3-methyluridine, 5-methylcytidine, 5-methyluridine and other nucleotides having a modification at the 5 position, 5- (2- amino) propyl uridine, 5-halocytidine, 5-halouridine, 4-acetylcytidine, 1-methyladenosine, 2-methyladenosine, 3-methylcytidine, 6-methyluridine, 2- methylguanosine, 7-methylguanosine, 2, 2-dimethylguanosine, 5- methylaminoethyluridine, 5-methoxyuridine, deazanucleotides (such as 7-deaza- adenosine, 6-azouridine, 6-azocytidine, or 6-azothymidine), 5-methyl-2-thiouridine, other thio bases (such as 2-thiouridine, 4-thiouridine, and 2-thiocytidine), dihydrouridine, pseudouridine, queuosine, archaeosine, naphthyl and substituted naphthyl groups,

any O- and N-alkylated purines and pyrimidines (such as N⁶-methyladenosine, 5-methylcarbonylmethyluridine, uridine 5-oxyacetic acid, pyridine-4-one, or pyridine-2-one), phenyl and modified phenyl groups (such as aminophenol or 2,4,6-trimethoxy benzene), modified cytosines that act as G-clamp nucleotides, 8-substituted adenines and guanines, 5-substituted uracils and thymines, azapyrimidines, carboxyhydroxyalkyl nucleotides, carboxyalkylaminoalkyl nucleotides, and alkylcarbonylalkylated nucleotides. Modified nucleotides also include those nucleotides that are modified with respect to the sugar moiety, as well as nucleotides having sugars or analogs thereof that are not ribosyl. For example, the sugar moieties, in some cases are, or are based on, mannoses, arabinoses, glucopyranoses, galactopyranoses, 4'-thioribose, and other sugars, heterocycles, or carbocycles. The term nucleotide also includes what are known in the art as universal bases. By way of example, universal bases include, but are not limited to, 3-nitropyrrole, 5-nitroindole, or nebularine.

[0067] In some embodiments, nucleotide analogues further comprise morpholinos, peptide nucleic acids (PNAs), methylphosphonate nucleotides, thiophosphonate nucleotides, 2'-fluoro N³-P^{5'}-phosphoramidites, 1', 5'-anhydrohexitol nucleic acids (HNAs), or a combination thereof. Morpholino or phosphorodiamidate morpholino oligo (PMO) comprises synthetic molecules whose structure mimics natural nucleic acid structure but deviates from the normal sugar and phosphate structures. In some instances, the five member ribose ring is substituted with a six member morpholino ring containing four carbons, one nitrogen and one oxygen. In some cases, the ribose monomers are linked by a phosphordiamidate group instead of a phosphate group. In such cases, the backbone alterations remove all positive and negative charges making morpholinos neutral molecules capable of crossing cellular membranes without the aid of cellular delivery agents such as those used by charged oligonucleotides.



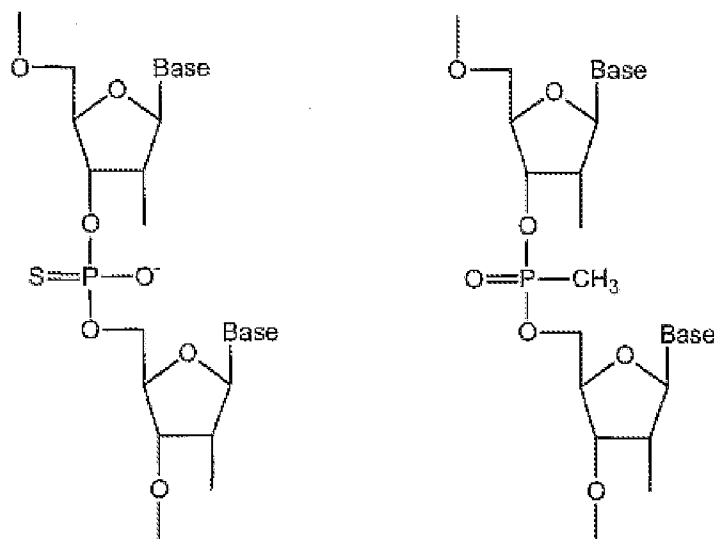
[0068] In some embodiments, peptide nucleic acid (PNA) does not contain sugar ring or phosphate linkage and the bases are attached and appropriately spaced by oligoglycine-like molecules, therefore eliminating a backbone charge.



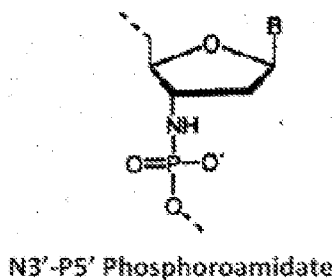
PNA

[0069] In some embodiments, one or more modifications optionally occur at the internucleotide linkage. In some instances, modified internucleotide linkage includes, but is not limited to, phosphorothioates; phosphorodithioates; methylphosphonates; 5'-alkylenephosphonates; 5'-methylphosphonate; 3'-alkylene phosphonates; borontrifluoridates; borano phosphate esters and selenophosphates of 3'-5'linkage or 2'-5'linkage; phosphotriesters; thionoalkylphosphotriesters; hydrogen phosphonate linkages; alkyl phosphonates; alkylphosphonothioates; arylphosphonothioates; phosphoroselenoates; phosphorodiselenoates; phosphinates; phosphoramidates; 3'-alkylphosphoramidates; aminoalkylphosphoramidates; thionophosphoramidates; phosphoropiperazidates; phosphoroanilothioates; phosphoroanilidates; ketones; sulfones; sulfonamides; carbonates; carbamates; methylenehydrazos; methylenedimethylhydrazos; formacetals; thioformacetals; oximes; methyleneiminos; methylenemethyliminos; thioamidates; linkages with riboacetyl groups; aminoethyl glycine; silyl or siloxane linkages; alkyl or cycloalkyl linkages with or without heteroatoms of, for example, 1 to 10 carbons that are saturated or unsaturated and/or substituted and/or contain heteroatoms; linkages with morpholino structures, amides, or polyamides wherein the bases are attached to the aza nitrogens of the backbone directly or indirectly; and combinations thereof.

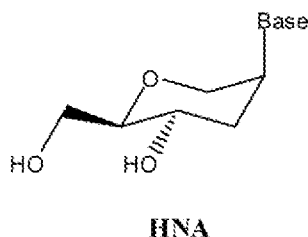
[0070] In some instances, the modification is a methyl or thiol modification such as methylphosphonate or thiolphosphonate modification. Exemplary thiolphosphonate nucleotide (left) and methylphosphonate nucleotide (right) are illustrated below.



[0071] In some instances, a modified nucleotide includes, but is not limited to, 2'-fluoro N3-P5'-phosphoramidites illustrated as:



[0072] In some instances, a modified nucleotide includes, but is not limited to, hexitol nucleic acid (or 1', 5'- anhydrohexitol nucleic acids (HNA)) illustrated as:



[0073] In some embodiments, one or more modifications further optionally include modifications of the ribose moiety, phosphate backbone and the nucleoside, or modifications of the nucleotide analogues at the 3' or the 5' terminus. For example, the 3' terminus optionally include a 3' cationic group, or by inverting the nucleoside at the 3'-terminus with a 3'-3' linkage. In another alternative, the 3'-terminus is optionally conjugated with an aminoalkyl group, e.g., a 3' C5-aminoalkyl dT. In an additional alternative, the 3'-terminus is optionally conjugated with an abasic site, e.g., with an apurinic or apyrimidinic site. In some instances, the 5'-terminus is conjugated with an aminoalkyl group, e.g., a 5'-O-alkylamino substituent. In some cases, the 5'-terminus is conjugated with an abasic site, e.g., with an apurinic or apyrimidinic site.

[0074] In some embodiments, a polynucleic acid molecule comprises one or more artificial nucleotide analogues described herein. In some instances, the polynucleic acid molecule comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 25, or more of the artificial nucleotide analogues described herein. In some embodiments, the artificial nucleotide analogues include 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl, 2'-deoxy, T-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), T-O-dimethylaminoethoxyethyl (2'-O-DMAEOE), or 2'-O-N-methylacetamido (2'-O-NMA) modified, LNA, ENA, PNA, HNA, morpholino, methylphosphonate nucleotides, thiophosphonate nucleotides, 2'-fluoro N3-P5'-phosphoramidites, or a combination thereof. In some instances, the polynucleic acid molecule comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 25, or more of the artificial nucleotide analogues selected from 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl, 2'-deoxy, T-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), T-O-dimethylaminoethoxyethyl (2'-O-DMAEOE), or 2'-O-N-methylacetamido (2'-O-NMA) modified, LNA, ENA, PNA, HNA, morpholino, methylphosphonate nucleotides, thiophosphonate nucleotides, 2'-fluoro N3-P5'-phosphoramidites, or a combination thereof. In some instances, the polynucleic acid molecule comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 25, or more of 2'-O-methyl modified nucleotides. In some instances, the polynucleic acid molecule comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 25, or more of 2'-O-methoxyethyl (2'-O-MOE) modified nucleotides. In some instances, the polynucleic acid molecule comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 25, or more of thiophosphonate nucleotides.

[0075] In some instances, a polynucleic acid molecule comprises at least one of: from about 5% to about 100% modification, from about 10% to about 100% modification, from about 20% to about 100% modification, from about 30% to about 100% modification, from about 40% to about 100% modification, from about 50% to about 100% modification, from about 60% to about 100% modification, from about 70% to about 100% modification, from about 80% to about 100% modification, and from about 90% to about 100% modification. In some instances, the polynucleic acid molecule is a polynucleic acid molecule of SEQ ID NOs: 51-150.

[0076] In some cases, a polynucleic acid molecule comprises at least one of: from about 10% to about 90% modification, from about 20% to about 90% modification, from about 30% to about 90% modification, from about 40% to about 90% modification, from about 50% to about 90% modification, from about 60% to about 90% modification, from about 70% to about 90%

modification, and from about 80% to about 100% modification. In some instances, the polynucleic acid molecule is a polynucleic acid molecule of SEQ ID NOs: 51-150.

[0077] In some cases, a polynucleic acid molecule comprises at least one of: from about 10% to about 80% modification, from about 20% to about 80% modification, from about 30% to about 80% modification, from about 40% to about 80% modification, from about 50% to about 80% modification, from about 60% to about 80% modification, and from about 70% to about 80% modification. In some instances, the polynucleic acid molecule is a polynucleic acid molecule of SEQ ID NOs: 51-150.

[0078] In some instances, a polynucleic acid molecule comprises at least one of: from about 10% to about 70% modification, from about 20% to about 70% modification, from about 30% to about 70% modification, from about 40% to about 70% modification, from about 50% to about 70% modification, and from about 60% to about 70% modification. In some instances, the polynucleic acid molecule is a polynucleic acid molecule of SEQ ID NOs: 51-150.

[0079] In some instances, a polynucleic acid molecule comprises at least one of: from about 10% to about 60% modification, from about 20% to about 60% modification, from about 30% to about 60% modification, from about 40% to about 60% modification, and from about 50% to about 60% modification. In some instances, the polynucleic acid molecule is a polynucleic acid molecule of SEQ ID NOs: 51-150.

[0080] In some cases, a polynucleic acid molecule comprises at least one of: from about 10% to about 50% modification, from about 20% to about 50% modification, from about 30% to about 50% modification, and from about 40% to about 50% modification. In some instances, the polynucleic acid molecule is a polynucleic acid molecule of SEQ ID NOs: 51-150.

[0081] In some cases, a polynucleic acid molecule comprises at least one of: from about 10% to about 40% modification, from about 20% to about 40% modification, and from about 30% to about 40% modification. In some instances, the polynucleic acid molecule is a polynucleic acid molecule of SEQ ID NOs: 51-150.

[0082] In some cases, a polynucleic acid molecule comprises at least one of: from about 10% to about 30% modification, and from about 20% to about 30% modification. In some instances, the polynucleic acid molecule is a polynucleic acid molecule of SEQ ID NOs: 51-150.

[0083] In some cases, a polynucleic acid molecule comprises from about 10% to about 20% modification. In some instances, the polynucleic acid molecule is a polynucleic acid molecule of SEQ ID NOs: 51-150.

[0084] In some cases, a polynucleic acid molecule comprises from about 15% to about 90%, from about 20% to about 80%, from about 30% to about 70%, or from about 40% to about 60%

modifications. In some instances, the polynucleic acid molecule is a polynucleic acid molecule of SEQ ID NOs: 51-150.

[0085] In additional cases, a polynucleic acid molecule comprises at least about 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 99% modification. In some instances, the polynucleic acid molecule is a polynucleic acid molecule of SEQ ID NOs: 51-150.

[0086] In some embodiments, a polynucleic acid molecule comprises at least about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, or more modifications. In some instances, the polynucleic acid molecule is a polynucleic acid molecule of SEQ ID NOs: 51-150.

[0087] In some instances, a polynucleic acid molecule comprises at least about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, or more modified nucleotides. In some instances, the polynucleic acid molecule is a polynucleic acid molecule of SEQ ID NOs: 51-150.

[0088] In some instances, from about 5 to about 100% of a polynucleic acid molecule comprise an artificial nucleotide analogue described herein. In some instances, about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of a polynucleic acid molecule comprise an artificial nucleotide analogue described herein. In some instances, about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of a polynucleic acid molecule of SEQ ID NOs: 51-290 comprise an artificial nucleotide analogue described herein. In some instances, about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of a polynucleic acid molecule of SEQ ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some instances, about 5% of a polynucleic acid molecule of SEQ ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some instances, about 10% of a polynucleic acid molecule of SEQ ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some instances, about 15% of a polynucleic acid molecule of SEQ ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some instances, about 20% of a polynucleic acid molecule of SEQ ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some instances, about 25% of a polynucleic acid molecule of SEQ ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some instances, about 30% of a polynucleic acid molecule of SEQ ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some instances, about 35% of a polynucleic acid molecule of SEQ

ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some instances, about 40% of a polynucleic acid molecule of SEQ ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some instances, about 45% of a polynucleic acid molecule of SEQ ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some instances, about 50% of a polynucleic acid molecule of SEQ ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some instances, about 55% of a polynucleic acid molecule of SEQ ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some instances, about 60% of a polynucleic acid molecule of SEQ ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some instances, about 65% of a polynucleic acid molecule of SEQ ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some instances, about 70% of a polynucleic acid molecule of SEQ ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some instances, about 75% of a polynucleic acid molecule of SEQ ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some instances, about 80% of a polynucleic acid molecule of SEQ ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some instances, about 85% of a polynucleic acid molecule of SEQ ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some instances, about 90% of a polynucleic acid molecule of SEQ ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some instances, about 95% of a polynucleic acid molecule of SEQ ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some instances, about 96% of a polynucleic acid molecule of SEQ ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some instances, about 97% of a polynucleic acid molecule of SEQ ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some instances, about 98% of a polynucleic acid molecule of SEQ ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some instances, about 99% of a polynucleic acid molecule of SEQ ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some instances, about 100% of a polynucleic acid molecule of SEQ ID NOs: 51-150 comprise an artificial nucleotide analogue described herein. In some embodiments, the artificial nucleotide analogues comprises 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl, 2'-deoxy, T-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), T-O-dimethylaminoethoxyethyl (2'-O-DMAEOE), or 2'-O-N-methylacetamido (2'-O-NMA) modified, LNA, ENA, PNA, HNA, morpholino, methylphosphonate nucleotides, thiolphosphonate nucleotides, 2'-fluoro N³-P⁵'-phosphoramidites, or a combination thereof.

[0089] In some embodiments, a polynucleic acid molecule comprises from about 1 to about 25 modifications in which the modification comprises an artificial nucleotide analogues described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises from about 1 to about 25 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 1 modification in which the modification comprises an artificial nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 2 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 3 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 4 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 5 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 6 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 7 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 8 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 9 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 10 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 11 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 12 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 13 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 14 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 15 modifications in which the modifications comprise an artificial

nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 16 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 17 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 18 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 19 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 20 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 21 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 22 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 23 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 24 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, a polynucleic acid molecule of SEQ ID NOs: 51-150 comprises about 25 modifications in which the modifications comprise an artificial nucleotide analogue described herein.

[0090] In some instances, a polynucleic acid molecule that comprises an artificial nucleotide analogue comprises SEQ ID NOs: 151-290.

[0091] In some embodiments, a polynucleic acid molecule is assembled from two separate polynucleotides wherein one polynucleotide comprises the sense strand and the second polynucleotide comprises the antisense strand of the polynucleic acid molecule. In other embodiments, the sense strand is connected to the antisense strand via a linker molecule, which in some instances, is a polynucleotide linker or a non-nucleotide linker.

[0092] In some embodiments, a polynucleic acid molecule comprises a sense strand and antisense strand, wherein pyrimidine nucleotides in the sense strand comprise 2'-O-methylpyrimidine nucleotides and purine nucleotides in the sense strand comprise 2'-deoxy purine nucleotides. In some embodiments, a polynucleic acid molecule comprises a sense strand and antisense strand, wherein pyrimidine nucleotides present in the sense strand comprise 2'-deoxy-2'-fluoro pyrimidine

nucleotides and wherein purine nucleotides present in the sense strand comprise 2'-deoxy purine nucleotides.

[0093] In some embodiments, a polynucleic acid molecule comprises a sense strand and antisense strand, wherein the pyrimidine nucleotides when present in said antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides when present in said antisense strand are 2'-O-methyl purine nucleotides.

[0094] In some embodiments, a polynucleic acid molecule comprises a sense strand and antisense strand, wherein the pyrimidine nucleotides when present in said antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides and wherein the purine nucleotides when present in said antisense strand comprise 2'-deoxy-purine nucleotides.

[0095] In some embodiments, a polynucleic acid molecule comprises a sense strand and antisense strand, wherein the sense strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense strand. In other embodiments, the terminal cap moiety is an inverted deoxy abasic moiety.

[0096] In some embodiments, a polynucleic acid molecule comprises a sense strand and an antisense strand, wherein the antisense strand comprises a phosphate backbone modification at the 3' end of the antisense strand. In some instances, the phosphate backbone modification is a phosphorothioate.

[0097] In some embodiments, a polynucleic acid molecule comprises a sense strand and an antisense strand, wherein the antisense strand comprises a glyceryl modification at the 3' end of the antisense strand.

[0098] In some embodiments, a polynucleic acid molecule comprises a sense strand and an antisense strand, in which the sense strand comprises one or more (for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or about one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and in which the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more, phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In other embodiments, one or more (for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more)

pyrimidine nucleotides of the sense and/or antisense strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more (for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

[0099] In some embodiments, a polynucleic acid molecule comprises a sense strand and an antisense strand, in which the sense strand comprises about 1 to about 25 (for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and in which the antisense strand comprises about 1 to about 25 or more (for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In other embodiments, one or more (for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) pyrimidine nucleotides of the sense and/or antisense strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without about 1 to about 25 or more (for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

[0100] In some embodiments, a polynucleic acid molecule comprises a sense strand and an antisense strand, in which the antisense strand comprises one or more (for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) phosphorothioate internucleotide linkages, and/or about one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more, phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the

5'-end, or both of the 3'- and 5'-ends of the antisense strand. In other embodiments, one or more (for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) pyrimidine nucleotides of the sense and/or antisense strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more (for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3' and 5'-ends, being present in the same or different strand.

[0101] In some embodiments, a polynucleic acid molecule comprises a sense strand and an antisense strand, in which the antisense strand comprises about 1 to about 25 or more (for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 25 or more (for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In other embodiments, one or more (for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) pyrimidine nucleotides of the sense and/or antisense strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without about 1 to about 5 (for example about 1, 2, 3, 4, 5 or more) phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

[0102] In some embodiments, a polynucleic acid molecule described herein is a chemically-modified short interfering nucleic acid molecule having about 1 to about 25 (for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more) phosphorothioate internucleotide linkages in each strand of the polynucleic acid molecule.

[0103] In another embodiment, a polynucleic acid molecule described herein comprises 2'-5' internucleotide linkages. In some instances, the 2'-5' internucleotide linkage(s) is at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of one or both sequence strands. In addition instances, the 2'-5' internucleotide linkage(s) is present at various other positions within one or both sequence strands, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more including every internucleotide

linkage of a pyrimidine nucleotide in one or both strands of the polynucleic acid molecule comprise a 2'-5' internucleotide linkage, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more including every internucleotide linkage of a purine nucleotide in one or both strands of the polynucleic acid molecule comprise a 2'-5' internucleotide linkage.

[0104] In some embodiments, a polynucleic acid molecule is a single-stranded polynucleic acid molecule that mediates RNAi activity in a cell or reconstituted in vitro system, wherein the polynucleic acid molecule comprises a single stranded polynucleotide having complementarity to a target nucleic acid sequence, and wherein one or more pyrimidine nucleotides present in the polynucleic acid are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein one or more purine nucleotides present in the polynucleic acid are 2'-deoxy purine nucleotides (e.g., wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides), and a terminal cap modification, that is optionally present at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the antisense sequence, the polynucleic acid molecule optionally further comprising about 1 to about 4 (e.g., about 1, 2, 3, or 4) terminal 2'-deoxynucleotides at the 3'-end of the polynucleic acid molecule, wherein the terminal nucleotides further comprise one or more (e.g., 1, 2, 3, or 4) phosphorothioate internucleotide linkages, and wherein the polynucleic acid molecule optionally further comprises a terminal phosphate group, such as a 5'-terminal phosphate group.

[0105] In some cases, one or more of the artificial nucleotide analogues described herein are resistant toward nucleases such as for example ribonuclease such as RNase H, deoxyribonuclease such as DNase, or exonuclease such as 5'-3' exonuclease and 3'-5' exonuclease when compared to natural polynucleic acid molecules. In some instances, artificial nucleotide analogues comprising 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl, 2'-deoxy, T-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), T-O-dimethylaminoethoxyethyl (2'-O-DMAEOE), or 2'-O-N-methylacetamido (2'-O-NMA) modified, LNA, ENA, PNA, HNA, morpholino, methylphosphonate nucleotides, thiophosphonate nucleotides, 2'-fluoro N3-P5'-phosphoramidites, or combinations thereof are resistant toward nucleases such as for example ribonuclease such as RNase H, deoxyribonuclease such as DNase, or exonuclease such as 5'-3' exonuclease and 3'-5' exonuclease. In some instances, 2'-O-methyl modified polynucleic acid molecule is nuclease resistant (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistant). In some instances, 2'-O-methoxyethyl (2'-O-MOE) modified polynucleic acid molecule is nuclease resistant (e.g., RNase H, DNase, 5'-3'

exonuclease or 3'-5' exonuclease resistant). In some instances, 2'-O-aminopropyl modified polynucleic acid molecule is nuclease resistant (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistant). In some instances, 2'-deoxy modified polynucleic acid molecule is nuclease resistant (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistant). In some instances, T-deoxy-2'-fluoro modified polynucleic acid molecule is nuclease resistant (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistant). In some instances, 2'-O-aminopropyl (2'-O-AP) modified polynucleic acid molecule is nuclease resistant (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistant). In some instances, 2'-O-dimethylaminoethyl (2'-O-DMAOE) modified polynucleic acid molecule is nuclease resistant (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistant). In some instances, 2'-O-dimethylaminopropyl (2'-O-DMAP) modified polynucleic acid molecule is nuclease resistant (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistant). In some instances, T-O- dimethylaminoethoxyethyl (2'-O-DMAEOE) modified polynucleic acid molecule is nuclease resistant (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistant). In some instances, 2'-O-N-methylacetamido (2'-O-NMA) modified polynucleic acid molecule is nuclease resistant (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistant). In some instances, LNA modified polynucleic acid molecule is nuclease resistant (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistant). In some instances, ENA modified polynucleic acid molecule is nuclease resistant (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistant). In some instances, HNA modified polynucleic acid molecule is nuclease resistant (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistant). In some instances, morpholinos are nuclease resistant (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistant). In some instances, PNA modified polynucleic acid molecule is resistant to nucleases (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistant). In some instances, methylphosphonate nucleotides modified polynucleic acid molecule is nuclease resistant (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistant). In some instances, thiophosphonate nucleotides modified polynucleic acid molecule is nuclease resistant (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistant). In some instances, polynucleic acid molecule comprising 2'-fluoro N3-P5'-phosphoramidites is nuclease resistant (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistant). In some instances, the 5' conjugates described herein inhibit 5'-3' exonucleolytic cleavage. In some instances, the 3' conjugates described herein inhibit 3'-5' exonucleolytic cleavage.

[0106] In some embodiments, one or more of the artificial nucleotide analogues described herein have increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. The one or more of the artificial nucleotide analogues comprising 2'-O-

methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl, 2'-deoxy, T-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), T-O-dimethylaminoethoxyethyl (2'-O-DMAEOE), or 2'-O-N-methylacetamido (2'-O-NMA) modified, LNA, ENA, PNA, HNA, morpholino, methylphosphonate nucleotides, thiophosphonate nucleotides, or 2'-fluoro N3-P5'-phosphoramidites have increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, 2'-O-methyl-modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, 2'-O-methoxyethyl (2'-O-MOE)-modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, 2'-O-aminopropyl-modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, 2'-deoxy-modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, T-deoxy-2'-fluoro-modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, 2'-O-aminopropyl (2'-O-AP) modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, 2'-O-dimethylaminoethyl (2'-O-DMAOE) modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, 2'-O-dimethylaminopropyl (2'-O-DMAP)-modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, T-O-dimethylaminoethoxyethyl (2'-O-DMAEOE) modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, 2'-O-N-methylacetamido (2'-O-NMA) modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, LNA-modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, ENA-modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, PNA-modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, HNA-modified polynucleic acid molecule has increased binding affinity toward their mRNA target

relative to an equivalent natural polynucleic acid molecule. In some instances, morpholino-modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, methylphosphonate nucleotide-modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, thiolphosphonate nucleotide-modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, polynucleic acid molecule comprising 2'-fluoro N3-P5'-phosphoramidites has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some cases, the increased affinity is illustrated with a lower K_d , a higher melt temperature (T_m), or a combination thereof.

[0107] In some embodiments, a polynucleic acid molecule described herein is a chirally pure (or stereo pure) polynucleic acid molecule, or a polynucleic acid molecule comprising a single enantiomer. In some instances, the polynucleic acid molecule comprises L-nucleotide. In some instances, the polynucleic acid molecule comprises D-nucleotides. In some instance, a polynucleic acid molecule composition comprises less than 30%, 25%, 20%, 15%, 10%, 5%, 4%, 3%, 2%, 1%, or less of its mirror enantiomer. In some cases, a polynucleic acid molecule composition comprises less than 30%, 25%, 20%, 15%, 10%, 5%, 4%, 3%, 2%, 1%, or less of a racemic mixture. In some instances, the polynucleic acid molecule is a polynucleic acid molecule described in: U.S. Patent Publication Nos: 2014/194610 and 2015/211006; and PCT Publication No.: WO2015107425.

[0108] In some embodiments, a polynucleic acid molecule described herein is further modified to include an aptamer-conjugating moiety. In some instances, the aptamer conjugating moiety is a DNA aptamer-conjugating moiety. In some instances, the aptamer conjugating moiety is Alphamer (Centauri Therapeutics), which comprises an aptamer portion that recognizes a specific cell-surface target and a portion that presents a specific epitopes for attaching to circulating antibodies. In some instance, a polynucleic acid molecule described herein is further modified to include an aptamer conjugating moiety as described in: U.S. Patent Nos: 8,604,184, 8,591,910, and 7,850,975.

[0109] In additional embodiments, a polynucleic acid molecule described herein is modified to increase its stability. In some embodiment, the polynucleic acid molecule is RNA (e.g., siRNA), and the polynucleic acid molecule is modified to increase its stability. In some instances, the polynucleic acid molecule is modified by one or more of the modifications described above to increase its stability. In some cases, the polynucleic acid molecule is modified at the 2' hydroxyl position, such as by 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl, 2'-deoxy, T-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-

dimethylaminopropyl (2'-O-DMAP), T-O- dimethylaminoethoxyethyl (2'-O-DMAEOE), or 2'-O-N-methylacetamido (2'-O-NMA) modification or by a locked or bridged ribose conformation (e.g., LNA or ENA). In some cases, the polynucleic acid molecule is modified by 2'-O-methyl and/or 2'-O-methoxyethyl ribose. In some cases, the polynucleic acid molecule also includes morpholinos, PNAs, HNA, methylphosphonate nucleotides, thiophosphonate nucleotides, and/or 2'-fluoro N3-P5'-phosphoramidites to increase its stability. In some instances, the polynucleic acid molecule is a chirally pure (or stereo pure) polynucleic acid molecule. In some instances, the chirally pure (or stereo pure) polynucleic acid molecule is modified to increase its stability. Suitable modifications to the RNA to increase stability for delivery will be apparent to the skilled person.

[0110] In some embodiments, a polynucleic acid molecule described herein has RNAi activity that modulates expression of RNA encoded by AR. In some instances, a polynucleic acid molecule described herein is a double-stranded siRNA molecule that down-regulates expression of AR, wherein one of the strands of the double-stranded siRNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence of AR or RNA encoded by AR or a portion thereof, and wherein the second strand of the double-stranded siRNA molecule comprises a nucleotide sequence substantially similar to the nucleotide sequence of AR or RNA encoded by AR or a portion thereof. In some cases, a polynucleic acid molecule described herein is a double-stranded siRNA molecule that down-regulates expression of AR, wherein each strand of the siRNA molecule comprises about 15 to 25, 18 to 24, or 19 to about 23 nucleotides, and wherein each strand comprises at least about 14, 17, or 19 nucleotides that are complementary to the nucleotides of the other strand. In some cases, a polynucleic acid molecule described herein is a double-stranded siRNA molecule that down-regulates expression of AR, wherein each strand of the siRNA molecule comprises about 19 to about 23 nucleotides, and wherein each strand comprises at least about 19 nucleotides that are complementary to the nucleotides of the other strand. In some instances, the RNAi activity occurs within a cell. In other instances, the RNAi activity occurs in a reconstituted in vitro system.

[0111] In some embodiments, a polynucleic acid molecule described herein has RNAi activity that modulates expression of RNA encoded by AR. In some instances, a polynucleic acid molecule described herein is a single-stranded siRNA molecule that down-regulates expression of AR, wherein the single-stranded siRNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence of AR or RNA encoded by AR or a portion thereof. In some cases, a polynucleic acid molecule described herein is a single-stranded siRNA molecule that down-regulates expression of AR, wherein the siRNA molecule comprises about 15 to 25, 18 to 24, or 19 to about 23 nucleotides. In some cases, a polynucleic acid molecule described herein is a

single-stranded siRNA molecule that down-regulates expression of AR, wherein the siRNA molecule comprises about 19 to about 23 nucleotides. In some instances, the RNAi activity occurs within a cell. In other instances, the RNAi activity occurs in a reconstituted in vitro system.

[0112] In some instances, a polynucleic acid molecule is a double-stranded polynucleotide molecule comprising self-complementary sense and antisense regions, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense region has a nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. In some instances, the polynucleic acid molecule is assembled from two separate polynucleotides, where one strand is the sense strand and the other is the antisense strand, wherein the antisense and sense strands are self-complementary (e.g., each strand comprises a nucleotide sequence that is complementary to a nucleotide sequence in the other strand; such as where the antisense strand and sense strand form a duplex or double-stranded structure, for example wherein the double-stranded region is about 19, 20, 21, 22, 23, or more base pairs); the antisense strand comprises a nucleotide sequence that is complementary to a nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense strand comprises a nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. Alternatively, the polynucleic acid molecule is assembled from a single oligonucleotide, where the self-complementary sense and antisense regions of the polynucleic acid molecule are linked by means of a nucleic acid based or non-nucleic acid-based linker(s).

[0113] In some cases, a polynucleic acid molecule is a polynucleotide with a duplex, asymmetric duplex, hairpin, or asymmetric hairpin secondary structure, having self-complementary sense and antisense regions, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence in a separate target nucleic acid molecule or a portion thereof and the sense region has a nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. In other cases, the polynucleic acid molecule is a circular single-stranded polynucleotide having two or more loop structures and a stem comprising self-complementary sense and antisense regions, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense region has a nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof, and wherein the circular polynucleotide is processed either in vivo or in vitro to generate an active polynucleic acid molecule capable of mediating RNAi. In additional cases, the polynucleic acid molecule also comprises a single-stranded polynucleotide having a nucleotide sequence complementary to a nucleotide sequence in a target nucleic acid molecule or a portion thereof (for example, where such polynucleic acid molecule does not require

the presence within the polynucleic acid molecule of a nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof), wherein the single stranded polynucleotide further comprises a terminal phosphate group, such as a 5'-phosphate (see for example Martinez et al., 2002, *Cell*, 110, 563-574 and Schwarz et al., 2002, *Molecular Cell*, 10, 537-568), or 5',3'-diphosphate.

[0114] In some instances, an asymmetric duplex is a linear polynucleic acid molecule comprising an antisense region, a loop portion that comprises nucleotides or non-nucleotides, and a sense region that comprises fewer nucleotides than the antisense region to the extent that the sense region has enough complimentary nucleotides to base pair with the antisense region and form a duplex with loop. For example, an asymmetric hairpin polynucleic acid molecule comprises an antisense region having length sufficient to mediate RNAi in a cell or in vitro system (e.g. about 19 to about 22 nucleotides) and a loop region comprising about 4 to about 8 nucleotides, and a sense region having about 3 to about 18 nucleotides that are complementary to the antisense region. In some cases, the asymmetric hairpin polynucleic acid molecule also comprises a 5'-terminal phosphate group that is chemically modified. In additional cases, the loop portion of the asymmetric hairpin polynucleic acid molecule comprises nucleotides, non-nucleotides, linker molecules, or conjugate molecules.

[0115] In some embodiments, an asymmetric duplex is a polynucleic acid molecule having two separate strands comprising a sense region and an antisense region, wherein the sense region comprises fewer nucleotides than the antisense region to the extent that the sense region has enough complimentary nucleotides to base pair with the antisense region and form a duplex. For example, an asymmetric duplex polynucleic acid molecule comprises an antisense region having length sufficient to mediate RNAi in a cell or in vitro system (e.g. about 19 to about 22 nucleotides) and a sense region having about 3 to about 18 nucleotides that are complementary to the antisense region.

[0116] In some cases, a universal base refers to nucleotide base analogs that form base pairs with each of the natural DNA/RNA bases with little discrimination between them. Non-limiting examples of universal bases include C-phenyl, C-naphthyl and other aromatic derivatives, inosine, azole carboxamides, and nitroazole derivatives such as 3-nitropyrrole, 4-nitroindole, 5-nitroindole, and 6-nitroindole as known in the art (see for example Loakes, 2001, *Nucleic Acids Research*, 29, 2437-2447).

Polynucleic Acid Molecule Synthesis

[0117] In some embodiments, a polynucleic acid molecule described herein is constructed using chemical synthesis and/or enzymatic ligation reactions using procedures known in the art. For

example, a polynucleic acid molecule is chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the polynucleic acid molecule and target nucleic acids. Exemplary methods include those described in: U.S. Patent Nos. 5,142,047; 5,185,444; 5,889,136; 6,008,400; and 6,111,086; PCT Publication No. WO2009099942; or European Publication No. 1579015. Additional exemplary methods include those described in: Griffey et al., "2'-O-aminopropyl ribonucleotides: a zwitterionic modification that enhances the exonuclease resistance and biological activity of antisense oligonucleotides," *J. Med. Chem.* **39**(26):5100-5109 (1997)); Obika, et al. "Synthesis of 2'-O,4'-C-methylneuridine and -cytidine. Novel bicyclic nucleosides having a fixed C3, -endo sugar puckering". *Tetrahedron Letters* **38** (50): 8735 (1997); Koizumi, M. "ENA oligonucleotides as therapeutics". *Current opinion in molecular therapeutics* **8** (2): 144-149 (2006); and Abramova et al., "Novel oligonucleotide analogues based on morpholino nucleoside subunits-antisense technologies: new chemical possibilities," *Indian Journal of Chemistry* **48B**:1721-1726 (2009). Alternatively, the polynucleic acid molecule is produced biologically using an expression vector into which a polynucleic acid molecule has been subcloned in an antisense orientation (i.e., RNA transcribed from the inserted polynucleic acid molecule will be of an antisense orientation to a target polynucleic acid molecule of interest).

[0118] In some embodiments, a polynucleic acid molecule is synthesized via a tandem synthesis methodology, wherein both strands are synthesized as a single contiguous oligonucleotide fragment or strand separated by a cleavable linker which is subsequently cleaved to provide separate fragments or strands that hybridize and permit purification of the duplex.

[0119] In some instances, a polynucleic acid molecule is also assembled from two distinct nucleic acid strands or fragments wherein one fragment includes the sense region and the second fragment includes the antisense region of the molecule.

[0120] Additional modification methods for incorporating, for example, sugar, base, and phosphate modifications include: Eckstein et al., International Publication PCT No. WO 92/07065; Perrault et al. *Nature*, 1990, 344, 565-568; Pieken et al. *Science*, 1991, 253, 314-317; Usman and Cedergren, *Trends in Biochem. Sci.*, 1992, 17, 334-339; Usman et al. International Publication PCT No. WO 93/15187; Sproat, U.S. Pat. No. 5,334,711 and Beigelman et al., 1995, *J. Biol. Chem.*, 270, 25702; Beigelman et al., International PCT publication No. WO 97/26270; Beigelman et al., U.S. Pat. No. 5,716,824; Usman et al., U.S. Pat. No. 5,627,053; Woolf et al., International PCT Publication No. WO 98/13526; Thompson et al., U.S. Ser. No. 60/082,404 which was filed on Apr. 20, 1998; Karpeisky et al., 1998, *Tetrahedron Lett.*, 39, 1131; Earnshaw and Gait, 1998, *Biopolymers (Nucleic Acid Sciences)*, 48, 39-55; Verma and Eckstein, 1998, *Annu. Rev. Biochem.*,

67, 99-134; and Burlina et al., 1997, *Bioorg. Med. Chem.*, 5, 1999-2010. Such publications describe general methods and strategies to determine the location of incorporation of sugar, base, and/or phosphate modifications and the like into nucleic acid molecules without modulating catalysis.

[0121] In some instances, while chemical modification of the polynucleic acid molecule internucleotide linkages with phosphorothioate, phosphorodithioate, and/or 5'-methylphosphonate linkages improves stability, excessive modifications sometimes cause toxicity or decreased activity. Therefore, when designing nucleic acid molecules, the amount of these internucleotide linkages in some cases is minimized. In such cases, the reduction in the concentration of these linkages lowers toxicity, and increases efficacy and specificity of these molecules.

Diseases

[0122] In some embodiments, a polynucleic acid molecule or a pharmaceutical composition described herein is used for the treatment of a disease or disorder. In some instances, the disease or disorder is a cancer. In some embodiments, a polynucleic acid molecule or a pharmaceutical composition described herein is used for the treatment of cancer. In some instances, the cancer is a solid tumor. In some instances, the cancer is a hematologic malignancy. In some instances, the cancer is a relapsed or refractory cancer, or a metastatic cancer. In some instances, the solid tumor is a relapsed or refractory solid tumor, or a metastatic solid tumor. In some cases, the hematologic malignancy is a relapsed or refractory hematologic malignancy, or a metastatic hematologic malignancy.

[0123] In some embodiments, the cancer is a solid tumor. Exemplary solid tumor includes, but is not limited to, anal cancer, appendix cancer, bile duct cancer (i.e., cholangiocarcinoma), bladder cancer, brain tumor, breast cancer, cervical cancer, colon cancer, cancer of Unknown Primary (CUP), esophageal cancer, eye cancer, fallopian tube cancer, gastroenterological cancer, kidney cancer, liver cancer, lung cancer, medulloblastoma, melanoma, oral cancer, ovarian cancer, pancreatic cancer, parathyroid disease, penile cancer, pituitary tumor, prostate cancer, rectal cancer, skin cancer, stomach cancer, testicular cancer, throat cancer, thyroid cancer, uterine cancer, vaginal cancer, or vulvar cancer.

[0124] In some instances, a polynucleic acid molecule or a pharmaceutical composition described herein is used for the treatment of a solid tumor. In some instances, a polynucleic acid molecule or a pharmaceutical composition described herein is used for the treatment of anal cancer, appendix cancer, bile duct cancer (i.e., cholangiocarcinoma), bladder cancer, brain tumor, breast cancer, cervical cancer, colon cancer, cancer of Unknown Primary (CUP), esophageal cancer, eye cancer, fallopian tube cancer, gastroenterological cancer, kidney cancer, liver cancer, lung cancer,

medulloblastoma, melanoma, oral cancer, ovarian cancer, pancreatic cancer, parathyroid disease, penile cancer, pituitary tumor, prostate cancer, rectal cancer, skin cancer, stomach cancer, testicular cancer, throat cancer, thyroid cancer, uterine cancer, vaginal cancer, or vulvar cancer. In some instances, the solid tumor is a relapsed or refractory solid tumor, or a metastatic solid tumor.

[0125] In some instances, the cancer is a hematologic malignancy. In some instances, the hematologic malignancy is a leukemia, a lymphoma, a myeloma, a non-Hodgkin's lymphoma, or a Hodgkin's lymphoma. In some instances, the hematologic malignancy comprises chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, a non-CLL/SLL lymphoma, prolymphocytic leukemia (PLL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenström's macroglobulinemia, multiple myeloma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, primary mediastinal B-cell lymphoma (PMBL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, B cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, or lymphomatoid granulomatosis.

[0126] In some instances, a polynucleic acid molecule or a pharmaceutical composition described herein is used for the treatment of a hematologic malignancy. In some instances, a polynucleic acid molecule or a pharmaceutical composition described herein is used for the treatment of a leukemia, a lymphoma, a myeloma, a non-Hodgkin's lymphoma, or a Hodgkin's lymphoma. In some instances, the hematologic malignancy comprises chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, a non-CLL/SLL lymphoma, prolymphocytic leukemia (PLL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenström's macroglobulinemia, multiple myeloma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, primary mediastinal B-cell lymphoma (PMBL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, B cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, or lymphomatoid granulomatosis. In some cases, the hematologic malignancy is a relapsed or refractory hematologic malignancy, or a metastatic hematologic malignancy.

[0127] In some instances, the cancer is an androgen receptor-associated cancer. In some instances, a polynucleic acid molecule or a pharmaceutical composition described herein is used for

the treatment of an androgen receptor-associated cancer. In some instances, the cancer is a solid tumor. In some instances, the cancer is a hematologic malignancy. In some instances, the solid tumor is a relapsed or refractory solid tumor, or a metastatic solid tumor. In some cases, the hematologic malignancy is a relapsed or refractory hematologic malignancy, or a metastatic hematologic malignancy. In some instances, the cancer comprises bladder cancer, breast cancer, colorectal cancer, endometrial cancer, esophageal cancer, glioblastoma multiforme, head and neck cancer, kidney cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, thyroid cancer, acute myeloid leukemia, CLL, DLBCL, or multiple myeloma.

Pharmaceutical Formulation

[0128] In some embodiments, the pharmaceutical formulations described herein are administered to a subject by multiple administration routes including, but not limited to, parenteral (e.g., intravenous, subcutaneous, intramuscular), oral, intranasal, buccal, rectal, or transdermal administration routes. In some instances, the pharmaceutical composition describe herein is formulated for parenteral (e.g., intravenous, subcutaneous, intramuscular) administration. In other instances, the pharmaceutical composition describe herein is formulated for oral administration. In still other instances, the pharmaceutical composition describe herein is formulated for intranasal administration.

[0129] In some embodiments, the pharmaceutical formulations include, but are not limited to, aqueous liquid dispersions, self-emulsifying dispersions, solid solutions, liposomal dispersions, aerosols, solid dosage forms, powders, immediate release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations (e.g., nanoparticle formulations), and mixed immediate- and controlled-release formulations.

[0130] In some instances, the pharmaceutical formulation includes multiparticulate formulations. In some instances, the pharmaceutical formulation includes nanoparticle formulations. In some instances, nanoparticles comprise cMAP, cyclodextrin, or lipids. In some cases, nanoparticles comprise solid lipid nanoparticles, polymeric nanoparticles, self-emulsifying nanoparticles, liposomes, microemulsions, or micellar solutions. Additional exemplary nanoparticles include, but are not limited to, paramagnetic nanoparticles, superparamagnetic nanoparticles, metal nanoparticles, fullerene-like materials, inorganic nanotubes, dendrimers (such as with covalently attached metal chelates), nanofibers, nanohorns, nano-onions, nanorods, nanoropes and quantum dots. In some instances, a nanoparticle is a metal nanoparticle, e.g., a nanoparticle of scandium, titanium, vanadium, chromium, manganese, iron, cobalt, nickel, copper, zinc, yttrium, zirconium,

niobium, molybdenum, ruthenium, rhodium, palladium, silver, cadmium, hafnium, tantalum, tungsten, rhenium, osmium, iridium, platinum, gold, gadolinium, aluminum, gallium, indium, tin, thallium, lead, bismuth, magnesium, calcium, strontium, barium, lithium, sodium, potassium, boron, silicon, phosphorus, germanium, arsenic, antimony, and combinations, alloys, or oxides thereof.

[0131] In some instances, a nanoparticle includes a core or a core and a shell, as in a core-shell nanoparticle.

[0132] In some instances, a nanoparticle is further coated with molecules for attachment of functional elements (e.g., with one or more of a polynucleic acid molecule or binding moiety described herein). In some instances, a coating comprises chondroitin sulfate, dextran sulfate, carboxymethyl dextran, alginic acid, pectin, carrageenan, fucoidan, agarose, agarpectin, porphyran, karaya gum, gellan gum, xanthan gum, hyaluronic acids, glucosamine, galactosamine, chitin (or chitosan), polyglutamic acid, polyaspartic acid, lysozyme, cytochrome C, ribonuclease, trypsinogen, chymotrypsinogen, α -chymotrypsin, polylysine, polyarginine, histone, protamine, ovalbumin, dextrin, or cyclodextrin. In some instances, a nanoparticle comprises a graphene-coated nanoparticle.

[0133] In some cases, a nanoparticle has at least one dimension of less than about 500nm, 400nm, 300nm, 200nm, or 100nm.

[0134] In some instances, the nanoparticle formulation comprises paramagnetic nanoparticles, superparamagnetic nanoparticles, metal nanoparticles, fullerene-like materials, inorganic nanotubes, dendrimers (such as with covalently attached metal chelates), nanofibers, nanohorns, nano-onions, nanorods, nanoropes or quantum dots. In some instances, a polynucleic acid molecule or a binding moiety described herein is conjugated either directly or indirectly to the nanoparticle. In some instances, at least 1, 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100 or more polynucleic acid molecules or binding moieties described herein are conjugated either directly or indirectly to a nanoparticle.

[0135] In some embodiments, the pharmaceutical formulation comprise a delivery vector, e.g., a recombinant vector, for the delivery of the polynucleic acid molecule into cells. In some instances, the recombinant vector is DNA plasmid. In other instances, the recombinant vector is a viral vector. Exemplary viral vectors include vectors derived from adeno-associated virus, retrovirus, adenovirus, or alphavirus. In some instances, the recombinant vectors capable of expressing the polynucleic acid molecules provide stable expression in target cells. In additional instances, viral vectors are used that provide for transient expression of polynucleic acid molecules.

[0136] In some embodiments, the pharmaceutical formulations include a carrier or carrier materials selected on the basis of compatibility with the composition disclosed herein, and the

release profile properties of the desired dosage form. Exemplary carrier materials include, e.g., binders, suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, diluents, and the like. Pharmaceutically compatible carrier materials include, but are not limited to, acacia, gelatin, colloidal silicon dioxide, calcium glycerophosphate, calcium lactate, maltodextrin, glycerine, magnesium silicate, polyvinylpyrrolidone (PVP), cholesterol, cholesterol esters, sodium caseinate, soy lecithin, taurocholic acid, phosphatidylcholine, sodium chloride, tricalcium phosphate, dipotassium phosphate, cellulose and cellulose conjugates, sugars sodium stearyl lactylate, carrageenan, monoglyceride, diglyceride, pregelatinized starch, and the like. See, e.g., *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y., 1980; and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed. (Lippincott Williams & Wilkins 1999).

[0137] In some instances, the pharmaceutical formulations further include pH-adjusting agents or buffering agents which include acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases, and buffers are included in an amount required to maintain pH of the composition in an acceptable range.

[0138] In some instances, the pharmaceutical formulation includes one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite, and ammonium sulfate.

[0139] In some instances, the pharmaceutical formulations further include diluent which are used to stabilize compounds because they provide a more stable environment. Salts dissolved in buffered solutions (which also provide pH control or maintenance) are utilized as diluents in the art, including, but not limited to a phosphate-buffered saline solution. In certain instances, diluents increase bulk of the composition to facilitate compression or create sufficient bulk for homogenous blend for capsule filling. Such compounds include e.g., lactose, starch, mannitol, sorbitol, dextrose, microcrystalline cellulose such as Avicel[®]; dibasic calcium phosphate, dicalcium phosphate dihydrate; tricalcium phosphate, calcium phosphate; anhydrous lactose, spray-dried lactose; pregelatinized starch, compressible sugar, such as Di-Pac[®] (Amstar); mannitol,

hydroxypropylmethylcellulose, hydroxypropylmethylcellulose acetate stearate, sucrose-based diluents, confectioner's sugar; monobasic calcium sulfate monohydrate, calcium sulfate dihydrate; calcium lactate trihydrate, dextrates; hydrolyzed cereal solids, amylose; powdered cellulose, calcium carbonate; glycine, kaolin; mannitol, sodium chloride; inositol, bentonite, and the like.

[0140] In some cases, the pharmaceutical formulations include disintegration agents or disintegrants to facilitate the breakup or disintegration of a substance. The term "disintegrate" includes both the dissolution and dispersion of the dosage form when contacted with gastrointestinal fluid. Examples of disintegration agents include a starch, e.g., a natural starch such as corn starch or potato starch, a pregelatinized starch such as National 1551 or Amijel[®], or sodium starch glycolate such as Promogel[®] or Explotab[®]; a cellulose such as a wood product, methylcrystalline cellulose, e.g., Avicel[®], Avicel[®] PH101, Avicel[®] PH102, Avicel[®] PH105, Elcema[®] P100, Emcocel[®], Vivacel[®], Ming Tia[®], and Solka-Floc[®], methylcellulose, croscarmellose, or a cross-linked cellulose, such as cross-linked sodium carboxymethylcellulose (Ac-Di-Sol[®]), cross-linked carboxymethylcellulose, or cross-linked croscarmellose; a cross-linked starch such as sodium starch glycolate, a cross-linked polymer such as crospovidone; a cross-linked polyvinylpyrrolidone, alginate such as alginic acid or a salt of alginic acid such as sodium alginate, a clay such as Veegum[®] HV (magnesium aluminum silicate); a gum such as agar, guar, locust bean, Karaya, pectin, or tragacanth; sodium starch glycolate; bentonite; a natural sponge; a surfactant; a resin such as a cation-exchange resin; citrus pulp; sodium lauryl sulfate; sodium lauryl sulfate in combination starch; and the like.

[0141] In some instances, the pharmaceutical formulations include filling agents such as lactose, calcium carbonate, calcium phosphate, dibasic calcium phosphate, calcium sulfate, microcrystalline cellulose, cellulose powder, dextrose, dextrates, dextran, starches, pregelatinized starch, sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, polyethylene glycol, and the like.

[0142] Lubricants and glidants are also optionally included in the pharmaceutical formulations described herein for preventing, reducing, or inhibiting adhesion or friction of materials. Exemplary lubricants include, e.g., stearic acid, calcium hydroxide, talc, sodium stearyl fumarate, a hydrocarbon such as mineral oil, or hydrogenated vegetable oil such as hydrogenated soybean oil (Stereotex[®]), higher fatty acids and their alkali-metal and alkaline earth metal salts, such as aluminum, calcium, magnesium, zinc, stearic acid, sodium stearates, glycerol, talc, waxes, Stearowet[®], boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine, a polyethylene glycol (e.g., PEG-4000) or a methoxypolyethylene glycol such as Carbowax[™], sodium oleate, sodium benzoate, glyceryl behenate, polyethylene glycol, magnesium or sodium lauryl sulfate,

colloidal silica such as Syloid™, Cab-O-Sil®, a starch such as corn starch, silicone oil, a surfactant, and the like.

[0143] Plasticizers include compounds used to soften the microencapsulation material or film coatings to make them less brittle. Suitable plasticizers include, e.g., polyethylene glycols such as PEG 300, PEG 400, PEG 600, PEG 1450, PEG 3350, and PEG 800, stearic acid, propylene glycol, oleic acid, triethyl cellulose and triacetin. Plasticizers also function as dispersing agents or wetting agents.

[0144] Solubilizers include compounds such as triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, sodium lauryl sulfate, sodium docusate, vitamin E TPGS, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropylmethyl cellulose, hydroxypropyl cyclodextrins, ethanol, n-butanol, isopropyl alcohol, cholesterol, bile salts, polyethylene glycol 200-600, glycofurol, transcitol, propylene glycol, dimethyl isosorbide, and the like.

[0145] Stabilizers include compounds such as any antioxidation agents, buffers, acids, preservatives, and the like.

[0146] Suspending agents include compounds such as polyvinylpyrrolidone (e.g., polyvinylpyrrolidone K12, polyvinylpyrrolidone K17, polyvinylpyrrolidone K25, or polyvinylpyrrolidone K30), vinyl pyrrolidone/vinyl acetate copolymer (S630), polyethylene glycol (e.g., the polyethylene glycol has a molecular weight of about 300 to about 6000, or about 3350 to about 4000, or about 7000 to about 5400), sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, hydroxymethylcellulose acetate stearate, polysorbate-80, hydroxyethylcellulose, sodium alginate, gums (such as, e.g., gum tragacanth and gum acacia, guar gum, xanthans, including xanthan gum), sugars, cellulosics (such as, e.g., sodium carboxymethylcellulose, methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose), polysorbate-80, sodium alginate, polyethoxylated sorbitan monolaurate, polyethoxylated sorbitan monolaurate, povidone, and the like.

[0147] Surfactants include compounds such as sodium lauryl sulfate, sodium docusate, Tween 60 or 80, triacetin, vitamin E TPGS, sorbitan monooleate, polyoxyethylene sorbitan monooleate, polysorbates, polaxomers, bile salts, glyceryl monostearate, copolymers of ethylene oxide and propylene oxide, e.g., Pluronic® (BASF), and the like. Additional surfactants include polyoxyethylene fatty acid glycerides and vegetable oils, e.g., polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, e.g., octoxynol 10, octoxynol 40. Sometimes, surfactants are included to enhance physical stability or for other purposes.

[0148] Viscosity enhancing agents include, e.g., methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose acetate stearate, hydroxypropylmethyl cellulose phthalate, carbomer, polyvinyl alcohol, alginates, acacia, chitosans, and combinations thereof.

[0149] Wetting agents include compounds such as oleic acid, glyceryl monostearate, sorbitan monooleate, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monolaurate, sodium docusate, sodium oleate, sodium lauryl sulfate, sodium docosate, triacetin, Tween 80, vitamin E TPGS, ammonium salts, and the like.

Therapeutic Regimens

[0150] In some embodiments, the pharmaceutical compositions described herein are administered for therapeutic applications. In some embodiments, the pharmaceutical composition is administered once per day, twice per day, three times per day, or more. The pharmaceutical composition is administered daily, every day, every alternate day, five days a week, once a week, every other week, two weeks per month, three weeks per month, once a month, twice a month, three times per month, or more. The pharmaceutical composition is administered for at least 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, 18 months, 2 years, 3 years, or more.

[0151] In some embodiments, one or more pharmaceutical compositions are administered simultaneously, sequentially, or at an interval period of time. In some embodiments, one or more pharmaceutical compositions are administered simultaneously. In some cases, one or more pharmaceutical compositions are administered sequentially. In additional cases, one or more pharmaceutical compositions are administered at an interval period of time (e.g., the first administration of a first pharmaceutical composition is on day one followed by an interval of at least 1, 2, 3, 4, 5, or more days prior to the administration of at least a second pharmaceutical composition).

[0152] In some embodiments, two or more different pharmaceutical compositions are coadministered. In some instances, the two or more different pharmaceutical compositions are coadministered simultaneously. In some cases, the two or more different pharmaceutical compositions are coadministered sequentially without a gap of time between administrations. In other cases, the two or more different pharmaceutical compositions are coadministered sequentially with a gap of about 0.5 hour, 1 hour, 2 hour, 3 hour, 12 hours, 1 day, 2 days, or more between administrations.

[0153] In the case wherein the patient's status does improve, upon the doctor's discretion the administration of the composition is given continuously; alternatively, the dose of the composition being administered is temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). In some instances, the length of the drug holiday varies between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, or 365 days. The dose reduction during a drug holiday is from 10%-100%, including, by way of example only, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%.

[0154] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, are optionally reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained.

[0155] In some embodiments, the amount of a given agent that correspond to such an amount varies depending upon factors such as the particular compound, the severity of the disease, the identity (e.g., weight) of the subject or host in need of treatment, but nevertheless is routinely determined in a manner known in the art according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the route of administration, and the subject or host being treated. In some instances, the desired dose is conveniently presented in a single dose or as divided doses administered simultaneously (or over a short period of time) or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[0156] The foregoing ranges are merely suggestive, as the number of variables in regard to an individual treatment regime is large, and considerable excursions from these recommended values are not uncommon. Such dosages are altered depending on a number of variables, not limited to the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[0157] In some embodiments, toxicity and therapeutic efficacy of such therapeutic regimens are determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it is expressed as the ratio between LD₅₀ and ED₅₀. Compounds exhibiting high therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used in formulating a range of dosage

for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with minimal toxicity. The dosage varies within this range depending upon the dosage form employed and the route of administration utilized.

Kits/Article of Manufacture

[0158] Disclosed herein, in certain embodiments, are kits and articles of manufacture for use with one or more of the compositions and methods described herein. Such kits include a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. In one embodiment, the containers are formed from a variety of materials such as glass or plastic.

[0159] The articles of manufacture provided herein contain packaging materials. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, bags, containers, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment.

[0160] For example, the container(s) include AR nucleic acid molecule described herein. Such kits optionally include an identifying description or label or instructions relating to its use in the methods described herein.

[0161] A kit typically includes labels listing contents and/or instructions for use and package inserts with instructions for use. A set of instructions will also typically be included.

[0162] In one embodiment, a label is on or associated with the container. In one embodiment, a label is on a container when letters, numbers, or other characters forming the label are attached, molded or etched into the container itself; a label is associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. In one embodiment, a label is used to indicate that the contents are to be used for a specific therapeutic application. The label also indicates directions for use of the contents, such as in the methods described herein.

[0163] In certain embodiments, the pharmaceutical compositions are presented in a pack or dispenser device which contains one or more unit dosage forms containing a compound provided herein. The pack, for example, contains metal or plastic foil, such as a blister pack. In one embodiment, the pack or dispenser device is accompanied by instructions for administration. In one embodiment, the pack or dispenser is also accompanied with a notice associated with the container in a form prescribed by a governmental agency regulating the manufacture, use, or sale of

pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, is the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. In one embodiment, compositions containing a compound provided herein formulated in a compatible pharmaceutical carrier are also prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

Certain Terminology

[0164] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the claimed subject matter belongs. It is to be understood that the general description and the detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. In this application, the use of “or” means “and/or” unless stated otherwise. Furthermore, use of the term “including” as well as other forms, such as “include,” “includes,” and “included,” is not limiting.

[0165] As used herein, ranges and amounts can be expressed as “about” a particular value or range. About also includes the exact amount. Hence “about 5 μ L” means “about 5 μ L” and also “5 μ L.” Generally, the term “about” includes an amount that is expected to be within experimental error, e.g., $\pm 5\%$, $\pm 10\%$, or $\pm 15\%$.

[0166] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0167] As used herein, the terms “individual(s),” “subject(s)” and “patient(s)” mean any mammal. In some embodiments, the mammal is a human. In some embodiments, the mammal is a non-human. None of the terms require or are limited to situations characterized by the supervision (e.g. constant or intermittent) of a health care worker (e.g. a doctor, a registered nurse, a nurse practitioner, a physician’s assistant, an orderly or a hospice worker).

EXAMPLES

[0168] These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

Example 1. Sequences

[0169] Table 1 illustrates androgen receptor target sequences. Tables 2, 3, and 6A illustrate polynucleic acid molecule sequences described herein.

Table 1. AR Target Sequences

Id #	19mer pos. in NM_000044.3	sequence of total 23mer target site in NM_000044.3	EXON	SEQ ID NO:
1201	1201-1219	GAGCGUGCGCGAAGUGAUCCAGA	1	1
1784	1784-1802	GACAAUACUUAGGGGGCACUUC	1	2
1968	1968-1986	GUGCCCCAUUGGCCGAAUGCAAA	1	3
1984	1984-2002	AUGCAAAGGUUCUCUGCUAGACG	1	4
1987	1987-2005	CAAAGGUUCUCUGCUAGACGACA	1	5
2045	2045-2063	UCCCCUUAAGGGAGGUUACAC	1	6
2185	2185-2203	AGCUGCGUACCAGAGUCGCGACU	1	7
2189	2189-2207	GCGUACCAGAGUCGCGACUACUA	1	8
2207	2207-2225	UACUACAACUUUCCACUGGCUCU	1	9
2263	2263-2281	UCCCCACGCUCGCAUCAAGCUGG	1	10
2739	2739-2757	AGACUGCCAGGGACCAUGUUUUG	2	11
2741	2741-2759	ACUGCCAGGGACCAUGUUUUGCC	2	12
2814	2814-2832	AAGCUUCUGGGUGUCACUAUGGA	2	13
2817	2817-2835	CUUCUGGGUGUCACUAUGGAGCU	2	14
2819	2819-2837	UCUGGGUGUCACUAUGGAGCUCU	2	15
2820	2820-2838	CUGGGUGUCACUAUGGAGCUCUC	2	16
2822	2822-2840	GGGUGUCACUAUGGAGCUCUCAC	2	17
2824	2824-2842	GUGUCACUAUGGAGCUCUCACAU	2	18
2847	2847-2865	GUGGAAGCUGCAAGGUCUUCUUC	2	19
2920	2920-2938	UUGCACUAUUGAUAAAUUCCGAA	3	20
2922	2922-2940	GCACUAUUGAUAAAUUCCGAAGG	3	21
2923	2923-2941	CACUAUUGAUAAAUUCCGAAGGA	3	22
2924	2924-2942	ACUAUUGAUAAAUUCCGAAGGAA	3	23
2925	2925-2943	CUAUUGAUAAAUUCCGAAGGAAA	3	24
2927	2927-2945	AUUGAUAAAUUCCGAAGGAAAAA	3	25
2931	2931-2949	AUAAAUUCCGAAGGAAAAAUUGU	3	26
2933	2933-2951	AAAUUCCGAAGGAAAAAUUGUCC	3	27
2935	2935-2953	AUCCGAAGGAAAAAUUGUCCAUC	3	28
2936	2936-2954	UCCGAAGGAAAAAUUGUCCAUC	3	29
2940	2940-2958	GAAGGAAAAAUUGUCCAUCUUGU	3	30
2961	2961-2979	GUCGUCUUCGGAAUGUUAUGAA	3	31
2962	2962-2980	UCGUCUUCGGAAUGUUAUGAAG	3	32
2966	2966-2984	CUUCGGAAUGUUAUGAAGCAGG	3	33
2975	2975-2993	UGUUAUGAAGCAGGGAUGACUCU	3	34
3020	3020-3038	CUUGGUAAUCUGAAACUACAGGA	4	35
3101	3101-3119	GUGUCACACAUUGAAGGCUAUGA	4	36
3105	3105-3123	CACACAUUGAAGGCUAUGAAUGU	4	37
3107	3107-3125	CACAUUGAAGGCUAUGAAUGUCA	4	38

3217	3217-3235	CUUGCUCUCUAGCCUCAUAUGAAC	4	39
3218	3218-3236	UUGCUCUCUAGCCUCAUAUGAACU	4	40
3310	3310-3328	GGACGACCAGAUGGCUGUCAUUC	5	41
3416	3416-3434	CCUGAUCUGGUUUUCAUAUGAGUA	5	42
3462	3462-3480	ACAGCCAGUGUGUCCGAAUGAGG	6	43
3469	3469-3487	GUGUGUCCGAAUGAGGCACCUCU	6	44
3473	3473-3491	GUCCGAAUGAGGCACCUCUCUCA	6	45
3475	3475-3493	CCGAAUGAGGCACCUCUCUCAAG	6	46
3481	3481-3499	GAGGCACCUCUCUCAAGAGUUUG	6	47
3629	3629-3647	GAACUCGAUCGUAUCAUUGCAUG	7	48
3779	3779-3797	GUGAGCGUGGACUUUCCGAAAU	8	49
3781	3781-3799	GAGCGUGGACUUUCCGAAUAUGA	8	50

Table 2. AR siRNA Sequences

Id #	19mer pos. in NM_00004 4.3	sense strand sequence (5'-3')	SEQ ID NO:	antisense strand sequence (5'-3')	SEQ ID NO:
1201	1201-1219	GCGUGCGCGAAGUGAUCC ATT	51	UGGAUCACUUCGCGCACG CTT	52
1784	1784-1802	CAAUUACUUAGGGGGCAC UTT	53	AGUGCCCCCUAAGUAAUU GTT	54
1968	1968-1986	GCCCCAUUGGCCGAAUGC ATT	55	UGCAUUCGGCCAAUGGGG CTT	56
1984	1984-2002	GCAAAGGUUCUCUGCUAG ATT	57	UCUAGCAGAGAACCUUUG CTT	58
1987	1987-2005	AAGGUUCUCUGCUAGACG ATT	59	UCGUCUAGCAGAGAACCU UTT	60
2045	2045-2063	CCCUUUAAGGGAGGUUA CTT	61	GUAACCUCCCUUGAAAGG GTT	62
2185	2185-2203	CUGCGUACCAGAGUCGCG ATT	63	UCGCGACUCUGGUACGCA GTT	64
2189	2189-2207	GUACCAGAGUCGCGACUA CTT	65	GUAGUCGCGACUCUGGUA CTT	66
2207	2207-2225	CUACAACUUUCCACUGGC UTT	67	AGCCAGUGGAAAGUUGU AGTT	68
2263	2263-2281	CCCACGCUCGCAUCAAGC UTT	69	AGCUUGAUGCGAGCGUG GGTT	70
2739	2739-2757	ACUGCCAGGGACCAUGUU UTT	71	AAACAUGGUCCCUGGCAG UTT	72
2741	2741-2759	UGCCAGGGACCAUGUUUU GTT	73	CAAAACAUGGUCCCUGGC ATT	74
2814	2814-2832	GCUUCUGGGUGUCACUAU GTT	75	CAUAGUGACACCCAGAAG CTT	76
2817	2817-2835	UCUGGGUGUCACUAUGG AGTT	77	CUCCAUAUGUGACACCCAG ATT	78
2819	2819-2837	UGGGUGUCACUAUGGAG CUTT	79	AGCUCCAUAUGUGACACCC ATT	80
2820	2820-2838	GGGUGUCACUAUGGAGC UCTT	81	GAGCUCCAUAUGUGACACC CTT	82
2822	2822-2840	GUGUCACUAUGGAGCUCU CTT	83	GAGAGCUCCAUAUGUGACA CTT	84

2824	2824-2842	GUCACUAUGGAGCUCUCA CTT	85	GUGAGAGCUCCAUAUGUG ACTT	86
2847	2847-2865	GGAAGCUGCAAGGUCUUC UTT	87	AGAAGACCUUGCAGCUUC CTT	88
2920	2920-2938	GCACUAUUGAUAAAUUCG GTT	89	CGGAAUUUAUCAUAGU GCTT	90
2922	2922-2940	ACUAUUGAUAAAUUCG AATT	91	UUCGGAAUUUAUCAUA GUTT	92
2923	2923-2941	CUAUUGAUAAAUUCG AGTT	93	CUUCGGAAUUUAUCAU AGTT	94
2924	2924-2942	UAUUGAUAAAUUCG GGTT	95	CCUUCGGAAUUUAUCAU ATT	96
2925	2925-2943	AUUGAUAAAUUCG GATT	97	UCCUUCGGAAUUUAUCAU UTT	98
2927	2927-2945	UGAUAAAUUCG AATT	99	UUUCCUUCGGAAUUUAUC ATT	100
2931	2931-2949	AAAUUCCGAAGGAAAA UUTT	101	AAUUUUUCCUUCGGAAU UUTT	102
2933	2933-2951	AUUCGGAAGGAAAAU GUTT	103	ACAAUUUUUCCUUCGGAA UTT	104
2935	2935-2953	UCCGAAGGAAAAUUGU CCTT	105	GGACAAUUUUUCCUUCGG ATT	106
2936	2936-2954	CCGAAGGAAAAUUGUCC ATT	107	UGGACAAUUUUUCCUUCG GTT	108
2940	2940-2958	AGGAAAAUUGUCCAUC UUTT	109	AAGAUGGACAAUUUUUC CUTT	110
2961	2961-2979	CGUCUUCGGAAAUGUUA UGTT	111	CAUAACAUAUUCGGAAGAC GTT	112
2962	2962-2980	GUCUUCGGAAAUGUUAU GATT	113	UCAUAACAUAUUCGGAAGA CTT	114
2966	2966-2984	UCGGAAAUGUUAUGAAG CATT	115	UGCUUCAUAACAUAUUCG ATT	116
2975	2975-2993	UUAUGAAGCAGGGAUGA CUTT	117	AGUCAUCCUGCUUCAUA ATT	118
3020	3020-3038	UGGUAUAUCUGAAACUAC AGTT	119	CUGUAGUUUCAGAUUACC ATT	120
3101	3101-3119	GUCACACAUUGAAGGCUA UTT	121	AUAGCCUUCAAUGUGUG ACTT	122
3105	3105-3123	CACAUUGAAGGCUAUGA AUTT	123	AUUCAUAGCCUUCAAUGU GTT	124
3107	3107-3125	CAUUGAAGGCUAUGAAU GUTT	125	ACAUUCAUAGCCUUCAAU GTT	126
3217	3217-3235	UGCUCUCUAGCCUCAAUG ATT	127	UCAUUGAGGCUAGAGAG CATT	128
3218	3218-3236	GCUCUCUAGCCUCAAUGA ATT	129	UUCAUUGAGGCUAGAGA GCTT	130
3310	3310-3328	ACGACCAGAUGGCUGUCA UTT	131	AUGACAGCCAUCUGGUCG UTT	132
3416	3416-3434	UGAUCUGGUUUUCAUUG AGTT	133	CUCAUUGAAAACCAGAU ATT	134
3462	3462-3480	AGCCAGUGUGUCCGAAUG ATT	135	UCAUUCGGACACACUGGC UTT	136
3469	3469-3487	GUGUCCGAAUGAGGCACC UTT	137	AGGUGCCUCAUUCGGACA CTT	138
3473	3473-3491	CCGAAUGAGGCACCUCUC	139	AGAGAGGUGCCUCAUUCG	140

		UTT		GTT	
3475	3475-3493	GAAUGAGGCACCUCUCUC ATT	141	UGAGAGAGGUGCCUCAU UCTT	142
3481	3481-3499	GGCACCUCUCUCAAGAGU UTT	143	AACUCUUGAGAGAGGUG CCTT	144
3629	3629-3647	ACUCGAUCGUAUCAUUGC ATT	145	UGCAAUGAUACGAUCGA GUTT	146
3779	3779-3797	GAGCGUGGACUUUCCGGA ATT	147	UUCCGGAAAGUCCACGCU CTT	148
3781	3781-3799	GCGUGGACUUUCCGAAA UTT	149	AUUUCCGGAAAGUCCACG CTT	150

Table 3. AR siRNA Sequences with Chemical Modification

Id #	duplex name	name	sense strand sequence (5'-3')	SEQ ID NO:	name	antisense strand sequence (5'-3')	SEQ ID NO:
1201	XD-01813	X05321	gcGfuGfcGfcGfaAfgU fgAfuCfcAfdTsdT	151	X05322	UfGfgAfuCfaCfuUfcG fcGfcAfcGfdTsdT	152
1784	XD-01814	X05323	caAfuUfaCfuUfaGfgG fgGfcAfcUfdTsdT	153	X05324	AfGfuGfcCfcCfcUfaA fgUfaAfuUfgdTsdT	154
1968	XD-01815	X05325	gcCfcCfaUfuGfgCfcGf aAfuGfcAfdTsdT	155	X05326	UfGfcAfuUfcGfgCfcA faUfgGfgGfdTsdT	156
1984	XD-01816	X05327	gcAfaAfgGfuUfcUfcU fgCfuAfgAfdTsdT	157	X05328	UfCfuAfgCfaGfaGfaA fcCfuUfuGfdTsdT	158
1987	XD-01817	X05329	aaGfgUfuCfuCfuGfcU faGfaCfgAfdTsdT	159	X05330	UfCfgUfcUfaGfcAfgA fgAfaCfcUfdTsdT	160
2045	XD-01818	X05331	ccCfuUfuCfaAfgGfgA fgGfuUfaCfdTsdT	161	X05332	GfUfaAfcCfuCfcCfuU fgAfaAfgGfgdTsdT	162
2185	XD-01819	X05333	cuGfcGfuAfcCfaGfaGf uCfgCfgAfdTsdT	163	X05334	UfCfgCfgAfcUfcUfgG fuAfcGfcAfgdTsdT	164
2189	XD-01820	X05335	guAfcCfaGfaGfuCfgCf gAfcUfaCfdTsdT	165	X05336	GfUfaGfuCfgCfgAfcU fcUfgGfuAfdTsdT	166
2207	XD-01821	X05337	cuAfcAfaCfuUfuCfcAf cUfgGfcUfdTsdT	167	X05338	AfGfcCfaGfuGfgAfaA fgUfuGfuAfgdTsdT	168
2263	XD-01822	X05339	ccCfaCfgCfuCfgCfaUf cAfaGfcUfdTsdT	169	X05340	AfGfcUfuGfaUfgCfgA fgCfgUfgGfgdTsdT	170
2739	XD-01823	X05341	acUfgCfcAfgGfgAfcCf aUfgUfuUfdTsdT	171	X05342	AfAfaCfaUfgGfuCfcC fuGfgCfaGfudTsdT	172
2741	XD-01824	X05343	ugCfcAfgGfgAfcCfaU fgUfuUfuGfdTsdT	173	X05344	CfAfaAfaCfaUfgGfuC fcCfuGfgCfadTsdT	174
2814	XD-01825	X05345	gcUfuCfuGfgGfuGfuC faCfuAfuGfdTsdT	175	X05346	CfAfuAfgUfgAfcAfcC fcAfgAfaGfdTsdT	176
2817	XD-01826	X05347	ucUfgGfgUfgUfcAfcU faUfgGfaGfdTsdT	177	X05348	CfUfcCfaUfaGfuGfaC faCfcCfaGfadTsdT	178
2819	XD-01827	X05349	ugGfgUfgUfcAfcUfaU fgGfaGfcUfdTsdT	179	X05350	AfGfcUfcCfaUfaGfuG faCfaCfcCfadTsdT	180
2820	XD-01828	X05351	ggGfuGfuCfaCfuAfuG fgAfgCfuCfdTsdT	181	X05352	GfAfgCfuCfcAfuAfgU fgAfcAfcCfdTsdT	182
2822	XD-01829	X05353	guGfuCfaCfuAfuGfgA fgCfuCfuCfdTsdT	183	X05354	GfAfgAfgCfuCfcAfuA fgUfgAfcAfdTsdT	184

2824	XD-01830	X05355	guCfaCfuAfuGfgAfgCfuCfuCfaCfdTsdT	185	X05356	GfUfgAfgAfgCfuCfcAfuAfgUfgAfedTsdT	186
2847	XD-01831	X05357	ggAfaGfcUfgCfaAfgGfuCfuUfcUfdTsdT	187	X05358	AfGfaAfgAfcCfuUfgCfaGfcUfuCfedTsdT	188
2920	XD-01832	X05359	gcAfcUfaUfuGfaUfaAfaUfuCfcGfdTsdT	189	X05360	CfGfgAfaUfuUfaUfcAfaUfaGfuGfedTsdT	190
2922	XD-01833	X05361	acUfaUfuGfaUfaAfaUfuCfcGfaAfdTsdT	191	X05362	UfUfcGfgAfaUfuUfaUfcAfaUfaGfudTsdT	192
2923	XD-01834	X05363	cuAfuUfgAfuAfaAfuUfcCfgAfaGfdTsdT	193	X05364	CfUfuCfcGfaAfuUfuAfuCfaAfuAfgdTsdT	194
2924	XD-01835	X05365	uaUfuGfaUfaAfaUfuCfcGfaAfgGfdTsdT	195	X05366	CfCfuUfcGfgAfaUfuUfaUfcAfaUfadTsdT	196
2925	XD-01836	X05367	auUfgAfuAfaAfuUfcCfgAfaGfgAfdTsdT	197	X05368	UfCfcUfuCfcGfaAfuUfuAfuCfaAfuUdTsdT	198
2927	XD-01837	X05369	ugAfuAfaAfuUfcCfgAfaGfgAfaAfdTsdT	199	X05370	UfUfuCfcUfuCfcGfaAfuUfuAfuCfadTsdT	200
2931	XD-01838	X05371	aaAfuUfcCfcAfaGfgAfaAfaAfuUfdTsdT	201	X05372	AfAfuUfuUfuCfcUfuCfcGfaAfuUfuUdTsdT	202
2933	XD-01839	X05373	auUfcCfcAfaGfgAfaAfaAfuUfgUfdTsdT	203	X05374	AfCfaAfuUfuUfuCfcUfuCfcGfaAfuUdTsdT	204
2935	XD-01840	X05375	ucCfcAfaGfgAfaAfaAfuUfgUfcCfdTsdT	205	X05376	GfGfaCfaAfuUfuUfuCfcUfuCfcGfadTsdT	206
2936	XD-01841	X05377	ccGfaAfgGfaAfaAfaUfuGfuCfcAfdTsdT	207	X05378	UfGfgAfcAfaUfuUfuUfcCfuUfcGfgdTsdT	208
2940	XD-01842	X05379	agGfaAfaAfaUfuGfuCfcAfuCfuUfdTsdT	209	X05380	AfAfgAfuGfgAfcAfaUfuUfuUfcCfuUdTsdT	210
2961	XD-01843	X05381	cgUfcUfuCfcGfaAfaUfuUfuAfuGfdTsdT	211	X05382	CfAfuAfaCfaUfuUfcCfcAfaGfaCfgdTsdT	212
2962	XD-01844	X05383	guCfuUfcGfgAfaAfuGfuUfaUfgAfdTsdT	213	X05384	UfCfaUfaAfcAfuUfuCfcGfaAfgAfedTsdT	214
2966	XD-01845	X05385	ucGfgAfaAfuGfuUfaUfgAfaGfcAfdTsdT	215	X05386	UfGfcUfuCfaUfaAfcAfuUfuCfcGfadTsdT	216
2975	XD-01846	X05387	uuAfuGfaAfgCfaGfgGfaUfgAfcUfdTsdT	217	X05388	AfGfuCfaUfcCfcUfgCfuUfcAfaUfadTsdT	218
3020	XD-01847	X05389	ugGfuAfaUfcUfgAfaAfcUfaCfaGfdTsdT	219	X05390	CfUfgUfaGfuUfuCfaGfaUfuAfcCfadTsdT	220
3101	XD-01848	X05391	guCfaCfaCfaUfuGfaAfgGfcUfaUfdTsdT	221	X05392	AfUfaGfcCfuUfcAfaUfgUfgAfedTsdT	222
3105	XD-01849	X05393	caCfaUfuGfaAfgGfcUfaUfgAfaUfdTsdT	223	X05394	AfUfuCfaUfaGfcCfuUfcAfaUfgUfgdTsdT	224
3107	XD-01850	X05395	caUfuGfaAfgGfcUfaUfgAfaUfgUfdTsdT	225	X05396	AfCfaUfuCfaUfaGfcCfuUfcAfaUfgdTsdT	226
3217	XD-01851	X05397	ugCfuCfuCfuAfgCfcUfcAfaUfgAfdTsdT	227	X05398	UfCfaUfuGfaGfgCfuAfgAfgAfcfadTsdT	228
3218	XD-01852	X05399	gcUfcUfcUfaGfcCfuCfaAfuGfaAfdTsdT	229	X05400	UfUfcAfuUfgAfgGfcUfaGfaGfaGfedTsdT	230
3310	XD-01853	X05401	acGfaCfcAfgAfuGfgCfuGfuCfaUfdTsdT	231	X05402	AfUfgAfcAfgCfcAfuCfuGfgUfcGfudTsdT	232
3416	XD-01854	X05403	ugAfuCfuGfgUfuUfuCfaAfuGfaGfdTsdT	233	X05404	CfUfcAfuUfgAfaAfaCfcAfgAfuCfadTsdT	234
3462	XD-01855	X05405	agCfcAfgUfgUfgUfcCfcAfaUfgAfdTsdT	235	X05406	UfCfaUfuCfcGfaCfaCfaCfuGfgCfudTsdT	236
3469	XD-01856	X05407	guGfuCfcGfaAfuGfaGfgCfaCfcUfdTsdT	237	X05408	AfGfgUfgCfcUfcAfuUfcGfgAfcAfedTsdT	238
3473	XD-	X05409	ccGfaAfuGfaGfgCfaCf	239	X05410	AfGfaGfaGfgUfgCfcU	240

	01857		cUfcUfcUfdTsdT			fcAfuUfcGfgdTsdT	
3475	XD-01858	X05411	gaAfuGfaGfgCfaCfcUfcUfcUfcAfdTsdT	241	X05412	UfGfaGfaGfaGfgUfgCfcUfcAfuUfdTsdT	242
3481	XD-01859	X05413	ggCfaCfcUfcUfcUfcAfaGfaGfuUfdTsdT	243	X05414	AfAfcUfcUfuGfaGfaGfaGfgUfgCfdTsdT	244
3629	XD-01860	X05415	acUfcGfaUfcGfuAfuCfaUfuGfcAfdTsdT	245	X05416	UfGfcAfaUfgAfuAfcGfaUfcGfaGfudTsdT	246
3779	XD-01861	X05417	gaGfcGfuGfgAfcUfuUfcCfgGfaAfdTsdT	247	X05418	UfUfcCfgGfaAfaGfuCfcAfcGfcUfdTsdT	248
3781	XD-01862	X05419	gcGfuGfgAfcUfuUfcCfaGfaAfaUfdTsdT	249	X05420	AfUfuUfcCfgGfaAfaGfuCfcAfcGfdTsdT	250

siRNA Sequence with Chemical Modification Info

lower case (n) = 2'-O-Me; Nf = 2'-F; dT = deoxy-T residue;

s = phosphorothioate backbone modification; iB = inverted abasic

Example 2. Identification of potent pan AR siRNAs

[0170] The Androgen Receptor (AR) is a hormone-regulated transcription factor and clinically validated driver of prostate cancer growth. AR is expressed as various splice variants that differ in their ability to respond to androgens. AR variants that lack the ligand binding domain are constitutively active and unable to interact with either androgens or AR antagonists. Several of these AR splice variants are upregulated in metastatic prostate cancer patients who are unresponsive to hormone therapy (Hu *et al.*, “Ligand-Independent Androgen Receptor Variants Derived from Splicing Cryptic Exons Signify Hormone-Refractory Prostate Cancer,” *Cancer Res* 2009; **69**:16-22). In contrast to hormone therapy, regulation of AR activity by RNAi has the potential to regulate the activity of all forms of AR.

[0171] In some instances, a set of AR siRNAs were identified that were predicted to be specific in human and non-human primates (NHP) and cross-reactive with NHPs but not rodent AR mRNA. To identify AR siRNAs that regulate both full length AR and clinically relevant AR splice variants, the search for AR siRNAs was focused primarily, but not exclusively, on exons 1, 2 and 3 of the AR gene, which are common to most AR isoforms. The resulting set of 50 AR siRNAs (Tables 1-3) was assessed in two prostate cancer lines that express high levels of either clinically relevant AR splice variants (22RV1, ATCC) or a full length AR T877A LBD mutant (LNCaP, ATCC). The response of LNCaP tumors in xenograft models to AR antagonists is known to correlate well with clinical responses.

[0172] To monitor their ability to downregulate various AR isoforms, each siRNA was formulated at a single final concentration of 5 nM with a commercially-available transfection reagent (Lipofectamine RNAiMAX, Life Technologies) according to the manufacturer’s “forward transfection” instructions. At 50 h (22RV1) and 72 h (LNCaP) post transfection, cells were harvested, and lysed in RIPA buffer (Pierce) supplemented with HALT protease inhibitors (Pierce)

using standard procedures. The protein concentration was determined using a BCA protein concentration kit (Pierce). To monitor AR levels in these lysates, proteins (30ug/lane) were separated by PAGE on BOLT 4-12% Bis-Tris PA gels (Life Technologies), transferred to nitrocellulose using an iBlot dry blot system (Thermo Fisher), and probed with specific antibodies against a region of the N-terminal domain of human AR that is common in known clinically relevant splice variants (N20, Santa Cruz Biotech). A second antibody against α -Tubulin was used as control (P16, Santa Cruz Biotech). Levels of these proteins in the respective cell lysates were quantified on an Odyssey imaging system (LICOR) using appropriate secondary antibodies linked to IRDyes (800CW, 680RD). These studies resulted in the identification of 10 siRNAs that at a concentration of 5 nM downregulated all 22RV1 and LNCaP AR isoforms detectable by Western blot analysis by more than 80% compared to controls (Table 4 and Fig. 3).

Table 4.

Exon	19mer pos. in NM_000044.3	duplex name	%KD AR Protein				%KD AR RNA	
			22RV1			LNCaP	22RV1	LNCaP
			AR FL(1)	AR-SV(2)	AR-SV(3)	AR FL		
1	1201-1219	XD-01813	73	77	80	98	53	66
	1784-1802	XD-01814	-7	20	-30	94		
	1968-1986	XD-01815	-10	5	-15	91		
	1984-2002	XD-01816	57	66	69	97	60	74
	1987-2005	XD-01817	83	91	86	99	83	87
	2045-2063	XD-01818	-6	-48	25	93		
	2185-2203	XD-01819	15	47	45	92		
	2189-2207	XD-01820	85	91	91	100	46	59
	2207-2225	XD-01821	73	80	7	96	68	81
	2263-2281	XD-01822	34	33	41	88		
2	2739-2757	XD-01823	-5	0	-19	79		
	2741-2759	XD-01824	3	-32	-44	45		
	2814-2832	XD-01825	90	93	95	91	91	82
	2817-2835	XD-01826	87	92	93	91	89	81
	2819-2837	XD-01827	89	92	93	90	89	86
	2820-2838	XD-01828	80	89	92	90	96	84
	2822-2840	XD-01829	97	99	97	91	86	92
	2824-2842	XD-01830	75	72	76	90		
	2847-2865	XD-01831	57	54	59	87		
3	2920-2938	XD-01832	93	93	73	92		

	2922-2940	XD-01833	94	91	77	91
	2923-2941	XD-01834	90	91	79	91
	2924-2942	XD-01835	89	85	83	92
	2925-2943	XD-01836	87	83	73	91
	2927-2945	XD-01837	87	94	86	91
	2931-2949	XD-01838	85	65	67	88
	2933-2951	XD-01839	76	62	56	93
	2935-2953	XD-01840	89	89	75	97
	2936-2954	XD-01841	85	85	74	99
	2940-2958	XD-01842	89	94	84	101
	2961-2979	XD-01843	78	75	47	94
	2962-2980	XD-01844	56	54	26	81
	2966-2984	XD-01845	92	92	72	99
	2975-2993	XD-01846	87	94	76	94
4	3020-3038	XD-01847	28	-10	-68	69
	3101-3119	XD-01848	87	31	27	101
	3105-3123	XD-01849	86	7	-40	92
	3107-3125	XD-01850	86	14	5	82
	3217-3235	XD-01851	50	2	8	84
	3218-3236	XD-01852	16	8	10	34
	3310-3328	XD-01853	91	-43	13	99
5	3416-3434	XD-01854	95	38	46	93
	3462-3480	XD-01855	12	-1	-18	75
6	3469-3487	XD-01856	77	-61	-74	99
	3473-3491	XD-01857	79	-7	1	100
	3475-3493	XD-01858	93	25	66	99
	3481-3499	XD-01859	87	-23	-49	100
7	3629-3647	XD-01860	90	-9	4	99
8	3779-3797	XD-01861	90	11	51	99
	3781-3799	XD-01862	92	24	40	87

[0173] Focusing on siRNAs targeting AR sequences exons 1 and 2, the ability of these siRNAs to downregulate AR mRNA at a concentration of 5 nM was determined by RT-qPCR. For this purpose, siRNAs were transfected into 22RV1 and LNCaP cells as described above. At 24 hrs post-transfection, RNA was harvested from cells using a Qiagen RNeasy® Plus Mini Kit or Stratagene InviTrap® RNA Cell HTS96 kit. The concentration of each isolated RNA was determined via A260 measurement using a NanoDrop spectrophotometer. RNA samples were reverse transcribed

to cDNA using the High Capacity RNA to cDNA Kit (Life Technologies) according to the manufacturer's instructions. cDNA samples were then quantified by qPCR using AR-specific probes and results normalized to either endogenous β -actin or PPIB using the standard $2^{-\Delta\Delta C_t}$ method. These studies identified 6 siRNAs that at a concentration of 5 nM down regulated AR mRNA in 22RV1 and LNCaP cells by more than 80% compared to controls (Table 4).

[0174] To determine the concentration required to reduce AR expression by 50% (IC₅₀) and maximal KD activity, these siRNAs were transfected into LNCaP, C4-2, and 22RV1 cells at various concentrations starting at 100 nM. C4-2 (MD Anderson) is an LNCaP subline that has been selected for resistance against clinically used AR antagonists (Wu *et al.*, "Derivation of androgen-independent human LNCaP prostatic cancer cell sublines: Role of bone stromal cells," *International J Cancer* 1994; **57**:406-412). Cells were harvested 48 h post-transfection; RNA was prepared and analyzed as stated above. For these experiments, specific AR qPCR probes located at the exon junctions 1/2 or 4/5 were used that recognize most mRNAs of relevant AR isoforms or primarily full length AR mRNA, respectively. All tested siRNAs lowered AR expression with subnanomolar potency to 70% in 22RV1 cells and to $\geq 90\%$ in LNCaP and C4-2 cells (Table 5).

Table 5.

siRNA duplex	LNCaP				C4-2				22RV1			
	Exon 1/2		Exon 4/5		Exon 1/2		Exon 4/5		Exon 1/2		Exon 4/5	
	IC ₅₀ (nM)	max KD (%)	IC ₅₀ (nM)	max KD (%)	IC ₅₀ (nM)	max KD (%)	IC ₅₀ (nM)	max KD (%)	IC ₅₀ (nM)	max KD (%)	IC ₅₀ (nM)	max KD (%)
XD-01817	0.018	83.4	0.017	87.2	0.021	83.6	0.023	84.1	0.059	49.3	0.043	61.1
XD-01825	0.020	82.5	0.018	84.9	0.024	83.5	0.026	84.6	0.067	53.5	0.055	60.7
XD-01826	0.041	84.6	0.035	86.0	0.049	86.5	0.046	87.0	0.146	52.4	0.057	64.8
XD-01827	0.053	81.7	0.060	84.5	0.052	83.2	0.052	85.7	0.108	38.7	0.068	54.0
XD-01828	0.023	84.8	0.028	81.7	0.022	81.1	0.020	77.7	0.042	51.7	0.028	50.7
XD-01829 (or XD-0189)	0.016	94.2	0.016	92.3	0.013	94.7	0.011	92.6	0.038	72.1	0.018	68.1

[0175] To monitor regulation of AR target genes as a consequence of siRNA-mediated changes in AR transfection, LNCaP cells were transfected with various concentrations of XD-01829 (also referred to as XD-0189), and the levels of AR and the Prostate Specific Antigen (PSA) monitored by qRT-PCR. PSA expression is positively regulated by AR and used clinically as a biomarker for AR activity in prostate cancer patients. As shown in Fig. 1A-Fig. 1C, at 3 days after transfection AR and PSA levels are highly correlated. A similar experiment compared the expression of AR, PSA and the Prostate-Specific Membrane Antigen (PSMA) in response to treatment with the AR antagonist Enzalutamide or AR siRNA XD-01829 (or XD-0189). PSMA expression is negatively regulated by AR. For these experiments, hormone therapy resistant 22RV1 cells were transfected

with 5 nM of either a scrambled control siRNA (negative control, Enzalutamide group) or XD-01829 (or XD-0189) as described above. After incubation for 24 hours, the negative control and XD-01829 (or XD-0189) groups were treated with DMSO, and the enzalutamide group with 10 μ M Enzalutamide. After incubation for 20 hours RNAs were prepared as outlined above and AR, PSA, and PSMA levels evaluated by qRT-PCR. The results from this experiment (Fig. 2A-Fig. 2C) demonstrate that downregulation of AR by XD-01829 (or XD-0189) but not the AR antagonist Enzalutamide regulate AR target gene expression in hormone therapy-resistant cells.

[0176] An array of chemical modification patterns were introduced to siRNAs XD-01817 and XD-01829 (Table 6A and Table 6B), and their effect on AR mRNA downregulation was tested in LNCaP, C4-2, and 22RV1 cells after transfection with RNAiMAX as described above. In these cell lines, the tested modifications were tolerated with a <10-fold loss in potency and a <6% reduction in maximal efficacy.

Table 6A.

ID #	19mer siRNA Start Site	Sense Strand Sequence (5'- 3') Passenger Strand (PS) ²	SEQ ID NO:	Antisense Strand Sequence (5'-3') Guide Strand (GS) ³	SEQ ID NO:
XD-02595K1	1987	AAGGUUCUCUGCUAGA CGAdTsdT	251	UCGUCUAGCAGAGAACC UdTsdt	252
XD-02598K1	1987	aAGGUUCUCUGCuaGACG AdTsdt	253	UCGUCuAGcAGAGAACCU UdTsdt	254
XD-02597K1	1987	aaGGUUCUCuGCuaGAcGA dTsdT	255	UCGUCuAGcAGAGAACCU UdTsdt	256
XD-02596K1	1987	aaGGuucucuGcuaGAcGAdT sdT	257	UCGUCuAGcAGAGAACCU UdTsdt	258
XD-01817K1	1987	aaGfgUfuCfuCfuGfcUfaGfa CfgAfdTsdt	159	UfCfgUfcUfaGfcAfgAfgAfaC fcUfudTsdt	160
XD-02728K1	1987	iBaaGfgUfuCfuCfuGfcUfaGf aCfgAfdTsdtTiB	259	UfCfgUfcUfaGfcAfgAfgAfaC fcUfudTsdt	260
XD-02729K1	1987	iBaaGfgUfuCfuCfuGfcUfaGf aCfgAfdTsdtTiB	261	UfsCfsgsUfcUfaGfcAfgAfgAf aCfcUfudTsdt	262
XD-02730K2	1987	iBaaGfgUfuCfuCfuGfcUfaGf aCfgAfdTsdtTiB	263	uCfgUfcUfaGfcAfgAfgAfaCf cUfudTsdt	264
XD-02731K1	1987	iBaaGfgUfuCfuCfuGfcUfaGf aCfgAfdTsdtTiB	265	usCfsgsUfcUfaGfcAfgAfgAfa CfcUfudTsdt	266
XD-02227K1	2822	GUGUCACUAUGGAGCU CUCUU	267	GAGAGCUCCAUAUGUGAC ACUU	268
XD-02227K1	2822	GUGUCACUAUGGAGCU CUCdTsdT	269	GAGAGCUCCAUAUGUGAC ACdTsdT	270
XD-02230K1	2822	gUGUcACuAUGGAgCUCU CdTsdt	271	GAGAGCUCcAuAGUGAcA CdTsdt	272
XD-02229K1	2822	guGUcACuAuGGAgCUCU CdTsdt	273	GAGAGCUCcAuAGUGAcA CdTsdt	274
XD-02228K1	2822	guGucAcuAuGGAgcucuedT sdT	275	GAGAGCUCcAuAGUGAcA CdTsdt	276
XD-01829K2	2822	guGfuCfaCfuAfuGfgAfgCfu CfuCfdTsdt	277	GfAfgAfgCfuCfcAfuAfgUfg AfcAfdTsdt	278

XD-02732K1	2822	iBguGfuCfaCfuAfuGfgAfgCfuCfuCfdTsdTiB	279	GfAfgAfgCfuCfcAfuAfgUfgAfcAfcdTsdT	280
XD-02733K1	2822	iBguGfuCfaCfuAfuGfgAfgCfuCfuCfdTsdTiB	281	GfsAfsAfgCfuCfcAfuAfgUfgAfcAfcdTsdT	282
XD-02734K2	2822	iBguGfuCfaCfuAfuGfgAfgCfuCfuCfdTsdTiB	283	gAfgAfgCfuCfcAfuAfgUfgAfcAfcdTsdT	284
XD-02735K1	2822	iBguGfuCfaCfuAfuGfgAfgCfuCfuCfdTsdTiB	285	gsAfsAfgCfuCfcAfuAfgUfgAfcAfcdTsdT	286
XD-03788K1	2822	iBguGfuCfaCfuAfuGfgAfgCfuCfuCfusuiB	287	GfsAfsAfgCfuCfcAfuAfgUfgAfcAfcusu	288
STOP-140901-001	2822	iBguGfuCfaCfuAfuGfgAfgCfuCfuCfusuiB	289	gsAfsAfgCfuCfcAfuAfgUfgAfcAfcusu	290

siRNA Sequence with Chemical Modification Info

lower case (n) = 2'-O-Me; Nf = 2'-F; dT = deoxy-T residue;

s = phosphorothioate backbone modification; iB = inverted abasic

Table 6B.

ID #	19mer siRNA Start Site	LNCaP		C4-2		22RV1	
		IC50 (nM)	max KD (%)	IC50 (nM)	max KD (%)	IC50 (nM)	max KD (%)
XD-02595K1	1987	0.008	88.6				
XD-02598K1	1987	0.019	87.2				
XD-02597K1	1987	0.015	89.8				
XD-02596K1	1987	0.013	88.2				
XD-01817K1	1987	0.009	89.5				
XD-02728K1	1987	0.037	89.1				
XD-02729K1	1987	0.014	91.0				
XD-02730K2	1987	0.025	90.2				
XD-02731K1	1987	0.054	90.0				
XD-02227K1	2822	0.017	92.7	0.023	94.3	0.056	64.5
XD-02227K1	2822	0.009	91.8				
XD-02230K1	2822	0.012	89.2	0.014	93.9	0.021	67.3
XD-02229K1	2822	0.011	88.1				
XD-02228K1	2822	0.013	88.4				
XD-01829K2	2822	0.015	91.9	0.011	92.6	0.018	68.1
XD-02732K1	2822	0.020	89.6				
XD-02733K1	2822	0.015	92.3				
XD-02734K2	2822	0.037	90.5				
XD-02735K1	2822	0.078	89.7				
XD-03788K1	2822	0.030	88.3	0.044	88.2	0.036	62.6
STOP-140901-001	2822	0.063	87.2	0.100	83.2	0.072	61.3

[0177] While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in

the art without departing from the disclosure. It should be understood that various alternatives to the embodiments of the disclosure described herein may be employed in practicing the disclosure. It is intended that the following claims define the scope of the disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. A polynucleic acid molecule that mediates RNA interference against androgen receptor, wherein the polynucleic acid molecule hybridizes to an androgen receptor target sequence selected from SEQ ID NOs: 1-50 with less than 4 mismatched bases, wherein the polynucleic acid molecule comprises at least one 2' modified nucleotide, at least one modified internucleotide linkage, or at least one inverted abasic moiety, and wherein the polynucleic acid molecule is from about 10 to about 50 nucleotides in length.
2. The polynucleic acid molecule of claim 1, wherein the polynucleic acid molecule hybridizes to a target sequence selected from SEQ ID NOs: 1-50 with less than 3 mismatched bases, less than 2 mismatched bases, or less than 1 mismatched bases.
3. The polynucleic acid molecule of claim 1 or 2, wherein the at least one 2' modified nucleotide comprises 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl, 2'-deoxy, T-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), T-O- dimethylaminoethoxyethyl (2'-O-DMAEOE), or 2'-O-N-methylacetamido (2'-O-NMA) modified nucleotide.
4. The polynucleic acid molecule of claim 1 or 2, wherein the at least one 2' modified nucleotide comprises locked nucleic acid (LNA) or ethylene nucleic acid (ENA).
5. The polynucleic acid molecule of claim 1 or 2, wherein the at least one inverted basic moiety is at at least one terminus.
6. The polynucleic acid molecule of claim 1 or 2, wherein the at least one modified internucleotide linkage comprises a phosphorothioate linkage or a phosphorodithioate linkage.
7. The polynucleic acid molecule of any one of the claims 1-6, wherein the polynucleic acid molecule is from about 10 to about 30 nucleotides in length.
8. The polynucleic acid molecule of any one of the claims 1-7, wherein the polynucleic acid molecule is at least 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleotides in length.
9. The polynucleic acid molecule of any one of the claims 1-8, wherein the polynucleic acid molecule comprises at least one of: from about 5% to about 100% modification, from about 10% to about 100% modification, from about 20% to about 100% modification, from about 30% to about 100% modification, from about 40% to about 100% modification, from about 50% to about 100% modification, from about 60% to about 100% modification, from about 70% to about 100% modification, from about 80% to about 100% modification, and from about 90% to about 100% modification.

10. The polynucleic acid molecule of any one of the claims 1-8, wherein the polynucleic acid molecule comprises at least one of: from about 10% to about 80% modification, from about 20% to about 80% modification, from about 30% to about 80% modification, from about 40% to about 80% modification, from about 50% to about 80% modification, from about 60% to about 80% modification, and from about 70% to about 80% modification.
11. The polynucleic acid molecule of any one of the claims 1-8, wherein the polynucleic acid molecule comprises at least one of: from about 10% to about 60% modification, from about 20% to about 60% modification, from about 30% to about 60% modification, from about 40% to about 60% modification, and from about 50% to about 60% modification.
12. The polynucleic acid molecule of any one of the claims 1-8, wherein the polynucleic acid molecule comprises at least 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 99% modification.
13. The polynucleic acid molecule of any one of the claims 1-8, wherein the polynucleic acid molecule comprises about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, or more modified nucleotides.
14. The polynucleic acid molecule of any one of the claims 1-13, wherein the polynucleic acid molecule comprises a single strand.
15. The polynucleic acid molecule of any one of the claims 1-13, wherein the polynucleic acid molecule comprises a first polynucleotide and a second polynucleotide hybridized to the first polynucleotide to form a double-stranded polynucleic acid molecule.
16. The polynucleic acid molecule of claim 15, wherein the second polynucleotide comprises at least one modification.
17. The polynucleic acid molecule of claim 15, wherein the first polynucleotide and the second polynucleotide are RNA molecules.
18. The polynucleic acid molecule of claim 15, wherein the first polynucleotide comprises a sequence having at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a sequence selected from SEQ ID NOs: 51-290.
19. The polynucleic acid molecule of claim 15, wherein the second polynucleotide comprises a sequence having at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a sequence selected from SEQ ID NOs: 51-290.
20. A polynucleic acid molecule that mediates RNA interference against androgen receptor, wherein the polynucleic acid molecule comprises at least 80% sequence identity to a sequence selected from SEQ ID NOs: 51-290.

21. The polynucleic acid molecule of claim 20, wherein the polynucleic acid molecule comprises at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a sequence selected from SEQ ID NOs: 51-290.
22. The polynucleic acid molecule of claim 20 or 21, wherein the polynucleic acid molecule is from about 10 to about 30 nucleotides in length.
23. The polynucleic acid molecule of claim 20 or 21, wherein the polynucleic acid molecule is at least about 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleotides in length.
24. The polynucleic acid molecule of any one of the claims 20-23, wherein the polynucleic acid molecule comprises at least one of: from about 5% to about 100% modification, from about 10% to about 100% modification, from about 20% to about 100% modification, from about 30% to about 100% modification, from about 40% to about 100% modification, from about 50% to about 100% modification, from about 60% to about 100% modification, from about 70% to about 100% modification, from about 80% to about 100% modification, and from about 90% to about 100% modification.
25. The polynucleic acid molecule of any one of the claims 20-23, wherein the polynucleic acid molecule comprises at least 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 99% modification.
26. The polynucleic acid molecule of any one of the claims 20-23, wherein the polynucleic acid molecule comprises about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, or more modified nucleotides.
27. A pharmaceutical composition comprising:
 - a) a molecule of claims 1-26; and
 - b) a pharmaceutically acceptable excipient.
28. The pharmaceutical composition of claim 27, wherein the pharmaceutical composition is formulated as a nanoparticle formulation.
29. The pharmaceutical composition of claim 27, wherein the pharmaceutical composition is formulated for parenteral, oral, intranasal, buccal, rectal, or transdermal administration.
30. A method of treating a disease or disorder in a patient in need thereof, comprising administering to the patient a composition comprising a molecule of claims 1-26.
31. The method of claim 30, wherein the disease or disorder is a cancer.
32. The method of claim 31, wherein the cancer comprises an androgen receptor-associated cancer.
33. The method of claim 31, wherein the cancer is a solid tumor.

34. The method of claim 31, wherein the cancer is a hematologic malignancy.
35. The method of claim 31, wherein the cancer comprises bladder cancer, breast cancer, colorectal cancer, endometrial cancer, esophageal cancer, glioblastoma multiforme, head and neck cancer, kidney cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, or thyroid cancer.
36. The method of claim 31, wherein the cancer comprises acute myeloid leukemia, CLL, DLBCL, or multiple myeloma.
37. A method of inhibiting the expression of an androgen receptor gene in a primary cell of a patient, comprising administering a molecule of claims 1-26 to the primary cell.
38. The method of claim 37, wherein the method is an *in vivo* method.
39. The method of claim 37, wherein the patient is a human.

1/4

Fig. 1A

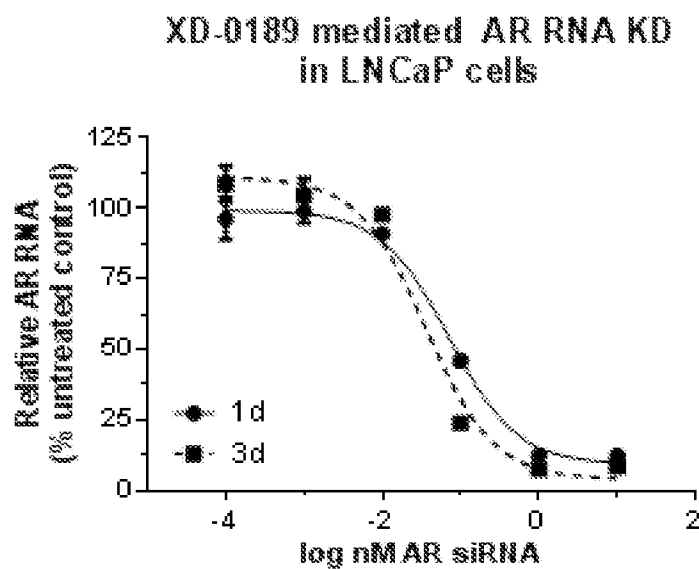


Fig. 1B

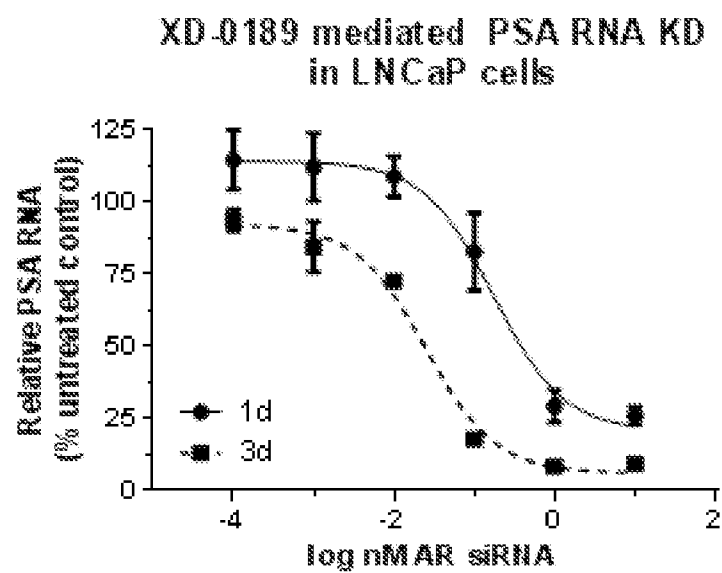


Fig. 1C

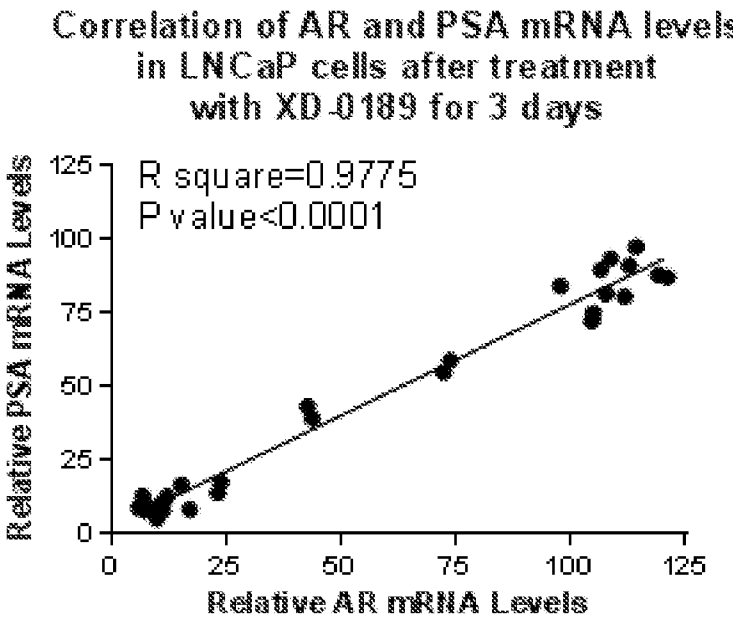


Fig. 2A

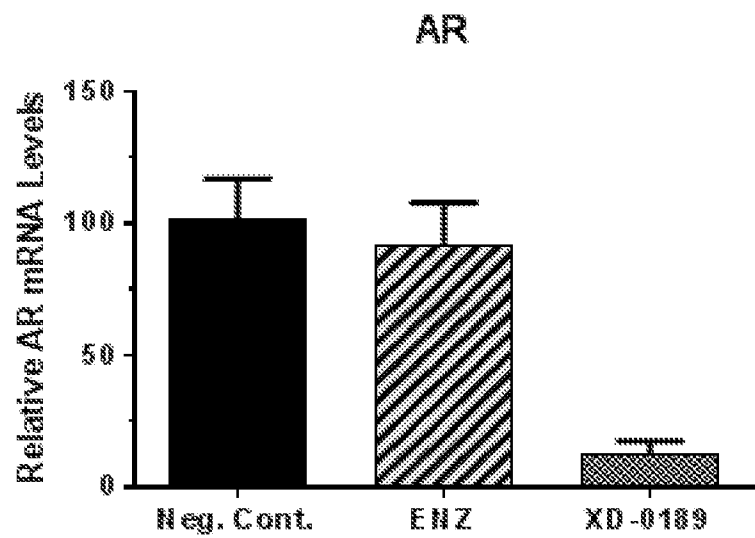


Fig. 2B

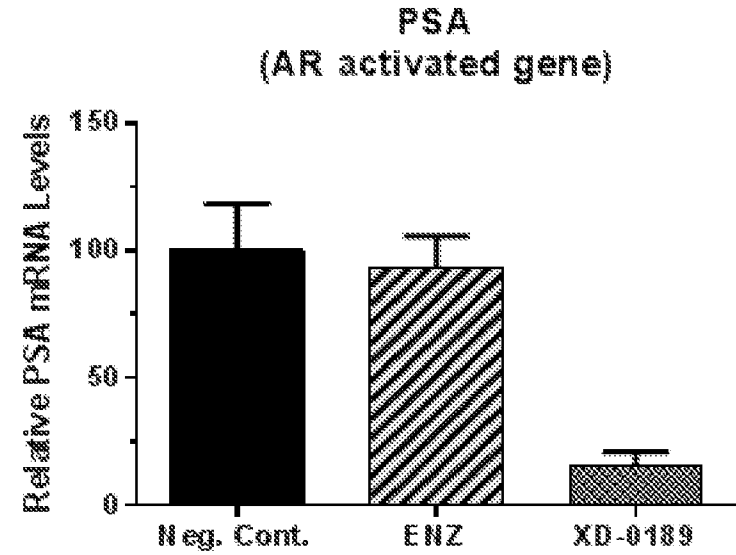


Fig. 2C

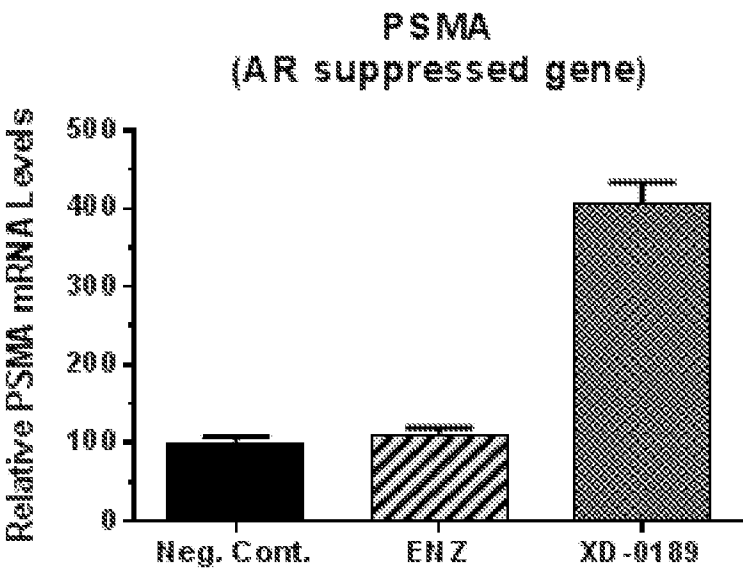
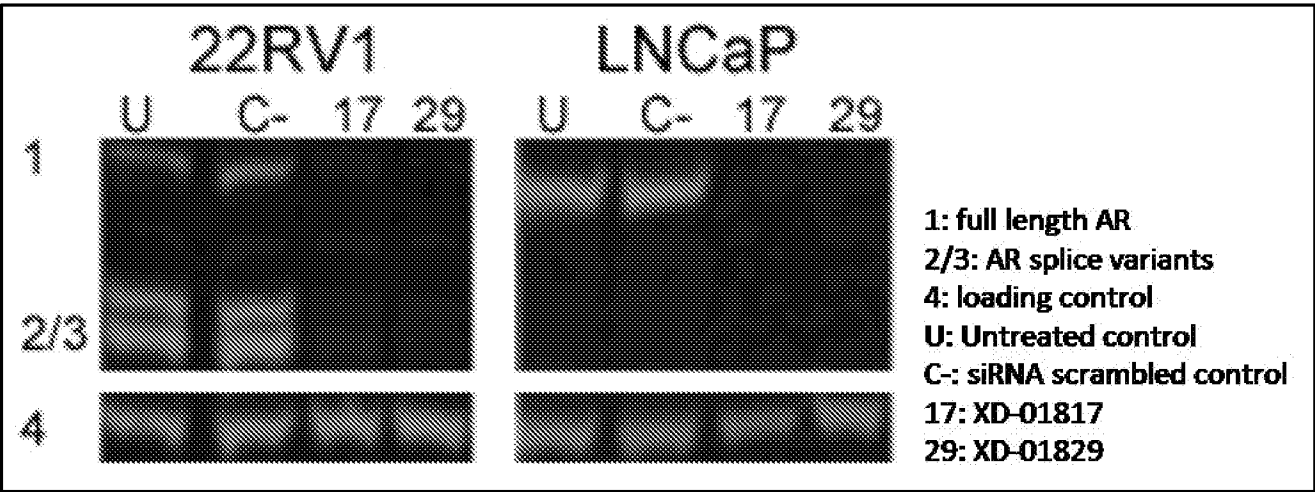


Fig. 3



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/025428

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

a. ☒ forming part of the international application as filed:

☒ in the form of an Annex C/ST.25 text file.

☐ on paper or in the form of an image file.

b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).

☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

A. CLASSIFICATION OF SUBJECT MATTER**C12N 15/113(2010.01)i, A61K 31/712(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C12N 15/113; A61K 31/70; C07H 21/02; A61K 48/00; C12Q 1/68; A61K 31/712

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & keywords: androgen receptor, RNA interference, target sequence, 2' modified nucleotide, modified internucleotide linkage, inverted abasic moiety, modification

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 8927515 B2 (DICERNA PHARMACEUTICALS, INC.) 6 January 2015 See columns 8, 22, 25 and 26; claims 1-7 and 34.	1-6, 20-23
X	US 2005-0164970 A1 (LI) 28 July 2005 See paragraphs [0054] and [0055]; claims 1, 27 and 28.	1-6, 20-23
A	WO 2014-154835 A2 (ISARNA THERAPEUTICS GMBH) 2 October 2014 See abstract; pages 7, 8, 15, 19 and 20; claims 1-5.	1-6, 20-23
A	US 2005-0176018 A1 (THOMPSON et al.) 11 August 2005 See abstract; claims 1-12.	1-6, 20-23
A	DELEAVEY et al., 'Designing chemically modified oligonucleotides for targeted gene silencing', Chemistry & Biology, Vol.19, pp.937-954 (24 August 2012) See abstract; pages 941-947.	1-6, 20-23
A	JACKSON et al., 'Position-specific chemical modification of siRNAs reduces "off-target" transcript silencing', RNA, Vol.12, pp.1197-1205 (2006) See abstract; page 1197.	1-6, 20-23



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

10 July 2017 (10.07.2017)

Date of mailing of the international search report

10 July 2017 (10.07.2017)

Name and mailing address of the ISA/KR

International Application Division

Korean Intellectual Property Office

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 30-39
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 30-39 are directed to a treatment method of the human body by therapy and thus relate to a subject matter which this International Searching Authority is not required, under PCT Article 17(2)(a)(i) and Rule 39.1(iv), to search.
2. ☒ Claims Nos.: 16-19,28,29,31-36,38,39
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 16-19, 28, 29, 31-36, 38 and 39 are regarded as unclear since they directly or indirectly refer to one of the multiple dependent claims which does not comply with PCT Rule 6.4(a).
3. ☒ Claims Nos.: 7-15,24-27,30,37
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2017/025428

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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