MODULATORS OF MALAT1 EXPRESSION

Sequence Listing

The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled BIOL00359WOSEQ_ST25.txt created February 20, 2020 which is 596 kb in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

Field

The present embodiments provide methods, compounds, and compositions useful for inhibiting MALAT1 expression, which can be useful for treating, preventing, or ameliorating a cancer associated with MALAT1.

Background

Metastasis associated lung adenocarcinoma transcript 1 (MALAT1) is a non-coding lncRNA expressed in many human cell types and is highly conserved across mammalian species. MALAT1 was initially identified from metastatic NSCLC patients and is upregulated in multiple types of cancer (Zhang X. et al., RNA Biol. 2017, Ping J et al., 2003).

Certain embodiments provided herein are directed to potent and tolerable compounds and compositions useful for inhibiting MALAT1 expression, which can be useful for treating, preventing, ameliorating, or slowing progression of cancer associated with MALAT1.

Detailed Description

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the embodiments, as claimed. Herein, the use of the singular includes the plural unless specifically stated otherwise. As used herein, the use of "or" means "and/or" unless stated otherwise. Furthermore, the use of the term "including" as well as other forms, such as "includes" and "included", is not limiting.

The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in this application, including, but not limited to, patents, patent applications, articles, books, treatises, and GenBank and NCBI reference sequence records are hereby expressly incorporated by reference for the portions of the document discussed herein, as well as in their entirety.

It is understood that the sequence set forth in each SEQ ID NO in the examples contained herein is independent of any modification to a sugar moiety, an internucleoside linkage, or a nucleobase. As such, compounds defined by a SEQ ID NO may comprise, independently, one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase. Compounds described by ION number indicate a combination of nucleobase sequence, chemical modification, and motif.

Unless otherwise indicated, the following terms have the following meanings:

"2'-deoxynucleoside" means a nucleoside comprising 2'-H(H) furanosyl sugar moiety, as found in naturally occurring deoxyribonucleic acids (DNA). In certain embodiments, a 2'-deoxynucleoside may comprise a modified nucleobase or may comprise an RNA nucleobase (uracil).

"2'-O-methoxyethyl" (also 2'-MOE and 2'-O(CH_2)$_2$-OCH_3) refers to an O-methoxy-ethyl modification at the 2' position of a furanosyl ring. A 2'-O-methoxyethyl modified sugar is a modified sugar.

"2'-MOE nucleoside" (also 2'-O-methoxyethyl nucleoside) means a nucleoside comprising a 2'-MOE modified sugar moiety.

"2'-substituted nucleoside" or "2-modified nucleoside" means a nucleoside comprising a 2'-substituted or 2'-modified sugar moiety. As used herein, "2'-substituted" or "2-modified" in reference to a sugar moiety means a sugar moiety comprising at least one 2'-substituent group other than H or OH.

"3' target site" refers to the nucleotide of a target nucleic acid which is complementary to the 3'-most nucleotide of a particular compound.

"5' target site" refers to the nucleotide of a target nucleic acid which is complementary to the 5'-most nucleotide of a particular compound.

"5-methylcytosine" means a cytosine with a methyl group attached to the 5 position.

"About" means within ±10% of a value. For example, if it is stated, "the compounds affected about 70% inhibition of MALAT1", it is implied that MALAT1 levels are inhibited within a range of 60% and 80%.

"Administration" or "administering" refers to routes of introducing a compound or composition provided herein to an individual to perform its intended function. An example of a route of administration that can be used includes, but is not limited to parenteral administration, such as subcutaneous, intravenous, or intramuscular injection or infusion.

"Administered concomitantly" or "co-administration" means administration of two or more compounds in any manner in which the pharmacological effects of both are manifest in the patient. Concomitant administration does not require that both compounds be administered in a single pharmaceutical composition, in the same dosage form, by the same route of administration, or at the same time. The effects of both compounds need not manifest themselves at the same time. The effects need only be overlapping for a

period of time and need not be coextensive. Concomitant administration or co-administration encompasses administration in parallel or sequentially.

"Amelioration" refers to an improvement or lessening of at least one indicator, sign, or symptom of an associated disease, disorder, or condition. In certain embodiments, amelioration includes a delay or slowing in the progression or severity of one or more indicators of a condition or disease. The progression or severity of indicators may be determined by subjective or objective measures, which are known to those skilled in the art.

"Animal" refers to a human or non-human animal, including, but not limited to, mice, rats, rabbits, dogs, cats, pigs, and non-human primates, including, but not limited to, monkeys and chimpanzees.

"Antibody," as used in this disclosure, refers to an immunoglobulin or a fragment or a derivative thereof, and encompasses any polypeptide comprising an antigen-binding site, regardless of whether it is produced in vitro or in vivo. The term includes, but is not limited to, polyclonal, monoclonal, monospecific, polyspecific, non-specific, humanized, single-chain, chimeric, synthetic, recombinant, hybrid, mutated, and grafted antibodies. Unless otherwise modified by the term "intact," as in "intact antibodies," for the purposes of this disclosure, the term "antibody" also includes antibody fragments such as Fab, F(ab')2, Fv, scFv, Fd, dAb, and other antibody fragments that retain antigen-binding function, i.e., the ability to bind, for example, CTLA-4 or PD-L1 specifically. Typically, such fragments would comprise an antigen-binding domain.

"Anti-CTLA-4 antibody" refers to an antibody or antigen binding fragment thereof that specifically binds a CTLA-4 polypeptide. Exemplary anti-CTLA-4 antibodies are described for example at U.S. Patent Nos. 6,682,736; 7,109,003; 7,123,281; 7,411,057; 7,824,679; 8,143,379; 7,807,797; and 8,491,895 (Tremelimumab is 11.2.1, therein), which are herein incorporated by reference. Tremelimumab (U.S. Patent No. 6,682,736) is an exemplary anti-CTLA-4 antibody. Tremelimumab VL, VH, and CDR amino acid sequences are provided at SEQ ID NOs: 1-8, herein.

"Anti-OX40 antibody" refers to an antibody or antigen binding fragment thereof that specifically binds OX40. OX40 antibodies include monoclonal and polyclonal antibodies that are specific for OX40 and antigen-binding fragments thereof. In certain aspects, anti-OX40 antibodies as described herein are monoclonal antibodies (or antigen-binding fragments thereof), e.g., murine, humanized, or fully human monoclonal antibodies. In one particular embodiment, the OX40 antibody is an OX40 receptor agonist, such as the mouse anti-human OX40 monoclonal antibody (9B12) described by Weinberg et al., J Immunother 29, 575-585 (2006). In another embodiment, an OX40 antibody is MEDI0562 as described in US 2016/0137740, incorporated herein by reference. MEDI0562 VH and VL amino acid sequences are provided at SEQ ID NOs: 25- 26, herein. In other embodiments, the antibody which specifically binds to OX40, or an antigen-binding fragment thereof, binds to the same OX40 epitope as mAb 9B12.

"Anti-PD-L1 antibody" refers to an antibody or antigen binding fragment thereof that specifically binds a PD-L1 polypeptide. Exemplary anti-PD-L1 antibodies are described for example at US2013/0034559, U.S.

Pat. Nos. 8,779,108 and 9,493,565 which are herein incorporated by reference. Durvalumab (MEDI4736) is an exemplary anti-PD-L1 antibody. Durvalumab VL, VH, and CDR amino acid sequences are provided at SEQ ID NOs: 9-16, herein. Other anti-PD-L1 antibodies include BMS-936559 (Bristol-Myers Squibb) and MPDL3280A (atezolizumab) (Roche).

"Anti-PD-1 antibody" refers to an antibody or antigen binding fragment thereof that specifically binds a PD-1 polypeptide. Exemplary anti-PD-1 antibodies are described for example at U.S. Pat. Nos. 7,521,051; 8,008,449; 8,354,509; 9,073,994; 9,393,301; 9402899; and 9,439,962, which are herein incorporated by reference. Exemplary anti-PD-1 antibodies include, without limitation, nivolumab, pembrolizumab, pidilizumab, and AMP-514.

"Antigen-binding domain," "antigen-binding fragment," and "binding fragment" refer to a part of an antibody molecule that comprises amino acids responsible for the specific binding between the antibody and the antigen. In instances, where an antigen is large, the antigen-binding domain may only bind to a part of the antigen. A portion of the antigen molecule that is responsible for specific interactions with the antigen-binding domain is referred to as "epitope" or "antigenic determinant." An antigen-binding domain typically comprises an antibody light chain variable region (VL) and an antibody heavy chain variable region (VH), however, it does not necessarily have to comprise both. For example, a so-called Fd antibody fragment consists only of a VH domain, but still retains some antigen-binding function of the intact antibody. Binding fragments of an antibody are produced by recombinant DNA techniques, or by enzymatic or chemical cleavage of intact antibodies. Binding fragments include Fab, Fab', F(ab')2, Fv, and single-chain antibodies. An antibody other than a "bispecific" or "bifunctional" antibody is understood to have each of its binding sites identical. Digestion of antibodies with the enzyme, papain, results in two identical antigen-binding fragments, known also as "Fab" fragments, and a "Fc" fragment, having no antigen-binding activity but having the ability to crystallize. Digestion of antibodies with the enzyme, pepsin, results in the a F(ab')2 fragment in which the two arms of the antibody molecule remain linked and comprise two-antigen binding sites. The F(ab')2 fragment has the ability to crosslink antigen. "Fv" when used herein refers to the minimum fragment of an antibody that retains both antigen-recognition and antigen-binding sites. "Fab" when used herein refers to a fragment of an antibody that comprises the constant domain of the light chain and the CH1 domain of the heavy chain.

"mAb" refers to monoclonal antibody. Antibodies of the present disclosure comprise without limitation whole native antibodies, bispecific antibodies; chimeric antibodies; Fab, Fab', single chain V region fragments (scFv), fusion polypeptides, and unconventional antibodies.

"Antisense activity" means any detectable and/or measurable activity attributable to the hybridization of an antisense compound to its target nucleic acid. In certain embodiments, antisense activity is a decrease in the amount or expression of a target nucleic acid or protein encoded by such target nucleic acid compared to target nucleic acid levels or target protein levels in the absence of the antisense compound to the target.

"Antisense compound" means a compound comprising an oligonucleotide and optionally one or more additional features, such as a conjugate group or terminal group. Examples of antisense compounds include single-stranded and double-stranded compounds, such as, oligonucleotides, ribozymes, siRNAs, shRNAs, ssRNAs, and occupancy-based compounds.

"Antisense inhibition" means reduction of target nucleic acid levels in the presence of an antisense compound complementary to a target nucleic acid compared to target nucleic acid levels in the absence of the antisense compound.

"Antisense mechanisms" are all those mechanisms involving hybridization of a compound with target nucleic acid, wherein the outcome or effect of the hybridization is either target degradation or target occupancy with concomitant stalling of the cellular machinery involving, for example, transcription or splicing.

"Antisense oligonucleotide" means an oligonucleotide having a nucleobase sequence that is complementary to a target nucleic acid or region or segment thereof. In certain embodiments, an antisense oligonucleotide is specifically hybridizable to a target nucleic acid or region or segment thereof.

"Bicyclic nucleoside" or "BNA" means a nucleoside comprising a bicyclic sugar moiety. "Bicyclic sugar" or "bicyclic sugar moiety" means a modified sugar moiety comprising two rings, wherein the second ring is formed via a bridge connecting two of the atoms in the first ring thereby forming a bicyclic structure. In certain embodiments, the first ring of the bicyclic sugar moiety is a furanosyl moiety. In certain embodiments, the bicyclic sugar moiety does not comprise a furanosyl moiety.

"Branching group" means a group of atoms having at least 3 positions that are capable of forming covalent linkages to at least 3 groups. In certain embodiments, a branching group provides a plurality of reactive sites for connecting tethered ligands to an oligonucleotide via a conjugate linker and/or a cleavable moiety.

"Cell-targeting moiety" means a conjugate group or portion of a conjugate group that is capable of binding to a particular cell type or particular cell types.

"cEt" or "constrained ethyl" means a bicyclic furanosyl sugar moiety comprising a bridge connecting the 4'-carbon and the 2'-carbon, wherein the bridge has the formula: 4'-$CH(CH_3)$-O-2'.

"cEt nucleoside" means a nucleoside comprising a cEt modified sugar moiety.

"Chemical modification" in a compound describes the substitutions or changes through chemical reaction, of any of the units in the compound relative to the original state of such unit. "Modified nucleoside" means a nucleoside having, independently, a modified sugar moiety and/or modified nucleobase. "Modified oligonucleotide" means an oligonucleotide comprising at least one modified internucleoside linkage, a modified sugar, and/or a modified nucleobase.

"Chemically distinct region" refers to a region of a compound that is in some way chemically different than another region of the same compound. For example, a region having 2'-O-methoxyethyl nucleotides is chemically distinct from a region having nucleotides without 2'-O-methoxyethyl modifications.

"Chimeric antisense compounds" means antisense compounds that have at least 2 chemically distinct regions, each position having a plurality of subunits.

"Chirally enriched population" means a plurality of molecules of identical molecular formula, wherein the number or percentage of molecules within the population that contain a particular stereochemical configuration at a particular chiral center is greater than the number or percentage of molecules expected to contain the same particular stereochemical configuration at the same particular chiral center within the population if the particular chiral center were stereorandom. Chirally enriched populations of molecules having multiple chiral centers within each molecule may contain one or more stereorandom chiral centers. In certain embodiments, the molecules are modified oligonucleotides. In certain embodiments, the molecules are compounds comprising modified oligonucleotides.

"Cleavable bond" means any chemical bond capable of being split. In certain embodiments, a cleavable bond is selected from among: an amide, a polyamide, an ester, an ether, one or both esters of a phosphodiester, a phosphate ester, a carbamate, a di-sulfide, or a peptide.

"Cleavable moiety" means a bond or group of atoms that is cleaved under physiological conditions, for example, inside a cell, an animal, or a human.

"Complementary" in reference to an oligonucleotide means the nucleobase sequence of such oligonucleotide or one or more regions thereof matches the nucleobase sequence of another oligonucleotide or nucleic acid or one or more regions thereof when the two nucleobase sequences are aligned in opposing directions. Nucleobase matches or complementary nucleobases, as described herein, are limited to the following pairs: adenine (A) and thymine (T), adenine (A) and uracil (U), cytosine (C) and guanine (G), and 5-methyl cytosine (^{m}C) and guanine (G) unless otherwise specified. Complementary oligonucleotides and/or nucleic acids need not have nucleobase complementarity at each nucleoside and may include one or more nucleobase mismatches. By contrast, "fully complementary" or "100% complementary" in reference to oligonucleotides means that such oligonucleotides have nucleobase matches at each nucleoside without any nucleobase mismatches.

"Conjugate group" means a group of atoms that is attached to an oligonucleotide. Conjugate groups include a conjugate moiety and a conjugate linker that attaches the conjugate moiety to the oligonucleotide.

"Conjugate linker" means a group of atoms comprising at least one bond that connects a conjugate moiety to an oligonucleotide.

"Conjugate moiety" means a group of atoms that is attached to an oligonucleotide via a conjugate linker.

"Contiguous" in the context of an oligonucleotide refers to nucleosides, nucleobases, sugar moieties, or internucleoside linkages that are immediately adjacent to each other. For example, "contiguous nucleobases" means nucleobases that are immediately adjacent to each other in a sequence.

"Designing" or "Designed to" refer to the process of designing a compound that specifically hybridizes with a selected nucleic acid molecule.

"Diluent" means an ingredient in a composition that lacks pharmacological activity, but is pharmaceutically necessary or desirable. For example, the diluent in an injected composition can be a liquid, e.g. saline solution.

"Differently modified" means chemical modifications or chemical substituents that are different from one another, including absence of modifications. Thus, for example, a MOE nucleoside and an unmodified DNA nucleoside are "differently modified," even though the DNA nucleoside is unmodified. Likewise, DNA and RNA are "differently modified," even though both are naturally-occurring unmodified nucleosides. Nucleosides that are the same but for comprising different nucleobases are not differently modified. For example, a nucleoside comprising a 2'-OMe modified sugar and an unmodified adenine nucleobase and a nucleoside comprising a 2'-OMe modified sugar and an unmodified thymine nucleobase are not differently modified.

"Dose" means a specified quantity of a compound or pharmaceutical agent provided in a single administration, or in a specified time period. In certain embodiments, a dose may be administered in two or more boluses, tablets, or injections. For example, in certain embodiments, where subcutaneous administration is desired, the desired dose may require a volume not easily accommodated by a single injection. In such embodiments, two or more injections may be used to achieve the desired dose. In certain embodiments, a dose may be administered in two or more injections to minimize injection site reaction in an individual. In other embodiments, the compound or pharmaceutical agent is administered by infusion over an extended period of time or continuously. Doses may be stated as the amount of pharmaceutical agent per hour, day, week or month.

"Dosing regimen" is a combination of doses designed to achieve one or more desired effects.

"Double-stranded antisense compound" means an antisense compound comprising two oligomeric compounds that are complementary to each other and form a duplex, and wherein one of the two said oligomeric compounds comprises an oligonucleotide.

"Effective amount" means the amount of compound sufficient to effectuate a desired physiological outcome in an individual in need of the compound. The effective amount may vary among individuals depending on the health and physical condition of the individual to be treated, the taxonomic group of the individuals to be treated, the formulation of the composition, assessment of the individual's medical condition, and other relevant factors.

"Efficacy" means the ability to produce a desired effect.

"Expression" includes all the functions by which a gene's coded information is converted into structures present and operating in a cell. Such structures include, but are not limited to, the products of transcription and translation.

"Gapmer" means an oligonucleotide comprising an internal region having a plurality of nucleosides that support RNase H cleavage positioned between external regions having one or more nucleosides, wherein the nucleosides comprising the internal region are chemically distinct from the nucleoside or nucleosides comprising the external regions. The internal region may be referred to as the "gap" and the external regions may be referred to as the "wings."

"Hybridization" means the annealing of oligonucleotides and/or nucleic acids. While not limited to a particular mechanism, the most common mechanism of hybridization involves hydrogen bonding, which may be Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding, between complementary nucleobases. In certain embodiments, complementary nucleic acid molecules include, but are not limited to, an antisense compound and a nucleic acid target. In certain embodiments, complementary nucleic acid molecules include, but are not limited to, an oligonucleotide and a nucleic acid target.

"Immediately adjacent" means there are no intervening elements between the immediately adjacent elements of the same kind (e.g. no intervening nucleobases between the immediately adjacent nucleobases).

"Immune checkpoint inhibitor" means an agent that inhibits the expression or activity of a protein that inhibits an immune response. In one embodiment, an immune checkpoint inhibitor is an agent that inhibits the CTLA-4 or PD-1 pathways. Particular checkpoint inhibitors include antibodies that inhibit PD-1, PD-L1 or CTLA-4.

"Immunomodulatory agent" means an agent that enhances an immune response (e.g., anti-tumor immune response). Exemplary immunomodulatory agents of the present disclosure include antibodies, such as an anti-CTLA-4 antibody, an anti-PD-L1 antibody, an anti-PD-1 antibody and antigenic fragments of any of these, and OX40 agonists, including proteins, such as OX40 ligand fusion protein, OX40 antibody, or fragments thereof. In one embodiment, the immunomodulatory agent is an immune checkpoint inhibitor.

"Individual" means a human or non-human animal selected for treatment or therapy.

"Inhibiting the expression or activity" refers to a reduction or blockade of the expression or activity relative to the expression of activity in an untreated or control sample and does not necessarily indicate a total elimination of expression or activity.

"Internucleoside linkage" means a group or bond that forms a covalent linkage between adjacent nucleosides in an oligonucleotide. "Modified internucleoside linkage" means any internucleoside linkage other

than a naturally occurring, phosphate internucleoside linkage. Non-phosphate linkages are referred to herein as modified internucleoside linkages.

"Lengthened oligonucleotides" are those that have one or more additional nucleosides relative to an oligonucleotide disclosed herein, e.g. a parent oligonucleotide.

"Linked nucleosides" means adjacent nucleosides linked together by an internucleoside linkage.

"Linker-nucleoside" means a nucleoside that links an oligonucleotide to a conjugate moiety. Linker-nucleosides are located within the conjugate linker of a compound. Linker-nucleosides are not considered part of the oligonucleotide portion of a compound even if they are contiguous with the oligonucleotide.

"Mismatch" or "non-complementary" means a nucleobase of a first oligonucleotide that is not complementary to the corresponding nucleobase of a second oligonucleotide or target nucleic acid when the first and second oligonucleotides are aligned. For example, nucleobases including but not limited to a universal nucleobase, inosine, and hypoxanthine, are capable of hybridizing with at least one nucleobase but are still mismatched or non-complementary with respect to nucleobase to which it hybridized. As another example, a nucleobase of a first oligonucleotide that is not capable of hybridizing to the corresponding nucleobase of a second oligonucleotide or target nucleic acid when the first and second oligonucleotides are aligned is a mismatch or non-complementary nucleobase.

"Modulating" refers to changing or adjusting a feature in a cell, tissue, organ or organism. For example, modulating MALAT1 RNA can mean to increase or decrease the level of MALAT1 RNA and/or MALAT1 protein in a cell, tissue, organ or organism. A "modulator" effects the change in the cell, tissue, organ or organism. For example, a MALAT1 compound can be a modulator that decreases the amount of MALAT1 RNA and/or MALAT1 protein in a cell, tissue, organ or organism.

"MOE" means methoxyethyl.

"Monomer" refers to a single unit of an oligomer. Monomers include, but are not limited to, nucleosides and nucleotides.

"Motif" means the pattern of unmodified and/or modified sugar moieties, nucleobases, and/or internucleoside linkages, in an oligonucleotide.

"Natural" or "naturally occurring" means found in nature.

"Non-bicyclic modified sugar" or "non-bicyclic modified sugar moiety" means a modified sugar moiety that comprises a modification, such as a substituent, that does not form a bridge between two atoms of the sugar to form a second ring.

"Nucleic acid" refers to molecules composed of monomeric nucleotides. A nucleic acid includes, but is not limited to, ribonucleic acids (RNA), deoxyribonucleic acids (DNA), single-stranded nucleic acids, and double-stranded nucleic acids.

"Nucleobase" means a heterocyclic moiety capable of pairing with a base of another nucleic acid. As used herein a "naturally occurring nucleobase" is adenine (A), thymine (T), cytosine (C), uracil (U), and guanine (G). A "modified nucleobase" is a naturally occurring nucleobase that is chemically modified. A "universal base" or "universal nucleobase" is a nucleobase other than a naturally occurring nucleobase and modified nucleobase, and is capable of pairing with any nucleobase.

"Nucleobase sequence" means the order of contiguous nucleobases in a nucleic acid or oligonucleotide independent of any sugar or internucleoside linkage.

"Nucleoside" means a compound comprising a nucleobase and a sugar moiety. The nucleobase and sugar moiety are each, independently, unmodified or modified. "Modified nucleoside" means a nucleoside comprising a modified nucleobase and/or a modified sugar moiety. Modified nucleosides include abasic nucleosides, which lack a nucleobase.

"Oligomeric compound" means a compound comprising a single oligonucleotide and optionally one or more additional features, such as a conjugate group or terminal group.

"Oligonucleotide" means a polymer of linked nucleosides each of which can be modified or unmodified, independent one from another. Unless otherwise indicated, oligonucleotides consist of 8-80 linked nucleosides. "Modified oligonucleotide" means an oligonucleotide, wherein at least one sugar, nucleobase, or internucleoside linkage is modified. "Unmodified oligonucleotide" means an oligonucleotide that does not comprise any sugar, nucleobase, or internucleoside modification.

"Parent oligonucleotide" means an oligonucleotide whose sequence is used as the basis of design for more oligonucleotides of similar sequence but with different lengths, motifs, and/or chemistries. The newly designed oligonucleotides may have the same or overlapping sequence as the parent oligonucleotide.

"Parenteral administration" means administration through injection or infusion. Parenteral administration includes subcutaneous administration, intravenous administration, intramuscular administration, intraarterial administration, intraperitoneal administration, or intracranial administration, e.g. intrathecal or intracerebroventricular administration.

"Pharmaceutically acceptable carrier or diluent" means any substance suitable for use in administering to an individual. For example, a pharmaceutically acceptable carrier can be a sterile aqueous solution, such as PBS or water-for-injection.

"Pharmaceutically acceptable salts" means physiologically and pharmaceutically acceptable salts of compounds, such as oligomeric compounds or oligonucleotides, i.e., salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto.

"Pharmaceutical agent" means a compound that provides a therapeutic benefit when administered to an individual.

"Pharmaceutical composition" means a mixture of substances suitable for administering to an individual. For example, a pharmaceutical composition may comprise one or more compounds or salt thereof and a sterile aqueous solution.

"Phosphorothioate linkage" means a modified phosphate linkage in which one of the non-bridging oxygen atoms is replaced with a sulfur atom. A phosphorothioate internucleoside linkage is a modified internucleoside linkage.

"Phosphorus moiety" means a group of atoms comprising a phosphorus atom. In certain embodiments, a phosphorus moiety comprises a mono-, di-, or tri-phosphate, or phosphorothioate.

"Portion" means a defined number of contiguous (i.e., linked) nucleobases of a nucleic acid. In certain embodiments, a portion is a defined number of contiguous nucleobases of a target nucleic acid. In certain embodiments, a portion is a defined number of contiguous nucleobases of an oligomeric compound.

"Prevent" refers to delaying or forestalling the onset, development or progression of a disease, disorder, or condition for a period of time from minutes to indefinitely.

"Prodrug" means a compound in a form outside the body which, when administered to an individual, is metabolized to another form within the body or cells thereof. In certain embodiments, the metabolized form is the active, or more active, form of the compound (e.g., drug). Typically conversion of a prodrug within the body is facilitated by the action of an enzyme(s) (e.g., endogenous or viral enzyme) or chemical(s) present in cells or tissues, and/or by physiologic conditions.

"Reduce" means to bring down to a smaller extent, size, amount, or number.

"RefSeq No." is a unique combination of letters and numbers assigned to a sequence to indicate the sequence is for a particular target transcript (e.g., target gene). Such sequence and information about the target gene (collectively, the gene record) can be found in a genetic sequence database. Genetic sequence databases include the NCBI Reference Sequence database, GenBank, the European Nucleotide Archive, and the DNA Data Bank of Japan (the latter three forming the International Nucleotide Sequence Database Collaboration or INSDC).

"Region" is defined as a portion of the target nucleic acid having at least one identifiable structure, function, or characteristic.

"RNAi compound" means an antisense compound that acts, at least in part, through RISC or Ago2, but not through RNase H, to modulate a target nucleic acid and/or protein encoded by a target nucleic acid. RNAi compounds include, but are not limited to double-stranded siRNA, single-stranded RNA (ssRNA), and microRNA, including microRNA mimics.

"Segments" are defined as smaller or sub-portions of regions within a nucleic acid.

"Side effects" means physiological disease and/or conditions attributable to a treatment other than the desired effects. In certain embodiments, side effects include injection site reactions, liver function test abnormalities, renal function abnormalities, liver toxicity, renal toxicity, central nervous system abnormalities, myopathies, and malaise. For example, increased aminotransferase levels in serum may indicate liver toxicity or liver function abnormality. For example, increased bilirubin may indicate liver toxicity or liver function abnormality.

"Single-stranded" in reference to a compound means the compound has only one oligonucleotide. "Self-complementary" means an oligonucleotide that at least partially hybridizes to itself. A compound consisting of one oligonucleotide, wherein the oligonucleotide of the compound is self-complementary, is a single-stranded compound. A single-stranded compound may be capable of binding to a complementary compound to form a duplex.

"Sites" are defined as unique nucleobase positions within a target nucleic acid.

"Specifically hybridizable" refers to an oligonucleotide having a sufficient degree of complementarity between the oligonucleotide and a target nucleic acid to induce a desired effect, while exhibiting minimal or no effects on non-target nucleic acids. In certain embodiments, specific hybridization occurs under physiological conditions.

"Specifically inhibit" with reference to a target nucleic acid means to reduce or block expression of the target nucleic acid while exhibiting fewer, minimal, or no effects on non-target nucleic acids. Reduction does not necessarily indicate a total elimination of the target nucleic acid's expression.

"Standard cell assay" means assay(s) described in the Examples and reasonable variations thereof.

"Standard in vivo experiment" means the procedure(s) described in the Example(s) and reasonable variations thereof.

"Stereorandom chiral center" in the context of a population of molecules of identical molecular formula means a chiral center having a random stereochemical configuration. For example, in a population of molecules comprising a stereorandom chiral center, the number of molecules having the (S) configuration of the stereorandom chiral center may be but is not necessarily the same as the number of molecules having the (R) configuration of the stereorandom chiral center. The stereochemical configuration of a chiral center is considered random when it is the result of a synthetic method that is not designed to control the stereochemical

configuration.. In certain embodiments, a stereorandom chiral center is a stereorandom phosphorothioate internucleoside linkage.

"Sugar moiety" means an unmodified sugar moiety or a modified sugar moiety. "Unmodified sugar moiety" or "unmodified sugar" means a 2'-OH(H) furanosyl moiety, as found in RNA (an "unmodified RNA sugar moiety"), or a 2'-H(H) moiety, as found in DNA (an "unmodified DNA sugar moiety"). Unmodified sugar moieties have one hydrogen at each of the 1', 3', and 4' positions, an oxygen at the 3' position, and two hydrogens at the 5' position. "Modified sugar moiety" or "modified sugar" means a modified furanosyl sugar moiety or a sugar surrogate. "Modified furanosyl sugar moiety" means a furanosyl sugar comprising a non-hydrogen substituent in place of at least one hydrogen of an unmodified sugar moiety. In certain embodiments, a modified furanosyl sugar moiety is a 2'-substituted sugar moiety. Such modified furanosyl sugar moieties include bicyclic sugars and non-bicyclic sugars.

"Sugar surrogate" means a modified sugar moiety having other than a furanosyl moiety that can link a nucleobase to another group, such as an internucleoside linkage, conjugate group, or terminal group in an oligonucleotide. Modified nucleosides comprising sugar surrogates can be incorporated into one or more positions within an oligonucleotide and such oligonucleotides are capable of hybridizing to complementary compounds or nucleic acids.

"Synergy" or "synergize" refers to an effect of a combination that is greater than additive of the effects of each component alone at the same doses.

"MALAT1" means any nucleic acid or protein of MALAT1. "MALAT1 nucleic acid" means any nucleic acid encoding MALAT1. For example, in certain embodiments, a MALAT1 nucleic acid includes a DNA sequence encoding MALAT1, an RNA sequence transcribed from DNA encoding MALAT1 (including genomic DNA comprising introns and exons), and an mRNA sequence encoding MALAT1. "MALAT1 mRNA" means an mRNA encoding a MALAT1 protein. The target may be referred to in either upper or lower case.

"MALAT1 specific inhibitor" refers to any agent capable of specifically inhibiting MALAT1 RNA and/or MALAT1 protein expression or activity at the molecular level. For example, MALAT1 specific inhibitors include nucleic acids (including antisense compounds), peptides, antibodies, small molecules, and other agents capable of inhibiting the expression of MALAT1 RNA and/or MALAT1 protein.

"Target gene" refers to a gene encoding a target.

"Targeting" means the specific hybridization of a compound to a target nucleic acid in order to induce a desired effect.

"Target nucleic acid," "target RNA," "target RNA transcript" and "nucleic acid target" all mean a nucleic acid capable of being targeted by compounds described herein.

"Target region" means a portion of a target nucleic acid to which one or more compounds is targeted.

"Target segment" means the sequence of nucleotides of a target nucleic acid to which a compound is targeted. "5' target site" refers to the 5'-most nucleotide of a target segment. "3' target site" refers to the 3'-most nucleotide of a target segment.

"Terminal group" means a chemical group or group of atoms that is covalently linked to a terminus of an oligonucleotide.

"Therapeutically effective amount" means an amount of a compound, pharmaceutical agent, or composition that provides a therapeutic benefit to an individual.

"Treat" refers to administering a compound or pharmaceutical composition to an animal in order to effect an alteration or improvement of a disease, disorder, or condition in the animal.

Certain Embodiments

Certain embodiments provide methods, compounds and compositions for inhibiting MALAT1 expression.

Certain embodiments provide compounds targeted to a MALAT1 nucleic acid. In certain embodiments, the MALAT1 nucleic acid has the sequence set forth in RefSeq or GENBANK Accession No. XR_001309.1 (SEQ ID NO: 1) (which is incorporated by reference in its entirety), or GENBANK Accession No. EF177381.1 (SEQ ID NO: 2824) (which is incorporated by reference in its entirety). In certain embodiments, the compound is an antisense compound or oligomeric compound. In certain embodiments, the compound is single-stranded. In certain embodiments, the compound is double-stranded.

Certain embodiments provide a compound comprising a modified oligonucleotide consisting of 8 to 80 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2-10 or 36-2813. In certain embodiments, the compound is an antisense compound or oligomeric compound. In certain embodiments, the compound is single-stranded. In certain embodiments, the compound is double-stranded. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides.

Certain embodiments provide a compound comprising a modified oligonucleotide consisting of 8 to 80 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2-10. In certain embodiments, the compound is an antisense compound or oligomeric compound. In certain embodiments, the compound is single-stranded. In certain embodiments, the compound is double-stranded. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides.

Certain embodiments provide a compound comprising a modified oligonucleotide consisting of 9 to 80 linked nucleosides and having a nucleobase sequence comprising at least 9 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2-10 or 36-2813. In certain embodiments, the compound is an

antisense compound or oligomeric compound. In certain embodiments, the compound is single-stranded. In certain embodiments, the compound is double-stranded. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides.

Certain embodiments provide a compound comprising a modified oligonucleotide consisting of 9 to 80 linked nucleosides and having a nucleobase sequence comprising at least 9 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2-10. In certain embodiments, the compound is an antisense compound or oligomeric compound. In certain embodiments, the compound is single-stranded. In certain embodiments, the compound is double-stranded. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides.

Certain embodiments provide a compound comprising a modified oligonucleotide consisting of 10 to 80 linked nucleosides and having a nucleobase sequence comprising at least 10 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2-10 or 36-2813. In certain embodiments, the compound is an antisense compound or oligomeric compound. In certain embodiments, the compound is single-stranded. In certain embodiments, the compound is double-stranded. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides.

Certain embodiments provide a compound comprising a modified oligonucleotide consisting of 10 to 80 linked nucleosides and having a nucleobase sequence comprising at least 10 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2-10. In certain embodiments, the compound is an antisense compound or oligomeric compound. In certain embodiments, the compound is single-stranded. In certain embodiments, the compound is double-stranded. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides.

Certain embodiments provide a compound comprising a modified oligonucleotide consisting of 11 to 80 linked nucleosides and having a nucleobase sequence comprising at least 11 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2-10 or 36-2813. In certain embodiments, the compound is an antisense compound or oligomeric compound. In certain embodiments, the compound is single-stranded. In certain embodiments, the compound is double-stranded. In certain embodiments, the modified oligonucleotide consists of 11 to 30 linked nucleosides.

Certain embodiments provide a compound comprising a modified oligonucleotide consisting of 11 to 80 linked nucleosides and having a nucleobase sequence comprising at least 11 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2-10. In certain embodiments, the compound is an antisense compound or oligomeric compound. In certain embodiments, the compound is single-stranded. In certain embodiments, the compound is double-stranded. In certain embodiments, the modified oligonucleotide consists of 11 to 30 linked nucleosides.

Certain embodiments provide a compound comprising a modified oligonucleotide consisting of 12 to 80 linked nucleosides and having a nucleobase sequence comprising at least 12 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2-10 or 36-2813. In certain embodiments, the compound is an

antisense compound or oligomeric compound. In certain embodiments, the compound is single-stranded. In certain embodiments, the compound is double-stranded. In certain embodiments, the modified oligonucleotide consists of 12 to 30 linked nucleosides.

Certain embodiments provide a compound comprising a modified oligonucleotide consisting of 12 to 80 linked nucleosides and having a nucleobase sequence comprising at least 12 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2-10. In certain embodiments, the compound is an antisense compound or oligomeric compound. In certain embodiments, the compound is single-stranded. In certain embodiments, the compound is double-stranded. In certain embodiments, the modified oligonucleotide consists of 12 to 30 linked nucleosides.

Certain embodiments provide a compound comprising a modified oligonucleotide consisting of 16 to 80 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 2-10 or 36-2813. In certain embodiments, the compound is an antisense compound or oligomeric compound. In certain embodiments, the compound is single-stranded. In certain embodiments, the compound is double-stranded. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides.

Certain embodiments provide a compound comprising a modified oligonucleotide consisting of 16 to 80 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 2-10. In certain embodiments, the compound is an antisense compound or oligomeric compound. In certain embodiments, the compound is single-stranded. In certain embodiments, the compound is double-stranded. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides.

Certain embodiments provide a compound comprising a modified oligonucleotide having a nucleobase sequence consisting of the nucleobase sequence of any one of SEQ ID NOs: 2-10 or 36-2813. In certain embodiments, the compound is an antisense compound or oligomeric compound. In certain embodiments, the compound is single-stranded. In certain embodiments, the compound is double-stranded.

Certain embodiments provide a compound comprising a modified oligonucleotide having a nucleobase sequence consisting of the nucleobase sequence of any one of SEQ ID NOs: 2-10. In certain embodiments, the compound is an antisense compound or oligomeric compound. In certain embodiments, the compound is single-stranded. In certain embodiments, the compound is double-stranded.

In certain embodiments, a compound comprises a modified oligonucleotide consisting of 8 to 80 linked nucleosides wherein the nucleobase sequence of the modified oligonucleotide comprises an at least 8, 9, 10, 11, 12, 13, 14, 15, or 16 contiguous nucleobase portion complementary to an equal length portion within nucleotides 1535-1550, 2034-2049, 2341-2356, 4821-4836, 4840-4855, 4931-4946, 5049-5064, 5494-5509, or 5495-5510 of SEQ ID NO: 1. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides.

In certain embodiments, a compound comprises a modified oligonucleotide consisting of 8 to 80 linked nucleosides wherein the nucleobase sequence of the modified oligonucleotide is complementary within

nucleotides 1535-1550, 2034-2049, 2341-2356, 4821-4836, 4840-4855, 4931-4946, 5049-5064, 5494-5509, or 5495-5510 of SEQ ID NO: 1. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides.

In certain embodiments, a compound comprises a modified oligonucleotide consisting of 8 to 80 linked nucleosides and having a nucleobase sequence comprising at least an 8, 9, 10, 11, 12, 13, 14, 15, or 16 contiguous nucleobase portion of the nucleobase sequence of any one of SEQ ID NOs: 2-10 or 36-2813. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides.

In certain embodiments, a compound comprises a modified oligonucleotide consisting of 8 to 80 linked nucleosides and having a nucleobase sequence comprising at least an 8, 9, 10, 11, 12, 13, 14, 15, or 16 contiguous nucleobase portion of the nucleobase sequence of any one of SEQ ID NOs: 2-10. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides.

In certain embodiments, a compound comprises a modified oligonucleotide consisting of 16 to 80 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 2-10 or 36-2813. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides.

In certain embodiments, a compound comprises a modified oligonucleotide consisting of 16 to 80 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 2-10. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides.

In certain embodiments, a compound comprises a modified oligonucleotide consisting of 16 linked nucleosides and having a nucleobase sequence consisting of the nucleobase sequence of any one of SEQ ID NOs: 2-10 or 36-2813.

In certain embodiments, a compound comprises a modified oligonucleotide consisting of 16 linked nucleosides and having a nucleobase sequence consisting of the nucleobase sequence of any one of SEQ ID NOs: 2-10.

In certain embodiments, at least one internucleoside linkage of any of the foregoing modified oligonucleotides is a modified internucleoside linkage, at least one sugar of any of the foregoing modified oligonucleotides is a modified sugar, and/or at least one nucleobase of any of the foregoing modified oligonucleotides is a modified nucleobase.

In certain embodiments, at least one nucleoside of any of the foregoing modified oligonucleotides comprises a modified sugar. In certain embodiments, the modified sugar comprises a 2'-O-methoxyethyl group. In certain embodiments, the modified sugar is a bicyclic sugar, such as a 4'-$CH(CH_3)$-O-2' group, a 4'-CH_2-O-2' group, or a 4'-$(CH_2)_2$-O-2'group.

In certain embodiments, at least one internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage, such as a phosphorothioate internucleoside linkage.

In certain embodiments, at least one nucleobase of any of the foregoing modified oligonucleotides is a modified nucleobase, such as 5-methylcytosine.

In certain embodiments, any of the foregoing modified oligonucleotides has:

a gap segment consisting of linked 2'-deoxynucleosides;

a 5' wing segment consisting of linked nucleosides; and

a 3' wing segment consisting of linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar. In certain embodiments, the modified oligonucleotide consists of 16 to 80 linked nucleosides and has a nucleobase sequence comprising the nucleobase sequence recited in any one of SEQ ID NOs: 2-10 or 36-2813. In certain embodiments, the modified oligonucleotide consists of 16 to 80 linked nucleosides and has a nucleobase sequence comprising the nucleobase sequence recited in any one of SEQ ID NOs: 2-10. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides and has a nucleobase sequence comprising the nucleobase sequence recited in any one of SEQ ID NOs: 2-10 or 36-2813. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides and has a nucleobase sequence comprising the nucleobase sequence recited in any one of SEQ ID NOs: 2-10. In certain embodiments, the modified oligonucleotide consists of 16 linked nucleosides and has a nucleobase sequence consisting of the nucleobase sequence recited in any one of SEQ ID NOs: 2-10 or 36-2813. In certain embodiments, the modified oligonucleotide consists of 16 linked nucleosides and has a nucleobase sequence consisting of the nucleobase sequence recited in any one of SEQ ID NOs: 2-10.

In certain embodiments, a compound comprises or consists of a modified oligonucleotide consisting of 16 to 80 linked nucleobases and having a nucleobase sequence comprising the nucleobase sequence recited in any one of SEQ ID NOs: 2-10 or 36-2813, wherein the modified oligonucleotide has:

a gap segment consisting of linked 2'-deoxynucleosides;

a 5' wing segment consisting of linked nucleosides; and

a 3' wing segment consisting of linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides. In certain embodiments, the modified oligonucleotide consists of 16 linked nucleosides.

In certain embodiments, a compound comprises or consists of a modified oligonucleotide consisting of 16 to 80 linked nucleobases and having a nucleobase sequence comprising the nucleobase sequence recited in any one of SEQ ID NOs: 2-10, wherein the modified oligonucleotide has:

a gap segment consisting of linked 2'-deoxynucleosides;

a 5' wing segment consisting of linked nucleosides; and

a 3' wing segment consisting of linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides. In certain embodiments, the modified oligonucleotide consists of 16 linked nucleosides.

In certain embodiments, a compound comprises or consists of a modified oligonucleotide consisting of 16 to 80 linked nucleobases and having a nucleobase sequence comprising the nucleobase sequence recited in any one of SEQ ID NOs: 36-2646 or 2664-2813, wherein the modified oligonucleotide has:

a gap segment consisting of ten linked 2'-deoxynucleosides;

a 5' wing segment consisting of three linked nucleosides; and

a 3' wing segment consisting of three linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment; wherein each nucleoside of each wing segment comprises a cEt nucleoside; wherein each internucleoside linkage is a phosphorothioate linkage; and wherein each cytosine is 5-methylcytosine. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides. In certain embodiments, the modified oligonucleotide consists of 16 linked nucleosides.

In certain embodiments, a compound comprises or consists of a modified oligonucleotide consisting of 16 to 80 linked nucleobases and having a nucleobase sequence comprising the nucleobase sequence recited in any one of SEQ ID NOs: 2-7, wherein the modified oligonucleotide has:

a gap segment consisting of ten linked 2'-deoxynucleosides;

a 5' wing segment consisting of three linked nucleosides; and

a 3' wing segment consisting of three linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment; wherein each nucleoside of each wing segment comprises a cEt nucleoside; wherein each internucleoside linkage is a phosphorothioate linkage; and wherein each cytosine is 5-methylcytosine. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides. In certain embodiments, the modified oligonucleotide consists of 16 linked nucleosides.

In certain embodiments, a compound comprises or consists of a modified oligonucleotide having a nucleobase sequence comprising the nucleobase sequence recited in any of SEQ ID NOs: 8-10; wherein the modified oligonucleotide comprises the sugar motif kkk-d-y-d(8)-kkk, wherein "k" indicates a cEt modified

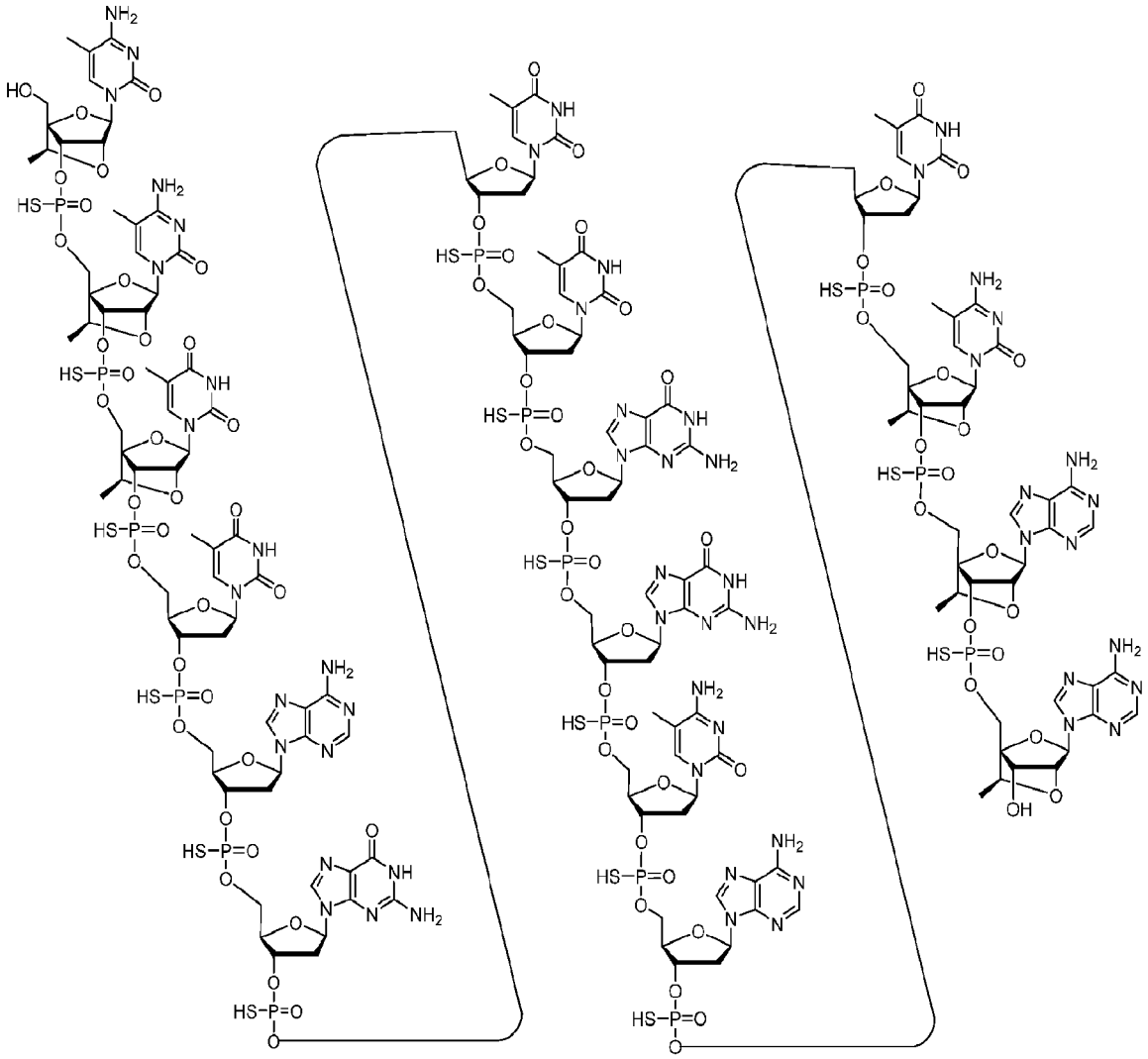
sugar moiety, "d" indicates an unmodified 2'-deoxyribosyl sugar moiety, and "y" indicates a 2'-O-methyl modified sugar moiety; wherein each internucleoside linkage is a phosphorothioate linkage; and wherein each cytosine is 5-methylcytosine. In certain embodiments, the modified oligonucleotide consisting of 16 to 30 linked nucleosides. In certain embodiments, the modified oligonucleotide consists of 16 linked nucleosides.

In certain embodiments, a compound comprises or consists of ION 1304884 having the nucleobase sequence and chemical motif: GksGksAksTdsUysAdsAdsTdsGdsTdsAdsGdsTdsGksTksAk (SEQ ID NO: 8), wherein "d" represents a 2'-deoxyribose sugar, "k" represents a cEt modified sugar, "y" represents a 2'-O-methyl modified sugar, "s" represents a phosphorothioate internucleoside linkage, and "mC" refers to 5-methylcytosine. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides. In certain embodiments, the modified oligonucleotide consists of 16 linked nucleosides.

In certain embodiments, a compound comprises or consists of ION 1304890 having the nucleobase sequence and chemical motif: GksGksTksTdsAysTdsAdsGdsmCdsTdsTdsGdsAdsmCksAksAk (SEQ ID NO: 9), wherein "d" represents a 2'-deoxyribose sugar, "k" represents a cEt modified sugar, "y" represents a 2'-O-methyl modified sugar, "s" represents a phosphorothioate internucleoside linkage, and "mC" refers to a 5-methylcytosine. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides. In certain embodiments, the modified oligonucleotide consists of 16 linked nucleosides.

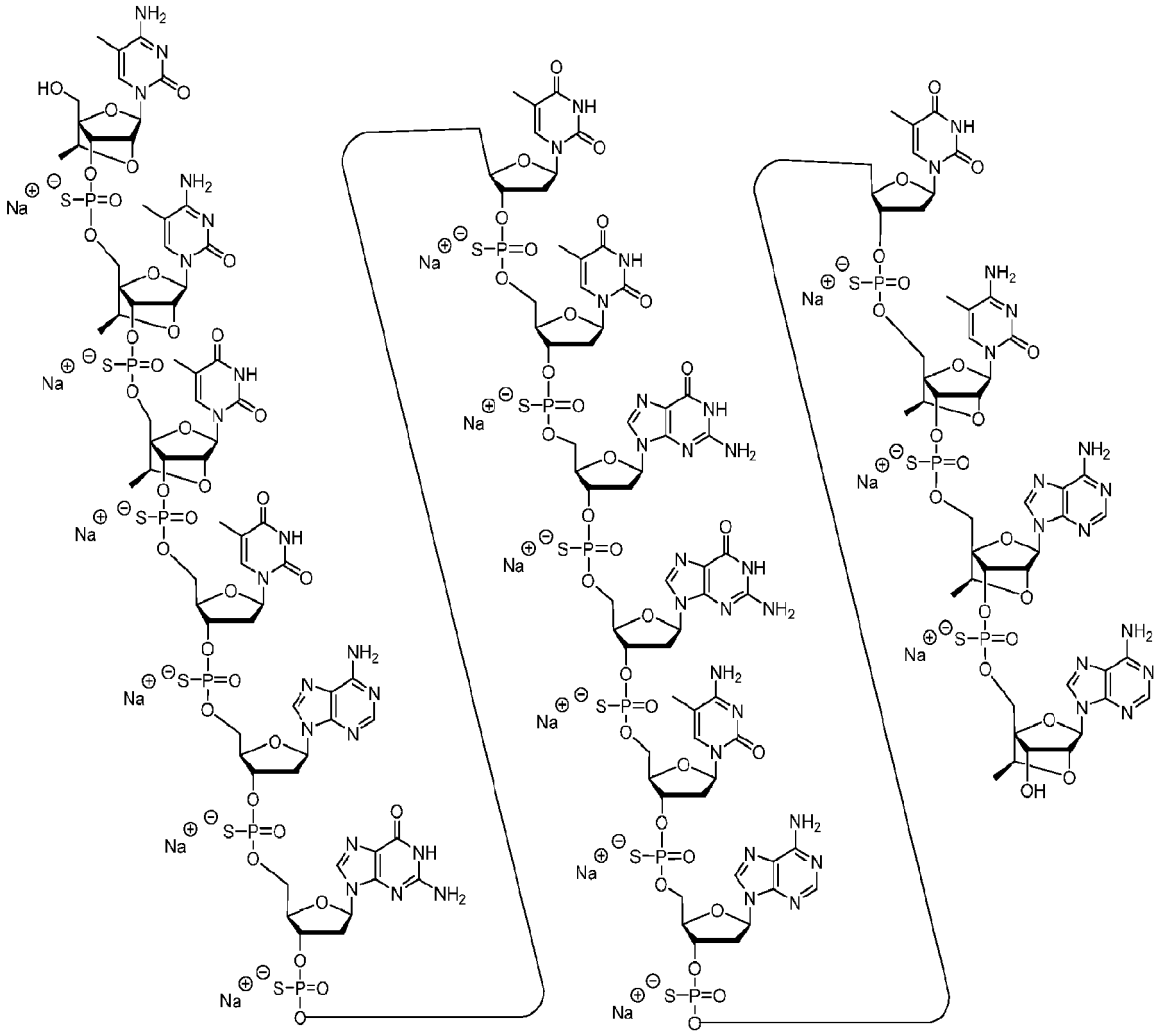
In certain embodiments, a compound comprises or consists of ION 1304906 having the nucleobase sequence and chemical motif: GksmCksAksGdsAysTdsAdsAdsTdsGdsTdsTdsmCdsTksmCksAk (SEQ ID NO: 10), wherein "d" represents a 2'-deoxyribose sugar, "k" represents a cEt modified sugar, "y" represents a 2'-O-methyl modified sugar, "s" represents a phosphorothioate internucleoside linkage, and "mC" refers to 5-methylcytosine. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides. In certain embodiments, the modified oligonucleotide consists of 16 linked nucleosides.

Certain embodiments provide a modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 6), or a salt thereof. In certain embodiments, the modified oligonucleotide is the sodium salt or potassium salt.

Certain embodiments provide a modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 6).

Under certain conditions, certain compounds disclosed herein act as acids. Although such compounds may be drawn or described in protonated (free acid) form, or ionized and in association with a cation (salt) form, aqueous solutions of such compounds exist in equilibrium among such forms. For example, a phosphate linkage of an oligonucleotide in aqueous solution exists in equilibrium among free acid, anion and salt forms. Unless otherwise indicated, compounds described herein are intended to include all such forms. Moreover, certain oligonucleotides have several such linkages, each of which is in equilibrium. Thus, oligonucleotides in solution exist in an ensemble of forms at multiple positions all at equilibrium. Unless otherwise indicated, an oligonucleotide described herein and the term "oligonucleotide" are intended to include all such forms. Drawn structures necessarily depict a single form. Nevertheless, unless otherwise indicated, such drawings are likewise intended to include corresponding forms. Herein, a structure depicting the free acid of a compound followed by the term "or a salt thereof" expressly includes all such forms that may be fully or partially protonated/de-protonated/in association with a cation. In certain instances, one or more specific cation is identified.

In any of the foregoing embodiments, the compound or oligonucleotide can be at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% complementary to a nucleic acid encoding MALAT1.

In any of the foregoing embodiments, the compound can be single-stranded. In certain embodiments, the compound comprises deoxyribonucleotides. In certain embodiments, the compound is double-stranded. In certain embodiments, the compound is double-stranded and comprises ribonucleotides. In any of the foregoing embodiments, the compound can be an antisense compound or oligomeric compound.

In any of the foregoing embodiments, the compound can consisting of 8 to 80, 10 to 30, 12 to 50, 13 to 30, 13 to 50, 14 to 30, 14 to 50, 15 to 30, 15 to 50, 16 to 30, 16 to 50, 17 to 30, 17 to 50, 18 to 22, 18 to 24, 18 to 30, 18 to 50, 19 to 22, 19 to 30, 19 to 50, or 20 to 30 linked nucleosides. In certain embodiments, the compound comprises or consists of an oligonucleotide.

In certain embodiments, compounds or compositions provided herein comprise a salt of the modified oligonucleotide. In certain embodiments, the salt is a sodium salt. In certain embodiments, the salt is a potassium salt.

In certain embodiments, the compounds or compositions as described herein are highly tolerable as demonstrated by having at least one of an increase an alanine transaminase (ALT) or aspartate transaminase (AST) value of no more than 4 fold, 3 fold, or 2 fold over saline treated animals or an increase in liver, spleen, or kidney weight of no more than 30%, 20%, 15%, 12%, 10%, 5%, or 2% compared to control treated animals. In certain embodiments, the compounds or compositions as described herein are highly tolerable as demonstrated by having no increase of ALT or AST over control treated animals. In certain embodiments, the compounds or compositions as described herein are highly tolerable as demonstrated by having no increase in liver, spleen, or kidney weight over control animals.

Certain embodiments provide a composition comprising the compound of any of the aforementioned embodiments or salt thereof and at least one of a pharmaceutically acceptable carrier or diluent. In certain embodiments, the composition has a viscosity less than about 40 centipoise (cP), less than about 30 centipose (cP), less than about 20 centipose (cP), less than about 15 centipose (cP), or less than about 10 centipose (cP). In certain embodiments, the composition having any of the aforementioned viscosities comprises a compound provided herein at a concentration of about 100 mg/mL, about 125 mg/mL, about 150 mg/mL, about 175 mg/mL, about 200 mg/mL, about 225 mg/mL, about 250 mg/mL, about 275 mg/mL, or about 300 mg/mL. In certain embodiments, the composition having any of the aforementioned viscosities and/or compound concentrations has a temperature of room temperature or about 20°C, about 21°C, about 22°C, about 23°C, about 24°C, about 25°C, about 26°C, about 27°C, about 28°C, about 29°C, or about 30°C.

Non-limiting numbered embodiments include:

E1. A compound comprising a modified oligonucleotide 8 to 80 linked nucleosides in length and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2-10.

E2. A compound comprising a modified oligonucleotide 9 to 80 linked nucleosides in length and having a nucleobase sequence comprising at least 9 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2-10.

E3. A compound comprising a modified oligonucleotide 10 to 80 linked nucleosides in length and having a nucleobase sequence comprising at least 10 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2-10.

E4. A compound comprising a modified oligonucleotide 11 to 80 linked nucleosides in length and having a nucleobase sequence comprising at least 11 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2-10.

E5. A compound comprising a modified oligonucleotide 12 to 80 linked nucleosides in length and having a nucleobase sequence comprising at least 12 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2-10.

E6. A compound comprising a modified oligonucleotide 16 to 80 linked nucleosides in length and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 2-10.

E7. A compound comprising a modified oligonucleotide 16 linked nucleosides in length and having a nucleobase sequence consisting of any one of SEQ ID NOs: 2-10.

E8. A compound comprising a modified oligonucleotide 8 to 80 linked nucleosides in length and complementary within nucleotides 1535-1550, 2034-2049, 2341-2356, 4821-4836, 4840-4855, 4931-4946, 5049-5064, 5494-5509, or 5495-5510 of SEQ ID NO: 1.

E9. The compound of any one of embodiments E1-E8, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage, at least one modified sugar, or at least one modified nucleobase.

E10. The compound of embodiment E9, wherein the modified internucleoside linkage is a phosphorothioate internucleoside linkage.

E11. The compound of embodiments E9 or E10, wherein the modified sugar is a bicyclic sugar.

E12. The compound of embodiment E11, wherein the bicyclic sugar is selected from the group consisting of: 4'-(CH_2)-O-2' (LNA); 4'-(CH_2)$_2$-O-2' (ENA); and 4'-CH(CH_3)-O-2' (cEt).

E13. The compound of embodiments E9 or E10, wherein the modified sugar is 2'-O-methoxyethyl.

E14. The compound of any one of embodiments E9-E13, wherein the modified nucleobase is a 5-methylcytosine.

E15. The compound of any one of embodiments E1-E14, wherein the modified oligonucleotide comprises:

a gap segment consisting of linked 2'-deoxynucleosides;

a 5' wing segment consisting of linked nucleosides; and

a 3' wing segment consisting of linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar.

E16. A compound comprising a modified oligonucleotide 16 to 80 linked nucleosides in length and having a nucleobase sequence comprising any one of SEQ ID NOs: 2-10, wherein the modified oligonucleotide comprises:

a gap segment consisting of linked 2'-deoxynucleosides;

a 5' wing segment consisting of linked nucleosides; and

a 3' wing segment consisting of linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar.

E17. A compound comprising a modified oligonucleotide 16-80 linked nucleobases in length having a nucleobase sequence comprising the sequence recited in any one of SEQ ID NOs: 2-7, wherein the modified oligonucleotide comprises:

a gap segment consisting of ten linked 2'-deoxynucleosides;

a 5' wing segment consisting of three linked nucleosides; and

a 3' wing segment consisting of three linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment; wherein each nucleoside of each wing segment comprises a cEt nucleoside; wherein each internucleoside linkage is a phosphorothioate linkage; and wherein each cytosine is a 5-methylcytosine.

E18. The compound of any one of embodiments E1-E17, wherein the oligonucleotide is at least 80%, 85%, 90%, 95% or 100% complementary to SEQ ID NO: 1.

E19. The compound of any one of embodiments E1-E18, wherein the compound is single-stranded.

E20. The compound of any one of embodiments E1-E18, wherein the compound is double-stranded.

E21. The compound of any one of embodiments E1-E20, wherein the compound comprises ribonucleotides.

E22. The compound of any one of embodiments E1-E20, wherein the compound comprises deoxyribonucleotides.

E23. The compound of any one of embodiments E1-E22, wherein the modified oligonucleotide consists of 16 to 30 linked nucleosides.

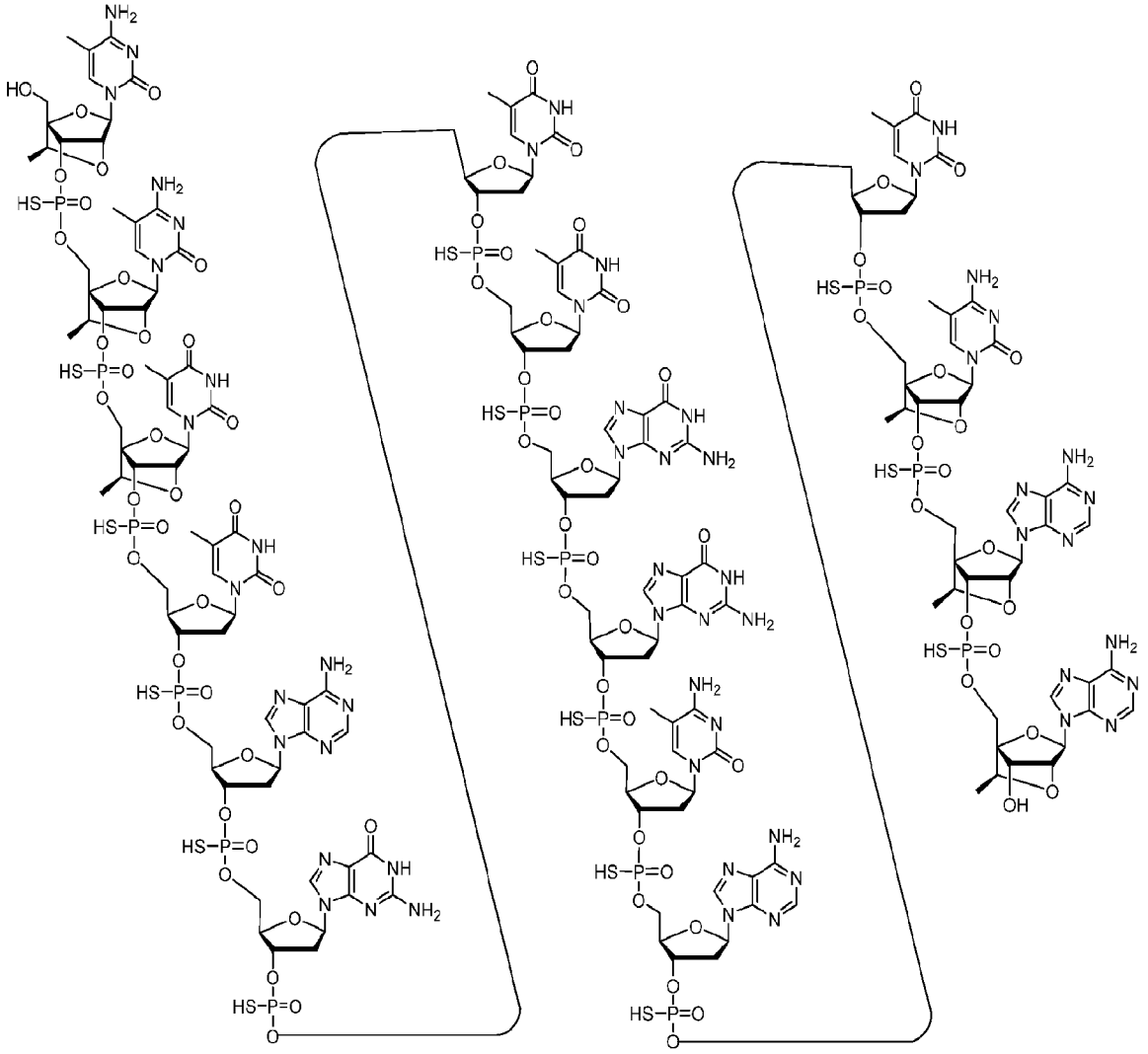
E24. The compound of any preceding embodiments, wherein the compound consists of the modified oligonucleotide.

E25. A compound consisting of a pharmaceutically acceptable salt of any of the compounds of embodiments E1-E24.

E26. The compound of embodiment 25, wherein the pharmaceutically acceptable salt is a sodium salt.

E27. The compound of embodiment 26, wherein the pharmaceutically acceptable salt is a potassium salt.

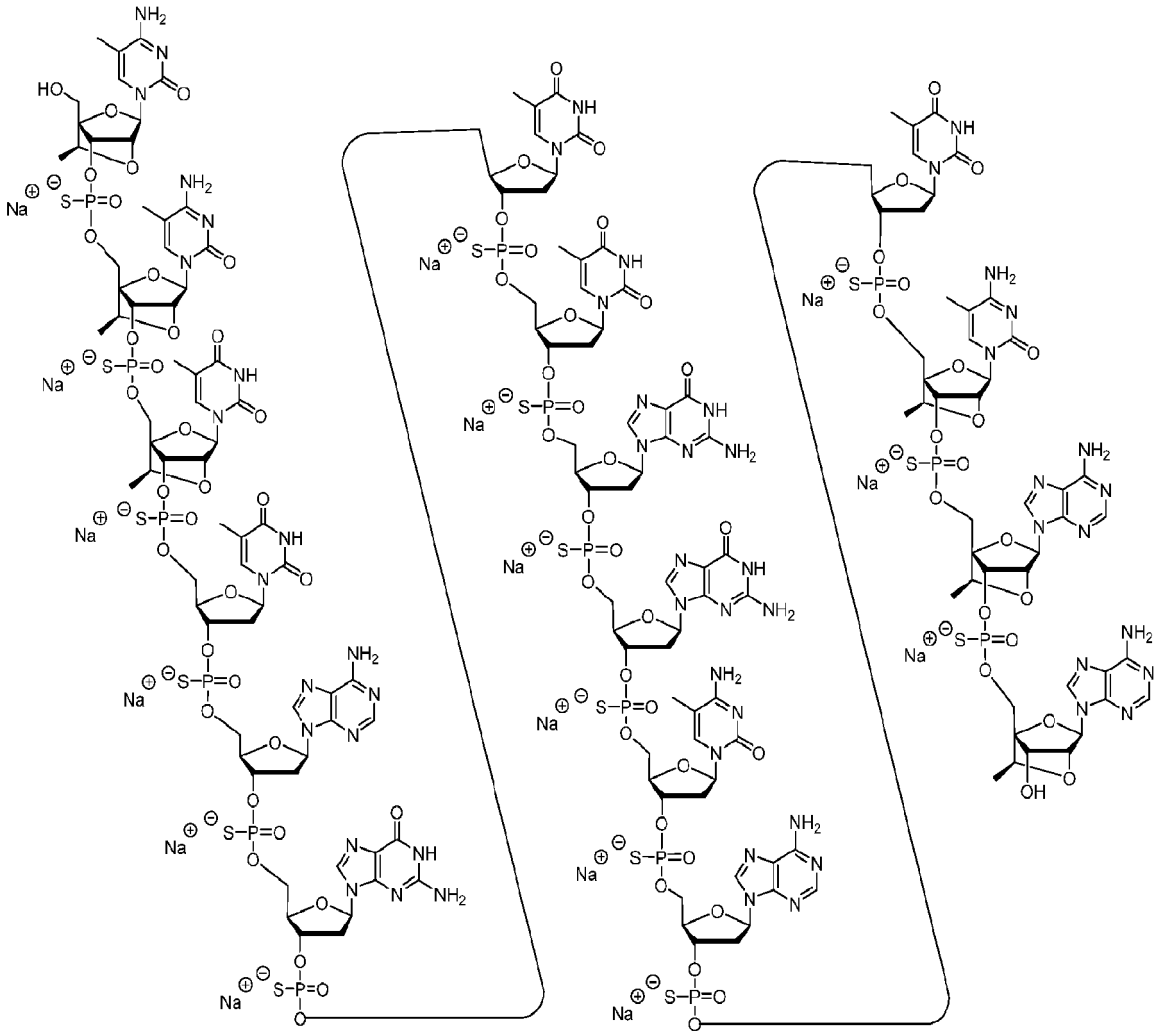
E28. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 6), or a salt thereof.

E29. The modified oligonucleotide of embodiment E28, wherein the modified oligonucleotide is the sodium salt or the potassium salt.

E30. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 6).

E31. A composition comprising the compound of any one of embodiments E1-E27 or the modified oligonucleotide of any one of embodiments E28-E30 and a pharmaceutically acceptable diluent or carrier.

E32. A composition comprising the compound of any one of embodiments E1-E27 or the modified oligonucleotide of any one of embodiments E28-E30 and water.

E33. A composition comprising the compound of any one of embodiments E1-E27 or the modified oligonucleotide of any one of embodiments E28-E30 for use in therapy.

E34. A method of treating or ameliorating cancer in an individual comprising administering to the individual a compound targeted to MALAT1, thereby treating or ameliorating the cancer.

E35. The method of embodiment E34, wherein the compound is an antisense compound targeted to MALAT1.

E36. The method of embodiments E34 or E35, wherein the cancer is breast cancer; inflammatory breast cancer; breast ductal carcinoma; breast lobular carcinoma; luminal A breast cancer; luminal B breast cancer; basal-like breast cancer; HER2 positive (HER2+) breast cancer; HER2 negative (HER2-) breast cancer;

Estrogen Receptor negative (ER-) breast cancer; Estrogen Receptor positive (ER+) breast cancer; Progesterone Receptor negative (PR-) breast cancer; Progesterone Receptor positive (PR+) breast cancer; ER positive (ER+) and PR positive (PR+) breast cancer; ER positive (ER+) and PR negative (PR-) breast cancer; ER negative (ER-) and PR positive (PR+) breast cancer; ER positive (ER+) and HER2 negative (HER2-) breast cancer; ER-, PR-, and HER2- triple negative breast cancer (ER-, PR-, HER2-; TNBC); hormone receptor negative breast cancer (ER- and PR-); ER+, PR+, and HER2+ triple positive breast cancer (ER+, PR+, HER2+; TPBC); hepatocellular carcinoma (HCC); head and neck squamous cell carcinoma (HNSCC); oral tongue squamous cell carcinoma (OTSCC); sarcomas (e.g. epitheloid, rhabdoid and synovial); esophageal cancer; gastric cancer; ovarian cancer; pancreatic cancer; lung cancer; non-small cell lung carcinoma (NSCLC); small-cell lung carcinoma (SCLC); squamous cell carcinoma (SCC); head and neck cancer; head and neck squamous cell carcinoma (HNSCC); gastrointestinal cancer; large intestinal cancer; small intestinal cancer; stomach cancer; colon cancer; colorectal cancer; bladder cancer; liver cancer; biliary tract cancer; urothelial cancer; endometrial cancer; cervical cancer; prostate cancer; mesothelioma; chordoma; renal cancer; renal cell carcinoma (RCC); brain cancer; neuroblastoma; glioblastoma; skin cancer; melanoma; basal cell carcinoma; merkel cell carcinoma; blood cancer; hematopoetic cancer; myeloma; multiple myeloma (MM); B cell malignancies; lymphoma; B cell lymphoma; Hodgkin lymphoma; T cell lymphoma; leukemia; or acute lymphocytic leukemia (ALL).

E37. The method of any of embodiments E34-E36, wherein administering the compound inhibits or reduces cancer cell proliferation, cancer cell migration, cancer cell branching morphogenesis, tumor progression, tumor growth, or metastasis.

E38. The method of any of embodiments E34-E37, wherein administering the compound increases or induces cancer cell differentiation, cancer cell adhesion, or tumor differentiation.

E39. The method of any of embodiments E34-E38, wherein administering the compound induces a cancer cell or tumor to have a cystic, ductular, or acinar phenotype or morphology.

E40. The method of any of embodiments E34-E39, wherein administering the compound induces a cancer cell or tumor to have a more differentiated phenotype or structure.

E41. The method of embodiment E40, wherein the more differentiated phenotype or structure comprises presence of secretory lipid droplets, increased desmosomal structures, polarized ductal structures, or increased levels of E-cadherin or casein.

E42. A method of inhibiting expression of MALAT1 in a cancer cell comprising contacting the cancer cell with a compound targeted to MALAT1, thereby inhibiting expression of MALAT1 in the cancer cell.

E43. The method of embodiment E42, wherein the cancer is breast cancer; inflammatory breast cancer; breast ductal carcinoma; breast lobular carcinoma; luminal A breast cancer; luminal B breast cancer; basal-like breast cancer; HER2 positive (HER2+) breast cancer; HER2 negative (HER2-) breast cancer; Estrogen Receptor negative (ER-) breast cancer; Estrogen Receptor positive (ER+) breast cancer; Progesterone

Receptor negative (PR-) breast cancer; Progesterone Receptor positive (PR+) breast cancer; ER positive (ER+) and PR positive (PR+) breast cancer; ER positive (ER+) and PR negative (PR-) breast cancer; ER negative (ER-) and PR positive (PR+) breast cancer; ER positive (ER+) and HER2 negative (HER2-) breast cancer; ER-, PR-, and HER2- triple negative breast cancer (ER-, PR-, HER2-; TNBC); hormone receptor negative breast cancer (ER- and PR-); ER+, PR+, and HER2+ triple positive breast cancer (ER+, PR+, HER2+; TPBC); hepatocellular carcinoma (HCC); head and neck squamous cell carcinoma (HNSCC); oral tongue squamous cell carcinoma (OTSCC); sarcomas (e.g. epitheloid, rhabdoid and synovial); esophageal cancer; gastric cancer; ovarian cancer; pancreatic cancer; lung cancer; non-small cell lung carcinoma (NSCLC); small-cell lung carcinoma (SCLC); squamous cell carcinoma (SCC); head and neck cancer; head and neck squamous cell carcinoma (HNSCC); gastrointestinal cancer; large intestinal cancer; small intestinal cancer; stomach cancer; colon cancer; colorectal cancer; bladder cancer; liver cancer; biliary tract cancer; urothelial cancer; endometrial cancer; cervical cancer; prostate cancer; mesothelioma; chordoma; renal cancer; renal cell carcinoma (RCC); brain cancer; neuroblastoma; glioblastoma; skin cancer; melanoma; basal cell carcinoma; merkel cell carcinoma; blood cancer; hematopoetic cancer; myeloma; multiple myeloma (MM); B cell malignancies; lymphoma; B cell lymphoma; Hodgkin lymphoma; T cell lymphoma; leukemia; or acute lymphocytic leukemia (ALL).

E44. A method of reducing or inhibiting cancer cell proliferation, cancer cell migration, cancer cell branching morphogenesis, tumor progression, tumor growth, or metastasis in an individual having cancer comprising administering a compound targeted to MALAT1 to the individual, thereby reducing or inhibiting cancer cell proliferation, cancer cell migration, cancer cell branching morphogenesis, tumor progression, tumor growth, or metastasis in the individual.

E45. A method of increasing or inducing cancer cell differentiation, cancer cell adhesion, or tumor differentiation in an individual having cancer comprising administering a compound targeted to MALAT1 to the individual, thereby increasing or inducing cancer cell differentiation, cancer cell adhesion, or tumor differentiation in the individual.

E46. A method of inducing a cancer cell or tumor to have a cystic, ductular, or acinar phenotype or morphology in an individual having cancer comprising administering a compound targeted to MALAT1 to the individual, thereby inducing the cancer cell or tumor to have a cystic, ductular, or acinar phenotype or morphology.

E47. A method of inducing a cancer cell or tumor to have a more differentiated phenotype or structure comprising administering a compound targeted to MALAT1 to the individual, thereby inducing the cancer cell or tumor to have a more differentiated phenotype or structure.

E48. The method of embodiment E47, wherein the more differentiated phenotype or structure comprises presence of secretory lipid droplets, increased desmosomal structures, polarized ductal structures, or increased levels of E-cadherin or casein.

E49. The method of any of embodiments E44-E48, wherein the individual has breast cancer; inflammatory breast cancer; breast ductal carcinoma; breast lobular carcinoma; luminal A breast cancer; luminal B breast cancer; basal-like breast cancer; HER2 positive (HER2+) breast cancer; HER2 negative (HER2-) breast cancer; Estrogen Receptor negative (ER-) breast cancer; Estrogen Receptor positive (ER+) breast cancer; Progesterone Receptor negative (PR-) breast cancer; Progesterone Receptor positive (PR+) breast cancer; ER positive (ER+) and PR positive (PR+) breast cancer; ER positive (ER+) and PR negative (PR-) breast cancer; ER negative (ER-) and PR positive (PR+) breast cancer; ER positive (ER+) and HER2 negative (HER2-) breast cancer; ER-, PR-, and HER2- triple negative breast cancer (ER-, PR-, HER2-; TNBC); hormone receptor negative breast cancer (ER- and PR-); ER+, PR+, and HER2+ triple positive breast cancer (ER+, PR+, HER2+; TPBC); hepatocellular carcinoma (HCC); head and neck squamous cell carcinoma (HNSCC); oral tongue squamous cell carcinoma (OTSCC); sarcomas (e.g. epitheloid, rhabdoid and synovial); esophageal cancer; gastric cancer; ovarian cancer; pancreatic cancer; lung cancer; non-small cell lung carcinoma (NSCLC); small-cell lung carcinoma (SCLC); squamous cell carcinoma (SCC); head and neck cancer; head and neck squamous cell carcinoma (HNSCC); gastrointestinal cancer; large intestinal cancer; small intestinal cancer; stomach cancer; colon cancer; colorectal cancer; bladder cancer; liver cancer; biliary tract cancer; urothelial cancer; endometrial cancer; cervical cancer; prostate cancer; mesothelioma; chordoma; renal cancer; renal cell carcinoma (RCC); brain cancer; neuroblastoma; glioblastoma; skin cancer; melanoma; basal cell carcinoma; merkel cell carcinoma; blood cancer; hematopoetic cancer; myeloma; multiple myeloma (MM); B cell malignancies; lymphoma; B cell lymphoma; Hodgkin lymphoma; T cell lymphoma; leukemia; or acute lymphocytic leukemia (ALL).

E50. The method of any one of embodiments E34-E49, wherein the compound is an antisense compound targeted to MALAT1.

E51. The method of any one of embodiments E34-E49, wherein the compound is the compound of any one of embodiments E1-E27, the modified oligonucleotide of any one of embodiments E28-E30, or the composition of embodiment E31 or E32.

E52. The method of any of embodiments E34-E51, wherein the compound is administered parenterally.

E53. Use of a compound targeted to MALAT1 for treating, preventing, or ameliorating a cancer associated with MALAT1.

E54. The use of embodiment E53, wherein the cancer is breast cancer; inflammatory breast cancer; breast ductal carcinoma; breast lobular carcinoma; luminal A breast cancer; luminal B breast cancer; basal-like breast cancer; HER2 positive (HER2+) breast cancer; HER2 negative (HER2-) breast cancer; Estrogen Receptor negative (ER-) breast cancer; Estrogen Receptor positive (ER+) breast cancer; Progesterone Receptor negative (PR-) breast cancer; Progesterone Receptor positive (PR+) breast cancer; ER positive (ER+) and PR positive (PR+) breast cancer; ER positive (ER+) and PR negative (PR-) breast cancer; ER negative (ER-) and PR positive (PR+) breast cancer; ER positive (ER+) and HER2 negative (HER2-) breast cancer; ER-, PR-, and

HER2- triple negative breast cancer (ER-, PR-, HER2-; TNBC); hormone receptor negative breast cancer (ER- and PR-); ER+, PR+, and HER2+ triple positive breast cancer (ER+, PR+, HER2+; TPBC); hepatocellular carcinoma (HCC); head and neck squamous cell carcinoma (HNSCC); oral tongue squamous cell carcinoma (OTSCC); sarcomas (e.g. epitheloid, rhabdoid and synovial); esophageal cancer; gastric cancer; ovarian cancer; pancreatic cancer; lung cancer; non-small cell lung carcinoma (NSCLC); small-cell lung carcinoma (SCLC); squamous cell carcinoma (SCC); head and neck cancer; head and neck squamous cell carcinoma (HNSCC); gastrointestinal cancer; large intestinal cancer; small intestinal cancer; stomach cancer; colon cancer; colorectal cancer; bladder cancer; liver cancer; biliary tract cancer; urothelial cancer; endometrial cancer; cervical cancer; prostate cancer; mesothelioma; chordoma; renal cancer; renal cell carcinoma (RCC); brain cancer; neuroblastoma; glioblastoma; skin cancer; melanoma; basal cell carcinoma; merkel cell carcinoma; blood cancer; hematopoetic cancer; myeloma; multiple myeloma (MM); B cell malignancies; lymphoma; B cell lymphoma; Hodgkin lymphoma; T cell lymphoma; leukemia; or acute lymphocytic leukemia (ALL).

E55. The use of embodiment E53 or E54, wherein the compound is an antisense compound targeted to MALAT1.

E56. The use of any one of embodiments E53-E55, wherein the compound is the compound of any one of embodiments E1-E27, the modified oligonucleotide of any one of embodiments E28-E30, or the composition of embodiment E31 or E32.

E57. Use of a compound targeted to MALAT1 in the manufacture of a medicament for treating or ameliorating a cancer associated with MALAT1.

E58. The use of embodiment E57, wherein the cancer is breast cancer; inflammatory breast cancer; breast ductal carcinoma; breast lobular carcinoma; luminal A breast cancer; luminal B breast cancer; basal-like breast cancer; HER2 positive (HER2+) breast cancer; HER2 negative (HER2-) breast cancer; Estrogen Receptor negative (ER-) breast cancer; Estrogen Receptor positive (ER+) breast cancer; Progesterone Receptor negative (PR-) breast cancer; Progesterone Receptor positive (PR+) breast cancer; ER positive (ER+) and PR positive (PR+) breast cancer; ER positive (ER+) and PR negative (PR-) breast cancer; ER negative (ER-) and PR positive (PR+) breast cancer; ER positive (ER+) and HER2 negative (HER2-) breast cancer; ER-, PR-, and HER2- triple negative breast cancer (ER-, PR-, HER2-; TNBC); hormone receptor negative breast cancer (ER- and PR-); ER+, PR+, and HER2+ triple positive breast cancer (ER+, PR+, HER2+; TPBC); hepatocellular carcinoma (HCC); head and neck squamous cell carcinoma (HNSCC); oral tongue squamous cell carcinoma (OTSCC); sarcomas (e.g. epitheloid, rhabdoid and synovial); esophageal cancer; gastric cancer; ovarian cancer; pancreatic cancer; lung cancer; non-small cell lung carcinoma (NSCLC); small-cell lung carcinoma (SCLC); squamous cell carcinoma (SCC); head and neck cancer; head and neck squamous cell carcinoma (HNSCC); gastrointestinal cancer; large intestinal cancer; small intestinal cancer; stomach cancer; colon cancer; colorectal cancer; bladder cancer; liver cancer; biliary tract cancer; urothelial cancer; endometrial cancer; cervical cancer; prostate cancer; mesothelioma; chordoma; renal cancer; renal cell carcinoma (RCC); brain cancer; neuroblastoma; glioblastoma; skin cancer; melanoma; basal cell carcinoma; merkel cell carcinoma; blood

cancer; hematopoetic cancer; myeloma; multiple myeloma (MM); B cell malignancies; lymphoma; B cell lymphoma; Hodgkin lymphoma; T cell lymphoma; leukemia; or acute lymphocytic leukemia (ALL).

E59. The use of embodiment E57 or E58, wherein the compound is an antisense compound targeted to MALAT1.

E60. The use of any one of embodiments E57-E59, wherein the compound is the compound of any one of embodiments E1-E27, the modified oligonucleotide of any one of embodiments E28-E30, or the composition of embodiment E31 or E32.

E61. Use of a compound targeted to MALAT1 in the preparation of a medicament for treating or ameliorating a cancer associated with MALAT1.

E62. The use of embodiment E61, wherein the cancer is breast cancer; inflammatory breast cancer; breast ductal carcinoma; breast lobular carcinoma; luminal A breast cancer; luminal B breast cancer; basal-like breast cancer; HER2 positive (HER2+) breast cancer; HER2 negative (HER2-) breast cancer; Estrogen Receptor negative (ER-) breast cancer; Estrogen Receptor positive (ER+) breast cancer; Progesterone Receptor negative (PR-) breast cancer; Progesterone Receptor positive (PR+) breast cancer; ER positive (ER+) and PR positive (PR+) breast cancer; ER positive (ER+) and PR negative (PR-) breast cancer; ER negative (ER-) and PR positive (PR+) breast cancer; ER positive (ER+) and HER2 negative (HER2-) breast cancer; ER-, PR-, and HER2- triple negative breast cancer (ER-, PR-, HER2-; TNBC); hormone receptor negative breast cancer (ER- and PR-); ER+, PR+, and HER2+ triple positive breast cancer (ER+, PR+, HER2+; TPBC); hepatocellular carcinoma (HCC); head and neck squamous cell carcinoma (HNSCC); oral tongue squamous cell carcinoma (OTSCC); sarcomas (e.g. epitheloid, rhabdoid and synovial); esophageal cancer; gastric cancer; ovarian cancer; pancreatic cancer; lung cancer; non-small cell lung carcinoma (NSCLC); small-cell lung carcinoma (SCLC); squamous cell carcinoma (SCC); head and neck cancer; head and neck squamous cell carcinoma (HNSCC); gastrointestinal cancer; large intestinal cancer; small intestinal cancer; stomach cancer; colon cancer; colorectal cancer; bladder cancer; liver cancer; biliary tract cancer; urothelial cancer; endometrial cancer; cervical cancer; prostate cancer; mesothelioma; chordoma; renal cancer; renal cell carcinoma (RCC); brain cancer; neuroblastoma; glioblastoma; skin cancer; melanoma; basal cell carcinoma; merkel cell carcinoma; blood cancer; hematopoetic cancer; myeloma; multiple myeloma (MM); B cell malignancies; lymphoma; B cell lymphoma; Hodgkin lymphoma; T cell lymphoma; leukemia; or acute lymphocytic leukemia (ALL).

E63. The use of embodiment E61 or E62, wherein the compound is an antisense compound targeted to MALAT1.

E64. The use of any one of embodiments E61-E63, wherein the compound is the compound of any one of embodiments E1-E27, the modified oligonucleotide of any one of embodiments E28-E30, or the composition of embodiment E31 or E32.

Certain Indications

Certain embodiments provided herein relate to methods of inhibiting MALAT1 expression, which can be useful for treating, preventing, or ameliorating a cancer associated with MALAT1 in an individual, by administration of a compound that targets MALAT1. In certain embodiments, the compound can be a MALAT1 specific inhibitor. In certain embodiments, the compound can be an antisense compound, oligomeric compound, or oligonucleotide targeted to MALAT1.

Examples of cancers associated with MALAT1 treatable, preventable, and/or ameliorable with the compounds and methods provided herein include breast cancer; inflammatory breast cancer; breast ductal carcinoma; breast lobular carcinoma; luminal A breast cancer; luminal B breast cancer; basal-like breast cancer; HER2 positive (HER2+) breast cancer; HER2 negative (HER2-) breast cancer; Estrogen Receptor negative (ER-) breast cancer; Estrogen Receptor positive (ER+) breast cancer; Progesterone Receptor negative (PR-) breast cancer; Progesterone Receptor positive (PR+) breast cancer; ER positive (ER+) and PR positive (PR+) breast cancer; ER positive (ER+) and PR negative (PR-) breast cancer; ER negative (ER-) and PR positive (PR+) breast cancer; ER positive (ER+) and HER2 negative (HER2-) breast cancer; ER-, PR-, and HER2- triple negative breast cancer (ER-, PR-, HER2-; TNBC); hormone receptor negative breast cancer (ER- and PR-); ER+, PR+, and HER2+ triple positive breast cancer (ER+, PR+, HER2+; TPBC); hepatocellular carcinoma (HCC); head and neck squamous cell carcinoma (HNSCC); oral tongue squamous cell carcinoma (OTSCC); sarcomas (e.g. epitheloid, rhabdoid and synovial); esophageal cancer; gastric cancer; ovarian cancer; pancreatic cancer; lung cancer; non-small cell lung carcinoma (NSCLC); small-cell lung carcinoma (SCLC); squamous cell carcinoma (SCC); head and neck cancer; head and neck squamous cell carcinoma (HNSCC); gastrointestinal cancer; large intestinal cancer; small intestinal cancer; stomach cancer; colon cancer; colorectal cancer; bladder cancer; liver cancer; biliary tract cancer; urothelial cancer; endometrial cancer; cervical cancer; prostate cancer; mesothelioma; chordoma; renal cancer; renal cell carcinoma (RCC); brain cancer; neuroblastoma; glioblastoma; skin cancer; melanoma; basal cell carcinoma; merkel cell carcinoma; blood cancer; hematopoetic cancer; myeloma; multiple myeloma (MM); B cell malignancies; lymphoma; B cell lymphoma; Hodgkin lymphoma; T cell lymphoma; leukemia; or acute lymphocytic leukemia (ALL).

In certain embodiments, the breast cancer has one or more of the following characteristics: Androgen Receptor positive, dependent on androgen for growth; Estrogen Receptor (ER) negative, independent of estrogen for growth; Progesterone Receptor (PR) negative, independent of progesterone for growth; or Her2/neu negative. In certain embodiments, the breast cancer is ER, PR, and HER2 triple negative (ER-, PR-, HER2-). In certain embodiments, the breast cancer is triple negative and AR positive (ER-, PR-, HER2-, AR+). In certain embodiments, the breast cancer is ER negative and AR positive (ER-, AR+). In certain embodiments, the breast cancer is ER positive and AR positive (ER+, AR+). In certain embodiments, the breast cancer is apocrine. Apocrine breast cancers are often "triple negative", meaning that the cells do not express ER, PR, or HER2 receptors, and usually, but not necessarily, AR positive. In certain embodiments, an

apocrine breast cancer is ER, PR, and HER2 triple negative and AR positive (ER-, PR-, HER2-, AR+). In certain embodiments, an apocrine breast cancer is ER negative and AR positive (ER-, AR+). In certain embodiments, an apocrine breast cancer originates from the sweat gland of the breast. In certain embodiments, an apocrine breast cancer is a ductal cancer or cancer cell of the breast. In certain embodiments, an apocrine breast cancer can have any one or more of the following features: a large amount of eosinophilic granular cytoplasm, well-defined margins, large vesicular nuclei, a nuclear to cytoplasmic ratio of about 1:2, and/or accumulations of secreted granules in the apical cytoplasm known as apical snouts. In certain embodiments, the breast cancer is an ER negative and AR positive (ER-, AR+) molecular apocrine breast cancer. In certain aspects, an ER negative and AR positive (ER-, AR+) molecular apocrine breast cancer can further be PR positive, PR negative, HER2 negative, or HER2 positive. In certain embodiments, the breast cancer is HER2 positive. In certain embodiments, the breast cancer is PR positive. In certain embodiments, the breast cancer is ER positive. Breast cancer can be identified as positive or negative with respect to hormone receptors, such as ER, PR, or HER2 by standard histological techniques. For example, in some embodiments histological breast cancer samples can be classified as "triple negative" (ER-, PR-, HER2-) when less than 1% of cells demonstrate nuclear staining for estrogen and progesterone receptors, and immunohistochemical staining for HER2 shows a 0, 1-fold, or a 2-fold positive score and a FISH ratio (HER2 gene signals to chromosome 17 signals) of less than 1.8 according to the relevant ASCO and CAP guidelines. (Meyer, P. et al., PLoS ONE 7(5): e38361 (2012)).

In certain embodiments, the B-cell lymphoma is a non-Hodgkin's B-cell lymphoma. Examples of non-Hodgkin's B-cell lymphoma of certain embodiments that can be treated with compounds provided herein include, but are not limited to, diffuse large B cell lymphoma (DLBCL), activated B-cell lymphoma (ABC-DLBCL), germinal center B-cell lymphoma (GCB DLBCL), follicular lymphoma, mucosa-associated lymphatic tissue lymphoma (MALT), small cell lymphocytic lymphoma, chronic lymphocytic leukemia, mantle cell lymphoma (MCL), Burkitt lymphoma, mediastinal large B cell lymphoma, Waldenström macroglobulinemia, nodal marginal zone B cell lymphoma (NMZL), splenic marginal zone lymphoma (SMZL), intravascular large B-cell lymphoma, primary effusion lymphoma, and lymphomatoid granulomatosis.

In certain embodiments, the T-cell lymphoma that can be treated with compounds provided herein include, but are not limited to, peripheral T-cell lymphoma, and anaplastic large cell lymphoma (ALCL).

In certain embodiments, the leukemia that can be treated with compounds provided herein includes, but is not limited to, acute lymphocytic leukemia (ALL).

In certain embodiments, a method of treating, preventing, or ameliorating a cancer associated with MALAT1 in an individual comprises administering to the individual a compound comprising a MALAT1

specific inhibitor, thereby treating, preventing, or ameliorating the cancer. In certain embodiments, the compound comprises an antisense compound targeted to MALAT1. In certain embodiments, the compound comprises an oligonucleotide targeted to MALAT1. In certain embodiments, a compound comprises a modified oligonucleotide consisting of 8 to 80 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2-10. In certain embodiments, a compound comprises a modified oligonucleotide consisting of 16 to 80 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 2-10. In certain embodiments, a compound comprises a modified oligonucleotide consisting of the nucleobase sequence of any one of SEQ ID NOs: 2-10. In certain embodiments, a compound comprises a modified oligonucleotide consisting of 8 to 80 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 36-2646 or 2664-2813. In certain embodiments, a compound comprises a modified oligonucleotide consisting of 16 to 80 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 36-2646 or 2664-2813. In certain embodiments, a compound comprises a modified oligonucleotide consisting of the nucleobase sequence of any one of SEQ ID NOs: SEQ ID NOs: 36-2646 or 2664-2813. In any of the foregoing embodiments, the modified oligonucleotide can consist of 10 to 30 linked nucleosides. In certain embodiments, the compound is ION 1157034, 1157111, 1157190, 1157929, 1158161, 1158162, 1304884, 1304890, or 1304906. In any of the foregoing embodiments, the compound can be single-stranded or double-stranded. In any of the foregoing embodiments, the compound can be an antisense compound or oligomeric compound. In certain embodiments, the compound is administered to the individual parenterally. In certain embodiments, administering the compound inhibits or reduces cancer cell proliferation, cancer cell migration, cancer cell branching morphogenesis, tumor progression, tumor growth, or metastasis. In certain embodiments, administering the compound increases or induces cancer cell differentiation, cancer cell adhesion, or tumor differentiation. In certain embodiments, administering the compound induces a breast cancer cell or breast tumor to have a cystic, ductular, or acinar phenotype or morphology. In certain embodiments, administering the compound induces a breast cancer cell or breast tumor to have a more differentiated phenotype or structure. In certain embodiments, the more differentiated phenotype or structure includes, but is not limited to, presence of secretory lipid droplets, increased desmosomal structures, polarized ductal structures, or increased levels of differentiation markers such as E-cadherin or milk proteins such as casein.

In certain embodiments, a method of treating or ameliorating caner comprises administering to the individual a compound comprising a MALAT1 specific inhibitor, thereby treating or ameliorating the cancer. In certain embodiments, the cancer is breast cancer; inflammatory breast cancer; breast ductal carcinoma; breast lobular carcinoma; luminal A breast cancer; luminal B breast cancer; basal-like breast cancer; HER2 positive (HER2+) breast cancer; HER2 negative (HER2-) breast cancer; Estrogen Receptor negative (ER-) breast cancer; Estrogen Receptor positive (ER+) breast cancer; Progesterone Receptor negative (PR-) breast cancer;

Progesterone Receptor positive (PR+) breast cancer; ER positive (ER+) and PR positive (PR+) breast cancer; ER positive (ER+) and PR negative (PR-) breast cancer; ER negative (ER-) and PR positive (PR+) breast cancer; ER positive (ER+) and HER2 negative (HER2-) breast cancer; ER-, PR-, and HER2- triple negative breast cancer (ER-, PR-, HER2-; TNBC); hormone receptor negative breast cancer (ER- and PR-); ER+, PR+, and HER2+ triple positive breast cancer (ER+, PR+, HER2+; TPBC); hepatocellular carcinoma (HCC); head and neck squamous cell carcinoma (HNSCC); oral tongue squamous cell carcinoma (OTSCC); sarcomas (e.g. epitheloid, rhabdoid and synovial); esophageal cancer; gastric cancer; ovarian cancer; pancreatic cancer; lung cancer; non-small cell lung carcinoma (NSCLC); small-cell lung carcinoma (SCLC); squamous cell carcinoma (SCC); head and neck cancer; head and neck squamous cell carcinoma (HNSCC); gastrointestinal cancer; large intestinal cancer; small intestinal cancer; stomach cancer; colon cancer; colorectal cancer; bladder cancer; liver cancer; biliary tract cancer; urothelial cancer; endometrial cancer; cervical cancer; prostate cancer; mesothelioma; chordoma; renal cancer; renal cell carcinoma (RCC); brain cancer; neuroblastoma; glioblastoma; skin cancer; melanoma; basal cell carcinoma; merkel cell carcinoma; blood cancer; hematopoetic cancer; myeloma; multiple myeloma (MM); B cell malignancies; lymphoma; B cell lymphoma; Hodgkin lymphoma; T cell lymphoma; leukemia; or acute lymphocytic leukemia (ALL). In certain embodiments, the compound comprises an antisense compound targeted to MALAT1. In certain embodiments, the compound comprises an oligonucleotide targeted to MALAT1. In certain embodiments, the compound comprises a modified oligonucleotide consisting of 8 to 80 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2-10. In certain embodiments, the compound comprises a modified oligonucleotide consisting of 16 to 80 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 2-10. In certain embodiments, the compound comprises a modified oligonucleotide consisting of the nucleobase sequence of any one of SEQ ID NOs: 2-10. In certain embodiments, a compound comprises a modified oligonucleotide consisting of 8 to 80 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 36-2646 or 2664-2813. In certain embodiments, a compound comprises a modified oligonucleotide consisting of 16 to 80 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 36-2646 or 2664-2813. In certain embodiments, a compound comprises a modified oligonucleotide consisting of the nucleobase sequence of any one of SEQ ID NOs: SEQ ID NOs: 36-2646 or 2664-2813. In any of the foregoing embodiments, the modified oligonucleotide can consist of 10 to 30 linked nucleosides. In certain embodiments, the compound is ION 1157034, 1157111, 1157190, 1157929, 1158161, 1158162, 1304884, 1304890, or 1304906. In any of the foregoing embodiments, the compound can be single-stranded or double-stranded. In any of the foregoing embodiments, the compound can be an antisense compound or oligomeric compound. In certain embodiments, the compound is administered to the individual parenterally. In certain embodiments, administering the compound inhibits or reduces cancer cell proliferation, cancer cell migration, cancer cell branching morphogenesis, tumor progression, tumor growth, or metastasis. In certain embodiments,

administering the compound increases or induces cancer cell differentiation, cancer cell adhesion, or tumor differentiation. In certain embodiments, administering the compound induces a breast cancer cell or breast tumor to have a cystic, ductular, or acinar phenotype or morphology. In certain embodiments, administering the compound induces a breast cancer cell or breast tumor to have a more differentiated phenotype or structure. In certain embodiments, the more differentiated phenotype or structure includes, but is not limited to, presence of secretory lipid droplets, increased desmosomal structures, polarized ductal structures, or increased levels of differentiation markers such as E-cadherin or milk proteins such as casein.

In certain embodiments, the individual is identified as having or at risk of having a cancer associated with MALAT1.

In certain embodiments, a method of inhibiting expression of MALAT1 in an individual having, or at risk of having, a cancer associated with MALAT1 comprises administering to the individual a compound comprising a MALAT1 specific inhibitor, thereby inhibiting expression of MALAT1 in the individual. In certain embodiments, administering the compound inhibits expression of MALAT1 in the breast. In certain embodiments, the individual has, or is at risk of having breast cancer; inflammatory breast cancer; breast ductal carcinoma; breast lobular carcinoma; luminal A breast cancer; luminal B breast cancer; basal-like breast cancer; HER2 positive (HER2+) breast cancer; HER2 negative (HER2-) breast cancer; Estrogen Receptor negative (ER-) breast cancer; Estrogen Receptor positive (ER+) breast cancer; Progesterone Receptor negative (PR-) breast cancer; Progesterone Receptor positive (PR+) breast cancer; ER positive (ER+) and PR positive (PR+) breast cancer; ER positive (ER+) and PR negative (PR-) breast cancer; ER negative (ER-) and PR positive (PR+) breast cancer; ER positive (ER+) and HER2 negative (HER2-) breast cancer; ER-, PR-, and HER2- triple negative breast cancer (ER-, PR-, HER2-; TNBC); hormone receptor negative breast cancer (ER- and PR-); ER+, PR+, and HER2+ triple positive breast cancer (ER+, PR+, HER2+; TPBC); hepatocellular carcinoma (HCC); head and neck squamous cell carcinoma (HNSCC); oral tongue squamous cell carcinoma (OTSCC); sarcomas (e.g. epitheloid, rhabdoid and synovial); esophageal cancer; gastric cancer; ovarian cancer; pancreatic cancer; lung cancer; non-small cell lung carcinoma (NSCLC); small-cell lung carcinoma (SCLC); squamous cell carcinoma (SCC); head and neck cancer; head and neck squamous cell carcinoma (HNSCC); gastrointestinal cancer; large intestinal cancer; small intestinal cancer; stomach cancer; colon cancer; colorectal cancer; bladder cancer; liver cancer; biliary tract cancer; urothelial cancer; endometrial cancer; cervical cancer; prostate cancer; mesothelioma; chordoma; renal cancer; renal cell carcinoma (RCC); brain cancer; neuroblastoma; glioblastoma; skin cancer; melanoma; basal cell carcinoma; merkel cell carcinoma; blood cancer; hematopoetic cancer; myeloma; multiple myeloma (MM); B cell malignancies; lymphoma; B cell lymphoma; Hodgkin lymphoma; T cell lymphoma; leukemia; or acute lymphocytic leukemia (ALL). In certain embodiments, the compound comprises an antisense compound targeted to MALAT1. In certain embodiments, the compound comprises an oligonucleotide targeted to MALAT1. In certain embodiments, the compound

comprises a modified oligonucleotide consisting of 8 to 80 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2-10. In certain embodiments, the compound comprises a modified oligonucleotide consisting of 16 to 80 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 2-10. In certain embodiments, the compound comprises a modified oligonucleotide consisting of the nucleobase sequence of any one of SEQ ID NOs: 2-10. In certain embodiments, a compound comprises a modified oligonucleotide consisting of 8 to 80 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 36-2646 or 2664-2813. In certain embodiments, a compound comprises a modified oligonucleotide consisting of 16 to 80 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 36-2646 or 2664-2813. In certain embodiments, a compound comprises a modified oligonucleotide consisting of the nucleobase sequence of any one of SEQ ID NOs: SEQ ID NOs: 36-2646 or 2664-2813. In any of the foregoing embodiments, the modified oligonucleotide can consist of 10 to 30 linked nucleosides. In certain embodiments, the compound is ION 1157034, 1157111, 1157190, 1157929, 1158161, 1158162, 1304884, 1304890, or 1304906. In any of the foregoing embodiments, the compound can be single-stranded or double-stranded. In any of the foregoing embodiments, the compound can be an antisense compound or oligomeric compound. In certain embodiments, the compound is administered to the individual parenterally. In certain embodiments, administering the compound inhibits or reduces cancer cell proliferation, cancer cell migration, cancer cell branching morphogenesis, tumor progression, tumor growth, or metastasis. In certain embodiments, administering the compound increases or induces cancer cell differentiation, cancer cell adhesion, or tumor differentiation. In certain embodiments, administering the compound induces a breast cancer cell or breast tumor to have a cystic, ductular, or acinar phenotype or morphology. In certain embodiments, administering the compound induces a breast cancer cell or breast tumor to have a more differentiated phenotype or structure. In certain embodiments, the more differentiated phenotype or structure includes, but is not limited to, presence of secretory lipid droplets, increased desmosomal structures, polarized ductal structures, or increased levels of differentiation markers such as E-cadherin or milk proteins such as casein.

In certain embodiments, the individual is identified as having or at risk of having a cancer associated with MALAT1.

In certain embodiments, a method of inhibiting expression of MALAT1 in a cell comprises contacting the cell with a compound comprising a MALAT1 specific inhibitor, thereby inhibiting expression of MALAT1 in the cell. In certain embodiments, the cell is a cancer cell. In certain embodiments, the cell is a breast cell. In certain embodiments, the cell is in the breast. In certain embodiments, the cell is in the breast of an individual who has, or is at risk of having cancer, such as breast cancer; inflammatory breast cancer; breast ductal carcinoma; breast lobular carcinoma; luminal A breast cancer; luminal B breast cancer; basal-like breast cancer;

HER2 positive (HER2+) breast cancer; HER2 negative (HER2-) breast cancer; Estrogen Receptor negative (ER-) breast cancer; Estrogen Receptor positive (ER+) breast cancer; Progesterone Receptor negative (PR-) breast cancer; Progesterone Receptor positive (PR+) breast cancer; ER positive (ER+) and PR positive (PR+) breast cancer; ER positive (ER+) and PR negative (PR-) breast cancer; ER negative (ER-) and PR positive (PR+) breast cancer; ER positive (ER+) and HER2 negative (HER2-) breast cancer; ER-, PR-, and HER2- triple negative breast cancer (ER-, PR-, HER2-; TNBC); hormone receptor negative breast cancer (ER- and PR-); ER+, PR+, and HER2+ triple positive breast cancer (ER+, PR+, HER2+; TPBC); hepatocellular carcinoma (HCC); head and neck squamous cell carcinoma (HNSCC); oral tongue squamous cell carcinoma (OTSCC); sarcomas (e.g. epitheloid, rhabdoid and synovial); esophageal cancer; gastric cancer; ovarian cancer; pancreatic cancer; lung cancer; non-small cell lung carcinoma (NSCLC); small-cell lung carcinoma (SCLC); squamous cell carcinoma (SCC); head and neck cancer; head and neck squamous cell carcinoma (HNSCC); gastrointestinal cancer; large intestinal cancer; small intestinal cancer; stomach cancer; colon cancer; colorectal cancer; bladder cancer; liver cancer; biliary tract cancer; urothelial cancer; endometrial cancer; cervical cancer; prostate cancer; mesothelioma; chordoma; renal cancer; renal cell carcinoma (RCC); brain cancer; neuroblastoma; glioblastoma; skin cancer; melanoma; basal cell carcinoma; merkel cell carcinoma; blood cancer; hematopoetic cancer; myeloma; multiple myeloma (MM); B cell malignancies; lymphoma; B cell lymphoma; Hodgkin lymphoma; T cell lymphoma; leukemia; or acute lymphocytic leukemia (ALL). In certain embodiments, the compound comprises an antisense compound targeted to MALAT1. In certain embodiments, the compound comprises an oligonucleotide targeted to MALAT1. In certain embodiments, the compound comprises a modified oligonucleotide consisting of 8 to 80 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2-10. In certain embodiments, the compound comprises a modified oligonucleotide consisting of 16 to 80 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 2-10. In certain embodiments, the compound comprises a modified oligonucleotide consisting of the nucleobase sequence of any one of SEQ ID NOs: 2-10. In certain embodiments, a compound comprises a modified oligonucleotide consisting of 8 to 80 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 36-2646 or 2664-2813. In certain embodiments, a compound comprises a modified oligonucleotide consisting of 16 to 80 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 36-2646 or 2664-2813. In certain embodiments, a compound comprises a modified oligonucleotide consisting of the nucleobase sequence of any one of SEQ ID NOs: SEQ ID NOs: 36-2646 or 2664-2813. In any of the foregoing embodiments, the modified oligonucleotide can consist of 10 to 30 linked nucleosides. In certain embodiments, the compound is ION 1157034, 1157111, 1157190, 1157929, 1158161, 1158162, 1304884, 1304890, or 1304906. In any of the foregoing embodiments, the compound can be single-stranded or double-stranded. In any of the foregoing embodiments, the compound can be an antisense compound or oligomeric compound.

In certain embodiments, a method of reducing or inhibiting cancer cell proliferation, cancer cell migration, cancer cell branching morphogenesis, tumor progression, tumor growth, or metastasis of an individual having, or at risk of having, a cancer associated with MALAT1 comprises administering to the individual a compound comprising a MALAT1 specific inhibitor, thereby reducing or inhibiting cancer cell proliferation, cancer cell migration, cancer cell branching morphogenesis, tumor progression, tumor growth, or metastasis in the individual. In certain embodiments, a method of increasing or inducing cancer cell differentiation, cancer cell adhesion, or tumor differentiation of an individual having, or at risk of having, a cancer associated with MALAT1 comprises administering to the individual a compound comprising a MALAT1 specific inhibitor, thereby increasing or inducing cancer cell differentiation, cancer cell adhesion, or tumor differentiation in the individual. In certain embodiments, administering the compound induces a breast cancer cell or breast tumor to have a cystic, ductular, or acinar phenotype or morphology. In certain embodiments, administering the compound induces a breast cancer cell or breast tumor to have a more differentiated phenotype or structure. In certain embodiments, the more differentiated phenotype or structure includes, but is not limited to, presence of secretory lipid droplets, increased desmosomal structures, polarized ductal structures, or increased levels of differentiation markers such as E-cadherin or milk proteins such as casein. In certain embodiments, the individual has, or is at risk of having, breast cancer; inflammatory breast cancer; breast ductal carcinoma; breast lobular carcinoma; luminal A breast cancer; luminal B breast cancer; basal-like breast cancer; HER2 positive (HER2+) breast cancer; HER2 negative (HER2-) breast cancer; Estrogen Receptor negative (ER-) breast cancer; Estrogen Receptor positive (ER+) breast cancer; Progesterone Receptor negative (PR-) breast cancer; Progesterone Receptor positive (PR+) breast cancer; ER positive (ER+) and PR positive (PR+) breast cancer; ER positive (ER+) and PR negative (PR-) breast cancer; ER negative (ER-) and PR positive (PR+) breast cancer; ER positive (ER+) and HER2 negative (HER2-) breast cancer; ER-, PR-, and HER2- triple negative breast cancer (ER-, PR-, HER2-; TNBC); hormone receptor negative breast cancer (ER- and PR-); ER+, PR+, and HER2+ triple positive breast cancer (ER+, PR+, HER2+; TPBC); hepatocellular carcinoma (HCC); head and neck squamous cell carcinoma (HNSCC); oral tongue squamous cell carcinoma (OTSCC); sarcomas (e.g. epitheloid, rhabdoid and synovial); esophageal cancer; gastric cancer; ovarian cancer; pancreatic cancer; lung cancer; non-small cell lung carcinoma (NSCLC); small-cell lung carcinoma (SCLC); squamous cell carcinoma (SCC); head and neck cancer; head and neck squamous cell carcinoma (HNSCC); gastrointestinal cancer; large intestinal cancer; small intestinal cancer; stomach cancer; colon cancer; colorectal cancer; bladder cancer; liver cancer; biliary tract cancer; urothelial cancer; endometrial cancer; cervical cancer; prostate cancer; mesothelioma; chordoma; renal cancer; renal cell carcinoma (RCC); brain cancer; neuroblastoma; glioblastoma; skin cancer; melanoma; basal cell carcinoma; merkel cell carcinoma; blood cancer; hematopoetic cancer; myeloma; multiple myeloma (MM); B cell malignancies; lymphoma; B cell lymphoma; Hodgkin lymphoma; T cell lymphoma; leukemia; or acute lymphocytic leukemia (ALL). In certain embodiments, the compound comprises an antisense compound targeted to MALAT1. In certain embodiments, the compound comprises an oligonucleotide targeted to MALAT1. In certain

embodiments, the compound comprises a modified oligonucleotide consisting of 8 to 80 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2-10. In certain embodiments, the compound comprises a modified oligonucleotide consisting of 16 to 80 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 2-10. In certain embodiments, the compound comprises a modified oligonucleotide consisting of the nucleobase sequence of any one of SEQ ID NOs: 2-10. In certain embodiments, a compound comprises a modified oligonucleotide consisting of 8 to 80 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 36-2646 or 2664-2813. In certain embodiments, a compound comprises a modified oligonucleotide consisting of 16 to 80 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 36-2646 or 2664-2813. In certain embodiments, a compound comprises a modified oligonucleotide consisting of the nucleobase sequence of any one of SEQ ID NOs: SEQ ID NOs: 36-2646 or 2664-2813. In any of the foregoing embodiments, the modified oligonucleotide can consist of 10 to 30 linked nucleosides. In certain embodiments, the compound is ION 1157034, 1157111, 1157190, 1157929, 1158161, 1158162, 1304884, 1304890, or 1304906. In any of the foregoing embodiments, the compound can be single-stranded or double-stranded. In any of the foregoing embodiments, the compound can be an antisense compound or oligomeric compound. In certain embodiments, the compound is administered to the individual parenterally. In certain embodiments, the individual is identified as having or at risk of having a cancer associated with MALAT1.

Certain embodiments are drawn to a compound comprising a MALAT1 specific inhibitor for use in treating cancer. In certain embodiments, the cancer is breast cancer; inflammatory breast cancer; breast ductal carcinoma; breast lobular carcinoma; luminal A breast cancer; luminal B breast cancer; basal-like breast cancer; HER2 positive (HER2+) breast cancer; HER2 negative (HER2-) breast cancer; Estrogen Receptor negative (ER-) breast cancer; Estrogen Receptor positive (ER+) breast cancer; Progesterone Receptor negative (PR-) breast cancer; Progesterone Receptor positive (PR+) breast cancer; ER positive (ER+) and PR positive (PR+) breast cancer; ER positive (ER+) and PR negative (PR-) breast cancer; ER negative (ER-) and PR positive (PR+) breast cancer; ER positive (ER+) and HER2 negative (HER2-) breast cancer; ER-, PR-, and HER2- triple negative breast cancer (ER-, PR-, HER2-; TNBC); hormone receptor negative breast cancer (ER- and PR-); ER+, PR+, and HER2+ triple positive breast cancer (ER+, PR+, HER2+; TPBC); hepatocellular carcinoma (HCC); head and neck squamous cell carcinoma (HNSCC); oral tongue squamous cell carcinoma (OTSCC); sarcomas (e.g. epitheloid, rhabdoid and synovial); esophageal cancer; gastric cancer; ovarian cancer; pancreatic cancer; lung cancer; non-small cell lung carcinoma (NSCLC); small-cell lung carcinoma (SCLC); squamous cell carcinoma (SCC); head and neck cancer; head and neck squamous cell carcinoma (HNSCC); gastrointestinal cancer; large intestinal cancer; small intestinal cancer; stomach cancer; colon cancer; colorectal cancer; bladder cancer; liver cancer; biliary tract cancer; urothelial cancer; endometrial cancer; cervical cancer;

prostate cancer; mesothelioma; chordoma; renal cancer; renal cell carcinoma (RCC); brain cancer; neuroblastoma; glioblastoma; skin cancer; melanoma; basal cell carcinoma; merkel cell carcinoma; blood cancer; hematopoetic cancer; myeloma; multiple myeloma (MM); B cell malignancies; lymphoma; B cell lymphoma; Hodgkin lymphoma; T cell lymphoma; leukemia; or acute lymphocytic leukemia (ALL). In certain embodiments, the compound comprises an antisense compound targeted to MALAT1. In certain embodiments, the compound comprises an oligonucleotide targeted to MALAT1. In certain embodiments, the compound comprises a modified oligonucleotide consisting of 8 to 80 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2-10. In certain embodiments, the compound comprises a modified oligonucleotide consisting of 16 to 80 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 2-10. In certain embodiments, the compound comprises a modified oligonucleotide consisting of the nucleobase sequence of any one of SEQ ID NOs: 2-10. In certain embodiments, a compound comprises a modified oligonucleotide consisting of 8 to 80 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 36-2646 or 2664-2813. In certain embodiments, a compound comprises a modified oligonucleotide consisting of 16 to 80 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 36-2646 or 2664-2813. In certain embodiments, a compound comprises a modified oligonucleotide consisting of the nucleobase sequence of any one of SEQ ID NOs: SEQ ID NOs: 36-2646 or 2664-2813. In any of the foregoing embodiments, the modified oligonucleotide can consist of 10 to 30 linked nucleosides. In certain embodiments, the compound is ION 1157034, 1157111, 1157190, 1157929, 1158161, 1158162, 1304884, 1304890, or 1304906. In any of the foregoing embodiments, the compound can be single-stranded or double-stranded. In any of the foregoing embodiments, the compound can be an antisense compound or oligomeric compound.

Certain embodiments are drawn to a compound comprising a MALAT1 specific inhibitor for use in reducing or inhibiting cancer cell proliferation, cancer cell migration, cancer cell branching morphogenesis, tumor progression, tumor growth, or metastasis in an individual having cancer. Certain embodiments are drawn to a compound comprising a MALAT1 specific inhibitor for use in increasing or inducing cancer cell differentiation, cancer cell adhesion, or tumor differentiation in an individual having cancer. In certain embodiments, administering the compound induces a breast cancer cell or breast tumor to have a cystic, ductular, or acinar phenotype or morphology. In certain embodiments, administering the compound induces a breast cancer cell or breast tumor to have a more differentiated phenotype or structure. In certain embodiments, the more differentiated phenotype or structure includes, but is not limited to, presence of secretory lipid droplets, increased desmosomal structures, polarized ductal structures, or increased levels of differentiation markers such as E-cadherin or milk proteins such as casein. In certain embodiments, the cancer is breast cancer; inflammatory breast cancer; breast ductal carcinoma; breast lobular carcinoma; luminal A breast cancer;

luminal B breast cancer; basal-like breast cancer; HER2 positive (HER2+) breast cancer; HER2 negative (HER2-) breast cancer; Estrogen Receptor negative (ER-) breast cancer; Estrogen Receptor positive (ER+) breast cancer; Progesterone Receptor negative (PR-) breast cancer; Progesterone Receptor positive (PR+) breast cancer; ER positive (ER+) and PR positive (PR+) breast cancer; ER positive (ER+) and PR negative (PR-) breast cancer; ER negative (ER-) and PR positive (PR+) breast cancer; ER positive (ER+) and HER2 negative (HER2-) breast cancer; ER-, PR-, and HER2- triple negative breast cancer (ER-, PR-, HER2-; TNBC); hormone receptor negative breast cancer (ER- and PR-); ER+, PR+, and HER2+ triple positive breast cancer (ER+, PR+, HER2+; TPBC); hepatocellular carcinoma (HCC); head and neck squamous cell carcinoma (HNSCC); oral tongue squamous cell carcinoma (OTSCC); sarcomas (e.g. epitheloid, rhabdoid and synovial); esophageal cancer; gastric cancer; ovarian cancer; pancreatic cancer; lung cancer; non-small cell lung carcinoma (NSCLC); small-cell lung carcinoma (SCLC); squamous cell carcinoma (SCC); head and neck cancer; head and neck squamous cell carcinoma (HNSCC); gastrointestinal cancer; large intestinal cancer; small intestinal cancer; stomach cancer; colon cancer; colorectal cancer; bladder cancer; liver cancer; biliary tract cancer; urothelial cancer; endometrial cancer; cervical cancer; prostate cancer; mesothelioma; chordoma; renal cancer; renal cell carcinoma (RCC); brain cancer; neuroblastoma; glioblastoma; skin cancer; melanoma; basal cell carcinoma; merkel cell carcinoma; blood cancer; hematopoetic cancer; myeloma; multiple myeloma (MM); B cell malignancies; lymphoma; B cell lymphoma; Hodgkin lymphoma; T cell lymphoma; leukemia; or acute lymphocytic leukemia (ALL). In certain embodiments, the compound comprises an antisense compound targeted to MALAT1. In certain embodiments, the compound comprises an oligonucleotide targeted to MALAT1. In certain embodiments, the compound comprises a modified oligonucleotide consisting of 8 to 80 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2-10. In certain embodiments, the compound comprises a modified oligonucleotide consisting of 16 to 80 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 2-10. In certain embodiments, the compound comprises a modified oligonucleotide consisting of the nucleobase sequence of any one of SEQ ID NOs: 2-10. In certain embodiments, a compound comprises a modified oligonucleotide consisting of 8 to 80 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 36-2646 or 2664-2813. In certain embodiments, a compound comprises a modified oligonucleotide consisting of 16 to 80 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 36-2646 or 2664-2813. In certain embodiments, a compound comprises a modified oligonucleotide consisting of the nucleobase sequence of any one of SEQ ID NOs: SEQ ID NOs: 36-2646 or 2664-2813. In any of the foregoing embodiments, the modified oligonucleotide can consist of 10 to 30 linked nucleosides. In certain embodiments, the compound is ION 1157034, 1157111, 1157190, 1157929, 1158161, 1158162, 1304884, 1304890, or 1304906. In any of the foregoing embodiments, the compound can be single-stranded or double-stranded. In any of the foregoing embodiments, the compound can be an antisense compound or oligomeric compound.

Certain embodiments are drawn to use of a compound comprising a MALAT1 specific inhibitor for the manufacture or preparation of a medicament for treating cancer. Certain embodiments are drawn to use of a compound comprising a MALAT1 specific inhibitor for the preparation of a medicament for treating a cancer associated with MALAT1. In certain embodiments, the cancer is breast cancer; inflammatory breast cancer; breast ductal carcinoma; breast lobular carcinoma; luminal A breast cancer; luminal B breast cancer; basal-like breast cancer; HER2 positive (HER2+) breast cancer; HER2 negative (HER2-) breast cancer; Estrogen Receptor negative (ER-) breast cancer; Estrogen Receptor positive (ER+) breast cancer; Progesterone Receptor negative (PR-) breast cancer; Progesterone Receptor positive (PR+) breast cancer; ER positive (ER+) and PR positive (PR+) breast cancer; ER positive (ER+) and PR negative (PR-) breast cancer; ER negative (ER-) and PR positive (PR+) breast cancer; ER positive (ER+) and HER2 negative (HER2-) breast cancer; ER-, PR-, and HER2- triple negative breast cancer (ER-, PR-, HER2-; TNBC); hormone receptor negative breast cancer (ER- and PR-); ER+, PR+, and HER2+ triple positive breast cancer (ER+, PR+, HER2+; TPBC); hepatocellular carcinoma (HCC); head and neck squamous cell carcinoma (HNSCC); oral tongue squamous cell carcinoma (OTSCC); sarcomas (e.g. epitheloid, rhabdoid and synovial); esophageal cancer; gastric cancer; ovarian cancer; pancreatic cancer; lung cancer; non-small cell lung carcinoma (NSCLC); small-cell lung carcinoma (SCLC); squamous cell carcinoma (SCC); head and neck cancer; head and neck squamous cell carcinoma (HNSCC); gastrointestinal cancer; large intestinal cancer; small intestinal cancer; stomach cancer; colon cancer; colorectal cancer; bladder cancer; liver cancer; biliary tract cancer; urothelial cancer; endometrial cancer; cervical cancer; prostate cancer; mesothelioma; chordoma; renal cancer; renal cell carcinoma (RCC); brain cancer; neuroblastoma; glioblastoma; skin cancer; melanoma; basal cell carcinoma; merkel cell carcinoma; blood cancer; hematopoetic cancer; myeloma; multiple myeloma (MM); B cell malignancies; lymphoma; B cell lymphoma; Hodgkin lymphoma; T cell lymphoma; leukemia; or acute lymphocytic leukemia (ALL). In certain embodiments, the compound comprises an antisense compound targeted to MALAT1. In certain embodiments, the compound comprises an oligonucleotide targeted to MALAT1. In certain embodiments, the compound comprises a modified oligonucleotide consisting of 8 to 80 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2-10. In certain embodiments, the compound comprises a modified oligonucleotide consisting of 16 to 80 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 2-10. In certain embodiments, the compound comprises a modified oligonucleotide consisting of the nucleobase sequence of any one of SEQ ID NOs: 2-10. In certain embodiments, a compound comprises a modified oligonucleotide consisting of 8 to 80 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 36-2646 or 2664-2813. In certain embodiments, a compound comprises a modified oligonucleotide consisting of 16 to 80 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 36-2646 or 2664-2813. In certain embodiments, a compound comprises a modified oligonucleotide consisting of the nucleobase sequence of any one of SEQ ID NOs: SEQ ID NOs: 36-2646 or 2664-2813. In any of the

foregoing embodiments, the modified oligonucleotide can consist of 10 to 30 linked nucleosides. In certain embodiments, the compound is ION 1157034, 1157111, 1157190, 1157929, 1158161, 1158162, 1304884, 1304890, or 1304906. In any of the foregoing embodiments, the compound can be single-stranded or double-stranded. In any of the foregoing embodiments, the compound can be an antisense compound or oligomeric compound.

Certain embodiments are drawn to use of a compound comprising a MALAT1 specific inhibitor for the manufacture or preparation of a medicament for reducing or inhibiting cancer cell proliferation, cancer cell migration, cancer cell branching morphogenesis, tumor progression, tumor growth, or metastasis in an individual having cancer. Certain embodiments are drawn to use of a compound comprising a MALAT1 specific inhibitor for the manufacture or preparation of a medicament for increasing or inducing cancer cell differentiation, cancer cell adhesion, or tumor differentiation in an individual having cancer. In certain embodiments, administering the compound induces a breast cancer cell or breast tumor to have a cystic, ductular, or acinar phenotype or morphology. In certain embodiments, administering the compound induces a breast cancer cell or breast tumor to have a more differentiated phenotype or structure. In certain embodiments, the more differentiated phenotype or structure includes, but is not limited to, presence of secretory lipid droplets, increased desmosomal structures, polarized ductal structures, or increased levels of differentiation markers such as E-cadherin or milk proteins such as casein. In certain embodiments, the cancer is breast cancer; inflammatory breast cancer; breast ductal carcinoma; breast lobular carcinoma; luminal A breast cancer; luminal B breast cancer; basal-like breast cancer; HER2 positive (HER2+) breast cancer; HER2 negative (HER2-) breast cancer; Estrogen Receptor negative (ER-) breast cancer; Estrogen Receptor positive (ER+) breast cancer; Progesterone Receptor negative (PR-) breast cancer; Progesterone Receptor positive (PR+) breast cancer; ER positive (ER+) and PR positive (PR+) breast cancer; ER positive (ER+) and PR negative (PR-) breast cancer; ER negative (ER-) and PR positive (PR+) breast cancer; ER positive (ER+) and HER2 negative (HER2-) breast cancer; ER-, PR-, and HER2- triple negative breast cancer (ER-, PR-, HER2-; TNBC); hormone receptor negative breast cancer (ER- and PR-); ER+, PR+, and HER2+ triple positive breast cancer (ER+, PR+, HER2+; TPBC); hepatocellular carcinoma (HCC); head and neck squamous cell carcinoma (HNSCC); oral tongue squamous cell carcinoma (OTSCC); sarcomas (e.g. epitheloid, rhabdoid and synovial); esophageal cancer; gastric cancer; ovarian cancer; pancreatic cancer; lung cancer; non-small cell lung carcinoma (NSCLC); small-cell lung carcinoma (SCLC); squamous cell carcinoma (SCC); head and neck cancer; head and neck squamous cell carcinoma (HNSCC); gastrointestinal cancer; large intestinal cancer; small intestinal cancer; stomach cancer; colon cancer; colorectal cancer; bladder cancer; liver cancer; biliary tract cancer; urothelial cancer; endometrial cancer; cervical cancer; prostate cancer; mesothelioma; chordoma; renal cancer; renal cell carcinoma (RCC); brain cancer; neuroblastoma; glioblastoma; skin cancer; melanoma; basal cell carcinoma; merkel cell carcinoma; blood cancer; hematopoetic cancer; myeloma; multiple myeloma (MM); B cell malignancies; lymphoma; B cell lymphoma; Hodgkin lymphoma; T cell lymphoma; leukemia;

or acute lymphocytic leukemia (ALL). In certain embodiments, the compound comprises an antisense compound targeted to MALAT1. In certain embodiments, the compound comprises an oligonucleotide targeted to MALAT1. In certain embodiments, the compound comprises a modified oligonucleotide consisting of 8 to 80 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2-10. In certain embodiments, the compound comprises a modified oligonucleotide consisting of 16 to 80 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 2-10. In certain embodiments, the compound comprises a modified oligonucleotide consisting of the nucleobase sequence of any one of SEQ ID NOs: 2-10. In certain embodiments, a compound comprises a modified oligonucleotide consisting of 8 to 80 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 36-2646 or 2664-2813. In certain embodiments, a compound comprises a modified oligonucleotide consisting of 16 to 80 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 36-2646 or 2664-2813. In certain embodiments, a compound comprises a modified oligonucleotide consisting of the nucleobase sequence of any one of SEQ ID NOs: SEQ ID NOs: 36-2646 or 2664-2813. In any of the foregoing embodiments, the modified oligonucleotide can consist of 10 to 30 linked nucleosides. In certain embodiments, the compound is ION 1157034, 1157111, 1157190, 1157929, 1158161, 1158162, 1304884, 1304890, or 1304906. In any of the foregoing embodiments, the compound can be single-stranded or double-stranded. In any of the foregoing embodiments, the compound can be an antisense compound or oligomeric compound.

In any of the foregoing methods or uses, the compound can be targeted to MALAT1. In certain embodiments, the compound comprises or consists of a modified oligonucleotide, for example a modified oligonucleotide can consist of 8 to 80 linked nucleosides, 10 to 30 linked nucleosides, 12 to 30 linked nucleosides, or 20 linked nucleosides. In certain embodiments, the modified oligonucleotide is at least 80%, 85%, 90%, 95% or 100% complementary to SEQ ID NO: 1. In certain embodiments, the modified oligonucleotide comprises at least one modified internucleoside linkage, at least one modified sugar and/or at least one modified nucleobase. In certain embodiments, the modified internucleoside linkage is a phosphorothioate internucleoside linkage, the modified sugar is a bicyclic sugar or a 2'-O-methoxyethyl, and the modified nucleobase is a 5-methylcytosine. In certain embodiments, the modified oligonucleotide comprises a gap segment consisting of linked 2'-deoxynucleosides; a 5' wing segment consisting of linked nucleosides; and a 3' wing segment consisting of linked nucleosides, wherein the gap segment is positioned immediately adjacent to and between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar.

In any of the foregoing embodiments, the modified oligonucleotide can consist of 12 to 30, 15 to 30, 15 to 25, 15 to 24, 16 to 24, 17 to 24, 18 to 24, 19 to 24, 20 to 24, 19 to 22, 20 to 22, 16 to 20, or 17 or 20 linked nucleosides. In certain embodiments, the modified oligonucleotide is at least 80%, 85%, 90%, 95% or 100%

complementary to SEQ ID NO: 1. In certain embodiments, at least one internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage, at least one sugar of the modified oligonucleotide is a modified sugar and/or at least one nucleobase of the modified oligonucleotide is a modified nucleobase. In certain embodiments, the modified internucleoside linkage is a phosphorothioate internucleoside linkage, the modified sugar is a bicyclic sugar or a 2'-O-methoxyethyl sugar, and the modified nucleobase is 5-methylcytosine. In certain embodiments, the modified oligonucleotide has a gap segment consisting of linked 2'-deoxynucleosides; a 5' wing segment consisting of linked nucleosides; and a 3' wing segment consisting of linked nucleosides, wherein the gap segment is positioned immediately adjacent to and between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar.

In any of the foregoing methods or uses, the compound can comprise or consist of a modified oligonucleotide having:

a gap segment consisting of linked 2'-deoxynucleosides;

a 5' wing segment consisting of linked nucleosides; and

a 3' wing segment consisting of linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar. In certain embodiments, the modified oligonucleotide consists of 16 to 80 linked nucleosides and has a nucleobase sequence comprising the nucleobase sequence recited in any one of SEQ ID NOs: 2-10 or 36-2813. In certain embodiments, the modified oligonucleotide consists of 16 to 80 linked nucleosides and has a nucleobase sequence comprising the nucleobase sequence recited in any one of SEQ ID NOs: 2-10. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides and has a nucleobase sequence comprising the nucleobase sequence recited in any one of SEQ ID NOs: 2-10 or 36-2813. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides and has a nucleobase sequence comprising the nucleobase sequence recited in any one of SEQ ID NOs: 2-10. In certain embodiments, the modified oligonucleotide consists of 16 linked nucleosides and has a nucleobase sequence consisting of the nucleobase sequence recited in any one of SEQ ID NOs: 2-10 or 36-2813. In certain embodiments, the modified oligonucleotide consists of 16 linked nucleosides and has a nucleobase sequence consisting of the nucleobase sequence recited in any one of SEQ ID NOs: 2-10.

In any of the foregoing methods or uses, the compound can comprise or consist of a modified oligonucleotide consisting of 16 to 80 linked nucleobases and having a nucleobase sequence comprising the nucleobase sequence recited in any one of SEQ ID NOs: 2-10 or 36-2813, wherein the modified oligonucleotide has:

a gap segment consisting of linked 2'-deoxynucleosides;

a 5' wing segment consisting of linked nucleosides; and

a 3' wing segment consisting of linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides. In certain embodiments, the modified oligonucleotide consists of 16 linked nucleosides.

In any of the foregoing methods or uses, the compound can comprise or consist of a modified oligonucleotide consisting of 16 to 80 linked nucleobases and having a nucleobase sequence comprising the nucleobase sequence recited in any one of SEQ ID NOs: 2-10, wherein the modified oligonucleotide has:

a gap segment consisting of linked 2'-deoxynucleosides;

a 5' wing segment consisting of linked nucleosides; and

a 3' wing segment consisting of linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides. In certain embodiments, the modified oligonucleotide consists of 16 linked nucleosides.

In any of the foregoing methods or uses, the compound can comprise or consist of a modified oligonucleotide consisting of 16 to 80 linked nucleobases and having a nucleobase sequence comprising the nucleobase sequence recited in any one of SEQ ID NOs: 36-2646 or 2664-2813, wherein the modified oligonucleotide has:

a gap segment consisting of ten linked 2'-deoxynucleosides;

a 5' wing segment consisting of three linked nucleosides; and

a 3' wing segment consisting of three linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment; wherein each nucleoside of each wing segment comprises a cEt nucleoside; wherein each internucleoside linkage is a phosphorothioate linkage; and wherein each cytosine is 5-methylcytosine. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides. In certain embodiments, the modified oligonucleotide consists of 16 linked nucleosides.

In any of the foregoing methods or uses, the compound can comprise or consist of a modified oligonucleotide consisting of 16 to 80 linked nucleobases and having a nucleobase sequence comprising the nucleobase sequence recited in any one of SEQ ID NOs: 2-7, wherein the modified oligonucleotide has:

a gap segment consisting of ten linked 2'-deoxynucleosides;

a 5' wing segment consisting of three linked nucleosides; and

a 3' wing segment consisting of three linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment; wherein each nucleoside of each wing segment comprises a cEt nucleoside; wherein each internucleoside linkage is a phosphorothioate linkage; and wherein each cytosine is 5-methylcytosine. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides. In certain embodiments, the modified oligonucleotide consists of 16 linked nucleosides.

In any of the foregoing methods or uses, the compound can comprise or consist of a modified oligonucleotide having a nucleobase sequence comprising the nucleobase sequence recited in any of SEQ ID NOs: 8-10; wherein the modified oligonucleotide comprises the sugar motif kkk-d-y-d(8)-kkk, wherein "k" indicates a cEt modified sugar moiety, "d" indicates an unmodified 2'-deoxyribosyl sugar moiety, and "y" indicates a 2'-O-methyl modified sugar moiety; wherein each internucleoside linkage is a phosphorothioate linkage; and wherein each cytosine is 5-methylcytosine. In certain embodiments, the modified oligonucleotide consisting of 16 to 30 linked nucleosides. In certain embodiments, the modified oligonucleotide consists of 16 linked nucleosides.

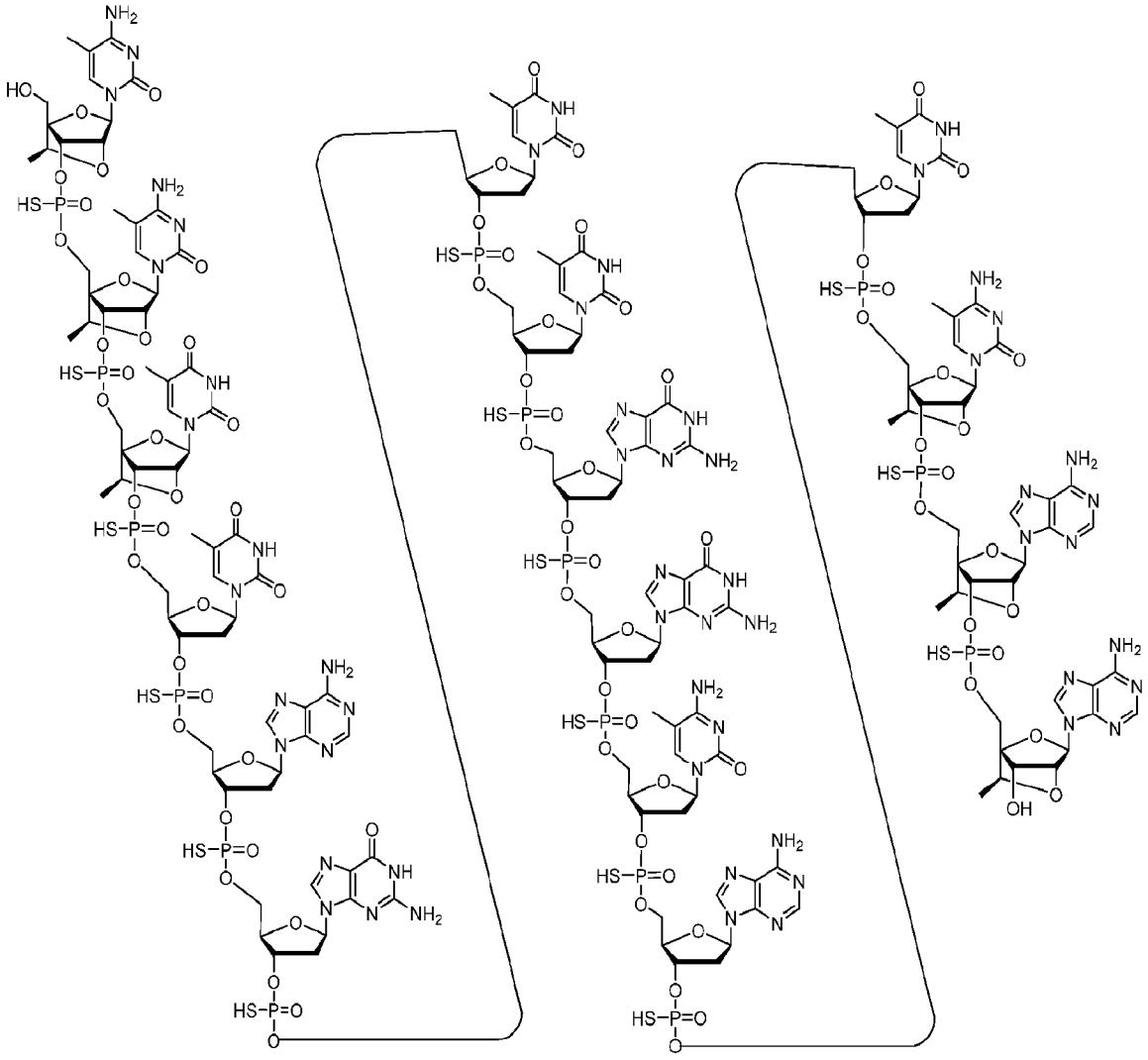
In any of the foregoing methods or uses, the compound can comprise or consist of ION 1304884 having the nucleobase sequence and chemical motif: GksGksAksTdsUysAdsAdsTdsGdsTdsAdsGdsTdsGksTksAk (SEQ ID NO: 8), wherein "d" represents a 2'-deoxyribose sugar, "k" represents a cEt modified sugar, "y" represents a 2'-O-methyl modified sugar, "s" represents a phosphorothioate internucleoside linkage, and "mC" refers to 5-methylcytosine. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides. In certain embodiments, the modified oligonucleotide consists of 16 linked nucleosides.

In any of the foregoing methods or uses, the compound can comprise or consist of ION 1304890 having the nucleobase sequence and chemical motif: GksGksTksTdsAysTdsAdsGdsmCdsTdsTdsGdsAdsmCksAksAk (SEQ ID NO: 9), wherein "d" represents a 2'-deoxyribose sugar, "k" represents a cEt modified sugar, "y" represents a 2'-O-methyl modified sugar, "s" represents a phosphorothioate internucleoside linkage, and "mC" refers to a 5-methylcytosine. In certain embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides. In certain embodiments, the modified oligonucleotide consists of 16 linked nucleosides.

In any of the foregoing methods or uses, the compound can comprise or consist of ION 1304906 having the nucleobase sequence and chemical motif: GksmCksAksGdsAysTdsAdsAdsTdsGdsTdsTdsmCdsTksmCksAk (SEQ ID NO: 10), wherein "d" represents a 2'-deoxyribose sugar, "k" represents a cEt modified sugar, "y" represents a 2'-O-methyl modified sugar, "s" represents a phosphorothioate internucleoside linkage, and "mC" refers to 5-methylcytosine. In certain

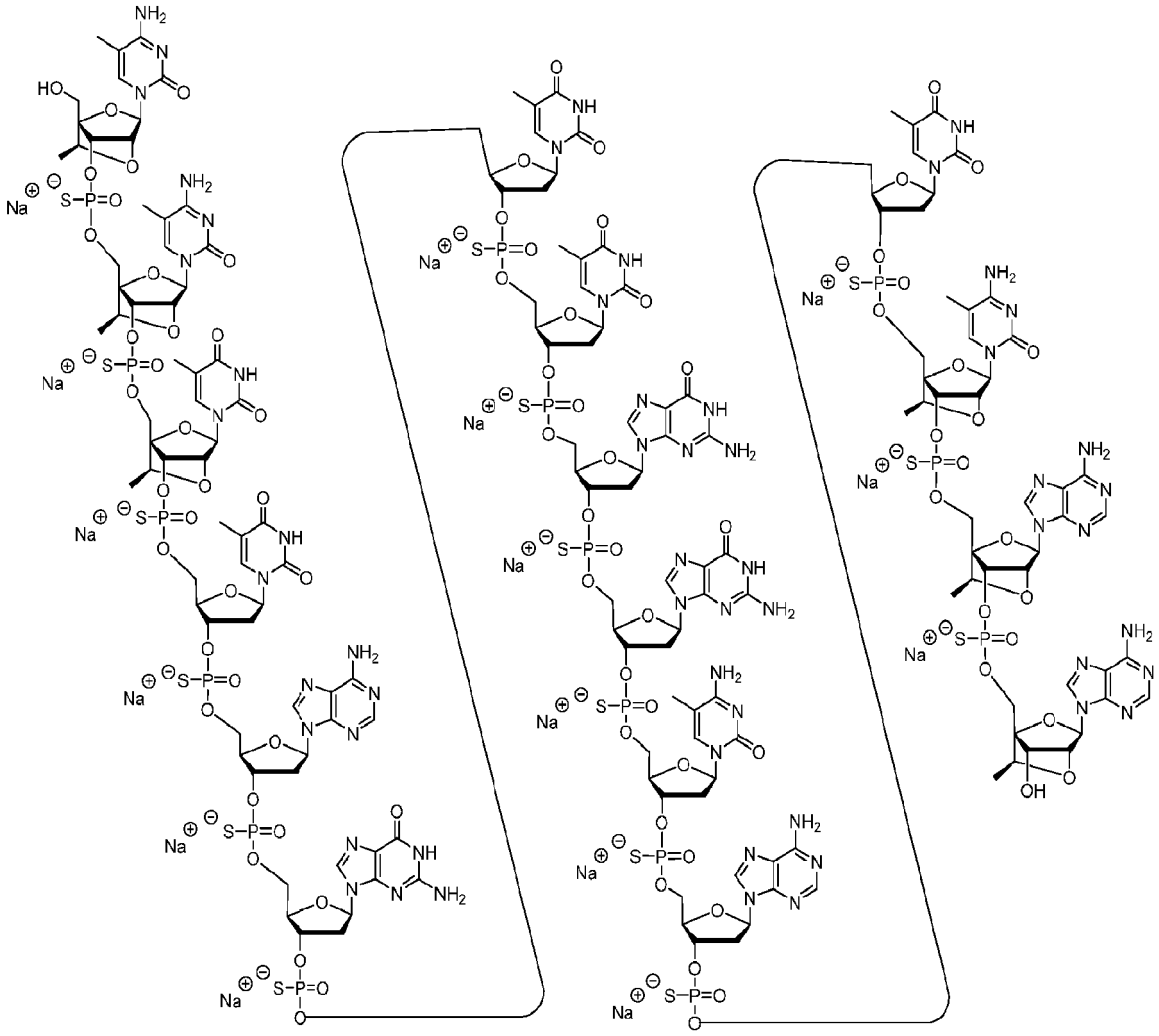
embodiments, the modified oligonucleotide consists of 16 to 30 linked nucleosides. In certain embodiments, the modified oligonucleotide consists of 16 linked nucleosides.

In any of the foregoing methods or uses, the compound can be a modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 6), or a salt thereof. In certain embodiments, the modified oligonucleotide is the sodium salt or potassium salt.

In any of the foregoing methods or uses, the compound can be a modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 6).

In any of the foregoing methods or uses, the compound can be administered parenterally. For example, in certain embodiments the compound can be administered through injection or infusion. Parenteral administration includes subcutaneous administration, intravenous administration, intramuscular administration, intraarterial administration, intraperitoneal administration, or intracranial administration, e.g. intrathecal or intracerebroventricular administration.

Certain Combinations and Combination Therapies

In certain embodiments, a first agent comprising a compound described herein is co-administered with one or more secondary agents. In certain embodiments, such second agents are designed to treat the same disease, disorder, or condition as the first agent described herein. In certain embodiments, such second agents are designed to treat a different disease, disorder, or condition as the first agent described herein. In certain embodiments, a first agent is designed to treat an undesired side effect of a second agent. In certain

embodiments, second agents are co-administered with the first agent to treat an undesired effect of the first agent. In certain embodiments, such second agents are designed to treat an undesired side effect of one or more pharmaceutical compositions as described herein. In certain embodiments, second agents are co-administered with the first agent to produce a combinational effect. In certain embodiments, second agents are co-administered with the first agent to produce a synergistic effect. In certain embodiments, the co-administration of the first and second agents permits use of lower dosages than would be required to achieve a therapeutic or prophylactic effect if the agents were administered as independent therapy.

In certain embodiments, one or more compounds or compositions provided herein are co-administered with one or more secondary agents. In certain embodiments, one or more compounds or compositions provided herein and one or more secondary agents, are administered at different times. In certain embodiments, one or more compounds or compositions provided herein and one or more secondary agents, are prepared together in a single formulation. In certain embodiments, one or more compounds or compositions provided herein and one or more secondary agents, are prepared separately. In certain embodiments, a secondary agent is selected from: a chemotherapeutic agent including, but not limited to, capecitabine (Xeloda), carboplatin, cisplatin, cyclophosphamide, docetaxel (Taxotere), doxorubicin, epirubicin (Ellence), eribulin (Halaven), fluorouracil (5-FU, Efudex), gemcitabine (Gemzar), ixabepilone (Ixempra), methotrexate (Rheumatrex, Trexall), paclitaxel (Taxol), or vinorelbine (Navelbine); a combination regiment including, but not limited to, AC (doxorubicin and cyclophosphamide), EC (epirubicin, cyclophosphamide), AC or EC (epirubicin and cyclophosphamide) followed by T (doxorubicin and cyclophosphamide, followed by paclitaxel or docetaxel), CAF (cyclophosphamide, doxorubicin, and 5-FU), CEF (cyclophosphamide, epirubicin, and 5-FU), CMF (cyclophosphamide, methotrexate, and 5-FU), TAC (docetaxel, doxorubicin, and cyclophosphamide), TC (docetaxel and cyclophosphamide), AC-TH (doxorubicin, cyclophosphamide, paclitaxel, trastuzumab), AC-THP (doxorubicin, cyclophosphamide, paclitaxel, trastuzumab, pertuzumab), TCHP (docetaxel, carboplatin, trastuzumab, pertuzumab), TCH (docetaxel, carboplatin, trastuzumab), or TH (paclitaxel, trastuzumab); hormone therapy including, but not limited to, selective estrogen receptor modulators, tamoxifen, toremifene (Fareston), fulvestrant (Faslodex), goserelin (Zoladex), or leuprolide (Eligard, Lupron); aromatase inhibitors (AIs) including, but not limited to, anastrozole (Arimidex), exemestane (Aromasin), or letrozole (Femara); HER2-targeted therapy including, but not limited to, trastuzumab (Herceptin), lapatinib (TYKERB), pertuzumab (Perjeta), or neratinib (Nerlynx).

Certain embodiments are directed to the use of a compound targeted to MALAT1 as described herein in combination with a secondary agent. In particular embodiments such use is in a method of treating a patient suffering from cancer including, but not limited to, breast cancer; inflammatory breast cancer; breast ductal carcinoma; breast lobular carcinoma; luminal A breast cancer; luminal B breast cancer; basal-like breast cancer; HER2 positive (HER2+) breast cancer; HER2 negative (HER2-) breast cancer; Estrogen Receptor negative (ER-) breast cancer; Estrogen Receptor positive (ER+) breast cancer; Progesterone Receptor negative (PR-) breast cancer; Progesterone Receptor positive (PR+) breast cancer; ER positive (ER+) and PR positive (PR+)

breast cancer; ER positive (ER+) and PR negative (PR-) breast cancer; ER negative (ER-) and PR positive (PR+) breast cancer; ER positive (ER+) and HER2 negative (HER2-) breast cancer; ER-, PR-, and HER2- triple negative breast cancer (ER-, PR-, HER2-; TNBC); hormone receptor negative breast cancer (ER- and PR-); ER+, PR+, and HER2+ triple positive breast cancer (ER+, PR+, HER2+; TPBC); hepatocellular carcinoma (HCC); head and neck squamous cell carcinoma (HNSCC); oral tongue squamous cell carcinoma (OTSCC); sarcomas (e.g. epitheloid, rhabdoid and synovial); esophageal cancer; gastric cancer; ovarian cancer; pancreatic cancer; lung cancer; non-small cell lung carcinoma (NSCLC); small-cell lung carcinoma (SCLC); squamous cell carcinoma (SCC); head and neck cancer; head and neck squamous cell carcinoma (HNSCC); gastrointestinal cancer; large intestinal cancer; small intestinal cancer; stomach cancer; colon cancer; colorectal cancer; bladder cancer; liver cancer; biliary tract cancer; urothelial cancer; endometrial cancer; cervical cancer; prostate cancer; mesothelioma; chordoma; renal cancer; renal cell carcinoma (RCC); brain cancer; neuroblastoma; glioblastoma; skin cancer; melanoma; basal cell carcinoma; merkel cell carcinoma; blood cancer; hematopoetic cancer; myeloma; multiple myeloma (MM); B cell malignancies; lymphoma; B cell lymphoma; Hodgkin lymphoma; T cell lymphoma; leukemia; or acute lymphocytic leukemia (ALL). In certain embodiments, a secondary agent is selected from: a chemotherapeutic agent including, but not limited to, capecitabine (Xeloda), carboplatin, cisplatin, cyclophosphamide, docetaxel (Taxotere), doxorubicin, epirubicin (Ellence), eribulin (Halaven), fluorouracil (5-FU, Efudex), gemcitabine (Gemzar), ixabepilone (Ixempra), methotrexate (Rheumatrex, Trexall), paclitaxel (Taxol), or vinorelbine (Navelbine); a combination regiment including, but not limited to, AC (doxorubicin and cyclophosphamide), EC (epirubicin, cyclophosphamide), AC or EC (epirubicin and cyclophosphamide) followed by T (doxorubicin and cyclophosphamide, followed by paclitaxel or docetaxel), CAF (cyclophosphamide, doxorubicin, and 5-FU), CEF (cyclophosphamide, epirubicin, and 5-FU), CMF (cyclophosphamide, methotrexate, and 5-FU), TAC (docetaxel, doxorubicin, and cyclophosphamide), TC (docetaxel and cyclophosphamide), AC-TH (doxorubicin, cyclophosphamide, paclitaxel, trastuzumab), AC-THP (doxorubicin, cyclophosphamide, paclitaxel, trastuzumab, pertuzumab), TCHP (docetaxel, carboplatin, trastuzumab, pertuzumab), TCH (docetaxel, carboplatin, trastuzumab), or TH (paclitaxel, trastuzumab); hormone therapy including, but not limited to, selective estrogen receptor modulators, tamoxifen, toremifene (Fareston), fulvestrant (Faslodex), goserelin (Zoladex), or leuprolide (Eligard, Lupron); aromatase inhibitors (AIs) including, but not limited to, anastrozole (Arimidex), exemestane (Aromasin), or letrozole (Femara); HER2-targeted therapy including, but not limited to, trastuzumab (Herceptin), lapatinib (TYKERB), pertuzumab (Perjeta), or neratinib (Nerlynx).

Certain embodiments are drawn to a combination of a compound targeted to MALAT1 as described herein and a secondary agent, such as a secondary agent selected from: a chemotherapeutic agent including, but not limited to, capecitabine (Xeloda), carboplatin, cisplatin, cyclophosphamide, docetaxel (Taxotere), doxorubicin, epirubicin (Ellence), eribulin (Halaven), fluorouracil (5-FU, Efudex), gemcitabine (Gemzar), ixabepilone (Ixempra), methotrexate (Rheumatrex, Trexall), paclitaxel (Taxol), or vinorelbine (Navelbine); a combination regiment including, but not limited to, AC (doxorubicin and cyclophosphamide), EC (epirubicin,

cyclophosphamide), AC or EC (epirubicin and cyclophosphamide) followed by T (doxorubicin and cyclophosphamide, followed by paclitaxel or docetaxel), CAF (cyclophosphamide, doxorubicin, and 5-FU), CEF (cyclophosphamide, epirubicin, and 5-FU), CMF (cyclophosphamide, methotrexate, and 5-FU), TAC (docetaxel, doxorubicin, and cyclophosphamide), TC (docetaxel and cyclophosphamide), AC-TH (doxorubicin, cyclophosphamide, paclitaxel, trastuzumab), AC-THP (doxorubicin, cyclophosphamide, paclitaxel, trastuzumab, pertuzumab), TCHP (docetaxel, carboplatin, trastuzumab, pertuzumab), TCH (docetaxel, carboplatin, trastuzumab), or TH (paclitaxel, trastuzumab); hormone therapy including, but not limited to, selective estrogen receptor modulators, tamoxifen, toremifene (Fareston), fulvestrant (Faslodex), goserelin (Zoladex), or leuprolide (Eligard, Lupron); aromatase inhibitors (AIs) including, but not limited to, anastrozole (Arimidex), exemestane (Aromasin), or letrozole (Femara); HER2-targeted therapy including, but not limited to, trastuzumab (Herceptin), lapatinib (TYKERB), pertuzumab (Perjeta), or neratinib (Nerlynx).

In certain embodiments the compound targeted to MALAT1 as described herein and the secondary agent are used in combination treatment by administering the two agents simultaneously, separately or sequentially. In certain embodiments the two agents are formulated as a fixed dose combination product. In other embodiments the two agents are provided to the patient as separate units which can then either be taken simultaneously or serially (sequentially).

In certain embodiments, a compound targeted to MALAT1 as described herein is used in combination with an immunomodulatory agent such as an anti-PD-L1 antibody (or an antigen-binding fragment thereof), an anti-PD-1 antibody (or an antigen-binding fragment thereof), an anti-CTLA-4 antibody (or an antigen-binding fragment thereof) or an OX40 agonist ((e.g., an OX40 ligand fusion protein, or an OX40 agonist antibody or antigen-binding fragment thereof).

In certain embodiments, a compound targeted to MALAT1 as described herein is used in combination with an immune checkpoint inhibitor such as an anti-PD-L1 antibody (or an antigen-binding fragment thereof), an anti-PD-1 antibody (or an antigen-binding fragment thereof), or an anti-CTLA-4 antibody (or an antigen-binding fragment thereof).

Anti-PD-L1 antibodies are known in the art. Exemplary anti-PD-L1 antibodies include: MEDI4736 (durvalumab), MPDL3280A, BMS936559, 2.7A4, AMP-714, MDX-1105 and MPDL3280A (atezolizumab).

Anti-PD-1 antibodies are known in the art. Exemplary anti-PD-1 antibodies include: nivolumab, pembrolizumab, pidilizumab, and AMP-514

Anti-CTLA-4 antibodies are known in the art. Exemplary anti-CTLA-4 antibodies include: tremelimumab and ipilimumab, also termed MDX-010 (or BMS-734016).

OX40 agonists and antibodies are known in the art. Exemplary OX40 agonists and/or antibodies include: MEDI6383, 9B12 and MEDI0562.

In one embodiment, the combination includes the antisense oligonucleotide Ionis 1158161 or a salt thereof, and at least one immunomodulator selected from the group consisting of: MEDI4736, MPDL3280A,

BMS936559, 2.7A4, AMP-714, MDX-1105, nivolumab, pembrolizumab, pidilizumab, MPDL3280A, tremelimumab, ipilimumab, MEDI0562 and MEDI0562.

Certain Anti-PD-L1 Antibodies

Antibodies that specifically bind and inhibit PD-L1 are included in the present disclosure.

Durvalumab (MEDI4736) is an exemplary anti-PD-L1 antibody that is selective for a PD-L1 polypeptide and blocks the binding of PD-L1 to the PD-1 and CD80 receptors. Durvalumab can relieve PD-L1-mediated suppression of human T-cell activation in vitro and inhibits tumor growth in a xenograft model via a T-cell dependent mechanism.

Information regarding durvalumab (or fragments thereof) for use in the methods provided herein can be found in U.S. Patent No. 8,779,108, the disclosure of which is incorporated herein by reference in its entirety. The fragment crystallizable (Fc) domain of durvalumab contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to the complement component C1q and the Fcγ receptors responsible for mediating antibody-dependent cell-mediated cytotoxicity (ADCC).

Durvalumab and antigen-binding fragments thereof for use in the methods provided herein comprises a heavy chain and a light chain or a heavy chain variable region and a light chain variable region. In certain embodiments, MEDI4736 or an antigen-binding fragment thereof for use in the methods provided herein comprises the variable heavy chain and variable light chain CDR sequences of the 2.14H9OPT antibody as disclosed in U.S. Patent Nos. 8,779,108 and 9493565, which is herein incorporated by reference in its entirety.

There are numerous anti-PD-L1 antibodies in the published literature that could feature in the present disclosure, including compounds in development and/or in clinical trials such as: durvalumab (MEDI4736), MPDL3280A, BMS936559, 2.7A4, AMP-714 and MDX-1105. Patent specifications disclosing anti-PD-L1 antibodies that may be useful in the present disclosure include: U.S. Pat. Nos. 7,943,743; 8,383,796; 9,102,725; 9,273,135 (BMS/Medarex), US2006/0153841 (Dana Farber), US2011/0271358 (Dana Farber), U.S. Pat. Nos. 8,552,154 and 9,102,727 (Dana Farber), U.S. Pat. No. 8,217,149 (Genentech), including issued U.S. Patent No. 8,217,149, US2012/0039906 (INSERM), US2016/0031990 (Amplimmune), U.S. Patent No. 8,779,108 (MedImmune - for durvalumab/MEDI4726 and 2.7A4), US2014/0044738 (Amplimmune - for AMP-714) and US2010/0285039 (John's Hopkins University). Each of these disclosures is herein incorporated by reference in its entirety.

Certain Anti-CTLA-4 Antibodies

Antibodies that specifically bind CTLA-4 and inhibit CTLA-4 activity are useful for enhancing an anti-tumor immune response. Information regarding tremelimumab (or antigen-binding fragments thereof) for use in the methods provided herein can be found in US 6,682,736 (where it is referred to as 11.2.1), the disclosure of which is incorporated herein by reference in its entirety. Tremelimumab (also known as CP-675,206, CP-675, CP-675206, and ticilimumab) is a human IgG2 monoclonal antibody that is highly selective for CTLA-4

and blocks binding of CTLA-4 to CD80 (B7.1) and CD86 (B7.2). It has been shown to result in immune activation in vitro and some patients treated with tremelimumab have shown tumor regression.

Tremelimumab for use in the methods provided herein comprises a heavy chain and a light chain or a heavy chain variable region and a light chain variable region. In a specific aspect, tremelimumab or an antigen-binding fragment thereof for use in the methods provided herein comprises a light chain variable region comprising the amino acid sequences shown herein above and a heavy chain variable region comprising the amino acid sequence shown herein above. In a specific aspect, tremelimumab or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the Kabat-defined CDR1, CDR2, and CDR3 sequences shown herein above, and wherein the light chain variable region comprises the Kabat-defined CDR1, CDR2, and CDR3 sequences shown herein above. Those of ordinary skill in the art would easily be able to identify Chothia-defined, Abm-defined or other CDR definitions known to those of ordinary skill in the art. In a specific aspect, tremelimumab or an antigen-binding fragment thereof for use in the methods provided herein comprises the variable heavy chain and variable light chain CDR sequences of the 11.2.1 antibody as disclosed in U.S. Pat. No. 6,682,736, which is herein incorporated by reference in its entirety.

Other anti-CTLA-4 antibodies are described, for example, in US 20070243184. In one embodiment, the anti-CTLA-4 antibody is Ipilimumab, also termed MDX-010; BMS-734016.

Certain OX40 Agonists

OX40 agonists interact with the OX40 receptor on CD4+ T-cells during, or shortly after, priming by an antigen resulting in an increased response of the CD4+ T-cells to the antigen. An OX40 agonist interacting with the OX40 receptor on antigen specific CD4+ T-cells can increase T cell proliferation as compared to the response to antigen alone. The elevated response to the antigen can be maintained for a period of time substantially longer than in the absence of an OX40 agonist. Thus, stimulation via an OX40 agonist enhances the antigen specific immune response by boosting T-cell recognition of antigens, e.g., tumor cells. OX40 agonists are described, for example, in U.S. Patent Nos. 6,312,700, 7,504,101, 7,622,444, and 7,959,925, which are incorporated herein by reference in their entireties. Methods of using such agonists in cancer treatment are described, for example, in US2015/0098942 and in US2015/0157710, each of which are incorporated herein by reference in its entirety.

OX40 agonists include, but are not limited to OX40 binding molecules, e.g., binding polypeptides, e.g., OX40 ligand ("OX40L") or an OX40-binding fragment, variant, or derivative thereof, such as soluble extracellular ligand domains and OX40L fusion proteins, and anti-OX40 antibodies (for example, monoclonal antibodies such as humanized monoclonal antibodies), or an antigen-binding fragment, variant or derivative thereof. Examples of anti-OX40 monoclonal antibodies are described, for example, in U.S. Patent Nos. 5,821,332 and 6,156,878, the disclosures of which are incorporated herein by reference in their entireties. In certain embodiments, the anti-OX40 monoclonal antibody is 9B12, or an antigen-binding fragment, variant, or

derivative thereof, as described in Weinberg, A.D., et al. J Immunother 29, 575-585 (2006), which is incorporated herein by reference in its entirety. In another embodiment, an OX40 antibody is MEDI0562 as described in US 2016/0137740.

In certain embodiments, the antibody which specifically binds to OX40, or an antigen-binding fragment thereof binds to the same OX40 epitope as mAb 9B12. An example of a humanized OX40 antibody is described by Morris et al., Mol Immunol. May 2007; 44(12): 3112–3121. 9B12 is a murine IgG1, anti-OX40 mAb directed against the extracellular domain of human OX40 (CD134) (Weinberg, A.D., et al. J Immunother 29, 575-585 (2006)). It was selected from a panel of anti-OX40 monoclonal antibodies because of its ability to elicit an agonist response for OX40 signaling, stability, and for its high level of production by the hybridoma. For use in clinical applications, 9B12 mAb is equilibrated with phosphate buffered saline, pH 7.0, and its concentration is adjusted to 5.0 mg/ml by diafiltration.

"OX40 ligand" ("OX40L") (also variously termed tumor necrosis factor ligand superfamily member 4, gp34, TAX transcriptionally-activated glycoprotein-1, and CD252) is found largely on antigen presenting cells (APCs), and can be induced on activated B cells, dendritic cells (DCs), Langerhans cells, plamacytoid DCs, and macrophages (Croft, M., (2010) Ann Rev Immunol 28:57-78). Other cells, including activated T cells, NK cells, mast cells, endothelial cells, and smooth muscle cells can express OX40L in response to inflammatory cytokines (Id.). OX40L specifically binds to the OX40 receptor. The human protein is described in U.S. Patent 6,156,878. The mouse OX40L is described in U.S. Patent 5,457,035. OX40L is expressed on the surface of cells and includes an intracellular, a transmembrane and an extracellular receptor-binding domain. A functionally active soluble form of OX40L can be produced by deleting the intracellular and transmembrane domains as described, e.g., in U.S. Pat. Nos. 5,457,035; 6,312,700; 6,156,878; 6,242,566; 6,528,055; 6,528,623; 7,098,184; and 7,125,670, the disclosures of which are incorporated herein for all purposes. A functionally active form of OX40L is a form that retains the capacity to bind specifically to OX40, that is, that possesses an OX40 "receptor binding domain." An example is amino acids 51 to 183 of human OX40L. Methods of determining the ability of an OX40L molecule or derivative to bind specifically to OX40 are discussed below. Methods of making and using OX40L and its derivatives (such as derivatives that include an OX40 binding domain) are described in U.S. Pat. Nos. 6,156,878; 6,242,566; 6,528,055; 6,528,623; 7,098,184; and 7,125,670, which also describe proteins comprising the soluble form of OX40L linked to other peptides, such as human immunoglobulin ("Ig") Fc regions, that can be produced to facilitate purification of OX40 ligand from cultured cells, or to enhance the stability of the molecule after in vivo administration to a mammal (see also, U.S. Pat. Nos. 5,457,035 and 7,959,925, both of which are incorporated by reference herein in their entireties).

Also included within the definition of OX40L are OX40 ligand variants which vary in amino acid sequence from naturally occurring OX40 ligand molecules but which retain the ability to specifically bind to an OX40 receptor. Such variants are described in U.S. Pat. Nos. 5,457,035; 6,156,878; 6,242,566; 6,528,055; 6,528,623; 7,098,184; and 7,125,670. In a related embodiment, a mutant of OX40L which has lost the ability

to specifically bind to OX40, for example amino acids 51 to 183, in which the phenylalanine at position 180 of the receptor-binding domain of human OX40L has been replaced with alanine (F180A) is used.

OX40 agonists include a fusion protein in which one or more domains of OX40L is covalently linked to one or more additional protein domains. Exemplary OX40L fusion proteins that can be used as OX40 agonists are described in U.S. Pat. No. 6,312,700, the disclosure of which is incorporated herein by reference in its entirety. In one embodiment, an OX40 agonist includes an OX40L fusion polypeptide that self-assembles into a multimeric (e.g., trimeric or hexameric) OX40L fusion protein. Such fusion proteins are described, e.g., in U.S. Patent No. 7,959,925, which is incorporated by reference herein in its entirety. The multimeric OX40L fusion protein exhibits increased efficacy in enhancing antigen specific immune response in a subject, particularly a human subject, due to its ability to spontaneously assemble into highly stable trimers and hexamers.

In another embodiment, an OX40 agonist capable of assembling into a multimeric form includes a fusion polypeptide comprising in an N-terminal to C-terminal direction: an immunoglobulin domain, wherein the immunoglobulin domain includes an Fc domain, a trimerization domain, wherein the trimerization domain includes a coiled coil trimerization domain, and a receptor binding domain, wherein the receptor binding domain is an OX40 receptor binding domain, e.g., an OX40L or an OX40-binding fragment, variant, or derivative thereof, where the fusion polypeptide can self-assemble into a trimeric fusion protein. In one aspect, an OX40 agonist capable of assembling into a multimeric form is capable of binding to the OX40 receptor and stimulating at least one OX40 mediated activity. In certain aspects, the OX40 agonist includes an extracellular domain of OX40 ligand.

The trimerization domain of an OX40 agonist capable of assembling into a multimeric form serves to promote self-assembly of individual OX40L fusion polypeptide molecules into a trimeric protein. Thus, an OX40L fusion polypeptide with a trimerization domain self-assembles into a trimeric OX40L fusion protein. In one aspect, the trimerization domain is an isoleucine zipper domain or other coiled coli polypeptide structure. Exemplary coiled coil trimerization domains include: TRAF2 (GENBANK® Accession No. Q12933, amino acids 299-348; Thrombospondin 1 (Accession No. PO7996, amino acids 291-314; Matrilin-4 (Accession No. O95460, amino acids 594-618; CMP (matrilin-1) (Accession No. NP—002370, amino acids 463-496; HSF1 (Accession No. AAX42211, amino acids 165-191; and Cubilin (Accession No. NP—001072 , amino acids 104-138. In certain specific aspects, the trimerization domain includes a TRAF2 trimerization domain, a Matrilin-4 trimerization domain, or a combination thereof.

OX40L FP is a human OX40 ligand IgG4P fusion protein that specifically binds to, and triggers signaling by, the human OX40 receptor, a member of the TNFR superfamily. OX40L FP is also disclosed in US2016/0024176, incorporated herein by reference in its entirety. OX40L FP is composed of three distinct domains: (1) human OX40 ligand extracellular receptor binding domains (RBDs) that form homotrimers and bind the OX40 receptor; (2) isoleucine zipper trimerization domains derived from TNFR-associated factor 2 that stabilize the homotrimeric structure of the OX40 ligand RBDs; and (3) human IgG4 fragment crystallizable

gamma (Fcγ) domains that facilitate Fcγ receptor clustering of the fusion protein when bound to OX40 receptors, and contain a serine to proline substitution at position 228 (according to EU numbering) in the hinge regions (IgG4P) to promote stability of two sets of OX40 ligand RBD homotrimers. The IgG4P Fc domain is fused directly to an isoleucine zipper trimerization domain derived from amino acid residues 310-349 of human tumor necrosis factor 2 (TRAF2). Fused to the c-terminus of the TRAF2 domain are amino acid residues 51-183 of the extracellular receptor binding domain (RBD) of human OX40L (gene name TNFSF4). The TRAF2 domain stabilizes the homotrimeric structure of OX40L RBDs to enable OX40 binding and activation, while the IgG4P Fc domain confers serum stability, dimerization of OX40L trimers, and facilitates Fcγ receptor clustering of the hexameric fusion protein. One OX40L FP variant possesses a phenylalanine (F) to alanine (A) mutation at the amino acid corresponding to position 180 in OX40L. Another OX40L FP variant has the IgG4P Fc domain replaced with a human IgG1 Fc domain. In particular embodiments, the OX40 agonist for use in the present disclosure is one of the OX40L FP variants.

In particular embodiments, the OX40 agonist for use in the present disclosure has been modified to increase its serum half-life. For example, the serum half-life of an OX40 agonist can be increased by conjugation to a heterologous molecule such as serum albumin, an antibody Fc region, or PEG. In certain embodiments, OX40 agonists can be conjugated to other therapeutic agents or toxins to form immunoconjugates and/or fusion proteins. In certain embodiments, the OX40 agonist can be formulated so as to facilitate administration and promote stability of the active agent.

Antibody Derivatives

Antibodies for use in the present disclosure (e.g., anti-CTLA-4, anti-PD-L1, anti-PD-1, anti-OX40) may include variants of these sequences that retain the ability to specifically bind their targets. Such variants may be derived from the sequence of these antibodies by a skilled artisan using techniques well known in the art. For example, amino acid substitutions, deletions, or additions, can be made in the FRs and/or in the CDRs. While changes in the FRs are usually designed to improve stability and immunogenicity of the antibody, changes in the CDRs are typically designed to increase affinity of the antibody for its target. Variants of FRs also include naturally occurring immunoglobulin allotypes. Such affinity-increasing changes may be determined empirically by routine techniques that involve altering the CDR and testing the affinity antibody for its target. For example, conservative amino acid substitutions can be made within any one of the disclosed CDRs. Various alterations can be made according to the methods described in Antibody Engineering, 2nd ed., Oxford University Press, ed. Borrebaeck, 1995. These include but are not limited to nucleotide sequences that are altered by the substitution of different codons that encode a functionally equivalent amino acid residue within the sequence, thus producing a "silent" change. For example, the nonpolar amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine. The polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine. The positively charged (basic)

amino acids include arginine, lysine, and histidine. The negatively charged (acidic) amino acids include aspartic acid and glutamic acid.

Derivatives and analogs of antibodies of the present disclosure can be produced by various techniques well known in the art, including recombinant and synthetic methods (Maniatis (1990) Molecular Cloning, A Laboratory Manual, 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., and Bodansky et al. (1995) The Practice of Peptide Synthesis, 2nd ed., Spring Verlag, Berlin, Germany). Analogous shuffling or combinatorial techniques are also disclosed by Stemmer (Nature (1994) 370: 389-391), who describes the technique in relation to a β-lactamase gene but observes that the approach may be used for the generation of antibodies.

One may generate novel VH or VL regions carrying one or more sequences derived from the sequences disclosed herein using random mutagenesis of one or more selected VH and/or VL genes. One such technique, error-prone PCR, is described by Gram et al. (Proc. Nat. Acad. Sci. U.S.A. (1992) 89: 3576-3580).

Another method that may be used is to direct mutagenesis to CDRs of VH or VL genes. Such techniques are disclosed by Barbas et al. (Proc. Nat. Acad. Sci. U.S.A. (1994) 91: 3809-3813) and Schier et al. (J. Mol. Biol. (1996) 263: 551-567).

Similarly, one or more, or all three CDRs may be grafted into a repertoire of VH or VL domains, which are then screened for an antigen-binding fragment specific for CTLA-4 or PD-L1.

A portion of an immunoglobulin variable domain will comprise at least one of the CDRs substantially as set out herein and, optionally, intervening framework regions from the scFv fragments as set out herein. The portion may include at least about 50% of either or both of FR1 and FR4, the 50% being the C-terminal 50% of FR1 and the N-terminal 50% of FR4. Additional residues at the N-terminal or C-terminal end of the substantial part of the variable domain may be those not normally associated with naturally occurring variable domain regions. For example, construction of antibodies by recombinant DNA techniques may result in the introduction of N- or C-terminal residues encoded by linkers introduced to facilitate cloning or other manipulation steps. Other manipulation steps include the introduction of linkers to join variable domains to further protein sequences including immunoglobulin heavy chain constant regions, other variable domains (for example, in the production of diabodies), or proteinaceous labels as discussed in further detail below.

A skilled artisan will recognize that antibodies for use in the present disclosure may comprise antigen-binding fragments containing only a single CDR from either VL or VH domain. Either one of the single chain specific binding domains can be used to screen for complementary domains capable of forming a two-domain specific antigen-binding fragment capable of, for example, binding to CTLA-4 and PD-L1.

Antibodies for use in the present disclosure described herein can be linked to another functional molecule, e.g., another peptide or protein (albumin, another antibody, etc.). For example, the antibodies can be linked by chemical cross-linking or by recombinant methods. The antibodies may also be linked to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol, polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Pat. Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192; or 4,179,337.

The antibodies can be chemically modified by covalent conjugation to a polymer, for example, to increase their circulating half-life. Exemplary polymers and methods to attach them are also shown in U.S. Pat. Nos. 4,766,106; 4,179,337; 4,495,285, and 4,609,546.

The antibodies may also be altered to have a glycosylation pattern that differs from the native pattern. For example, one or more carbohydrate moieties can be deleted and/or one or more glycosylation sites added to the original antibody. Addition of glycosylation sites to the presently disclosed antibodies may be accomplished by altering the amino acid sequence to contain glycosylation site consensus sequences known in the art. Another means of increasing the number of carbohydrate moieties on the antibodies is by chemical or enzymatic coupling of glycosides to the amino acid residues of the antibody. Such methods are described in WO 87/05330, and in Aplin et al. (1981) CRC Crit. Rev. Biochem., 22: 259-306. Removal of any carbohydrate moieties from the antibodies may be accomplished chemically or enzymatically, for example, as described by Hakimuddin et al. (1987) Arch. Biochem. Biophys., 259: 52; and Edge et al. (1981) Anal. Biochem., 118: 131 and by Thotakura et al. (1987) Meth. Enzymol., 138: 350. The antibodies may also be tagged with a detectable, or functional, label. Detectable labels include radiolabels such as 131I or 99Tc, which may also be attached to antibodies using conventional chemistry. Detectable labels also include enzyme labels such as horseradish peroxidase or alkaline phosphatase. Detectable labels further include chemical moieties such as biotin, which may be detected via binding to a specific cognate detectable moiety, e.g., labeled avidin.

Antibodies, in which CDR sequences differ only insubstantially from those set forth herein are encompassed within the scope of this present disclosure. Typically, an amino acid is substituted by a related amino acid having similar charge, hydrophobic, or stereochemical characteristics. Such substitutions would be within the ordinary skills of an artisan. Unlike in CDRs, more substantial changes can be made in FRs without adversely affecting the binding properties of an antibody. Changes to FRs include, but are not limited to, humanizing a non-human derived or engineering certain framework residues that are important for antigen contact or for stabilizing the binding site, e.g., changing the class or subclass of the constant region, changing specific amino acid residues which might alter the effector function such as Fc receptor binding, e.g., as described in U.S. Pat. Nos. 5,624,821 and 5,648,260 and Lund et al. (1991) J. Immun. 147: 2657-2662 and Morgan et al. (1995) Immunology 86: 319-324, or changing the species from which the constant region is derived.

One of skill in the art will appreciate that the modifications described above are not all-exhaustive, and that many other modifications would be obvious to a skilled artisan in light of the teachings of the present disclosure.

Certain Compounds

In certain embodiments, compounds described herein can be antisense compounds. In certain embodiments, the antisense compound comprises or consists of an oligomeric compound. In certain

embodiments, the oligomeric compound comprises a modified oligonucleotide. In certain embodiments, the modified oligonucleotide has a nucleobase sequence complementary to that of a target nucleic acid.

In certain embodiments, a compound described herein comprises or consists of a modified oligonucleotide. In certain embodiments, the modified oligonucleotide has a nucleobase sequence complementary to that of a target nucleic acid.

In certain embodiments, a compound or antisense compound is single-stranded. Such a single-stranded compound or antisense compound comprises or consists of an oligomeric compound. In certain embodiments, such an oligomeric compound comprises or consists of an oligonucleotide and optionally a conjugate group. In certain embodiments, the oligonucleotide is an antisense oligonucleotide. In certain embodiments, the oligonucleotide is modified. In certain embodiments, the oligonucleotide of a single-stranded antisense compound or oligomeric compound comprises a self-complementary nucleobase sequence.

In certain embodiments, compounds are double-stranded. Such double-stranded compounds comprise a first modified oligonucleotide having a region complementary to a target nucleic acid and a second modified oligonucleotide having a region complementary to the first modified oligonucleotide. In certain embodiments, the modified oligonucleotide is an RNA oligonucleotide. In such embodiments, the thymine nucleobase in the modified oligonucleotide is replaced by a uracil nucleobase. In certain embodiments, compound comprises a conjugate group. In certain embodiments, one of the modified oligonucleotides is conjugated. In certain embodiments, both the modified oligonucleotides are conjugated. In certain embodiments, the first modified oligonucleotide is conjugated. In certain embodiments, the second modified oligonucleotide is conjugated. In certain embodiments, the first modified oligonucleotide consists of 12-30 linked nucleosides and the second modified oligonucleotide consists of 12-30 linked nucleosides. In certain embodiments, one of the modified oligonucleotides has a nucleobase sequence comprising at least 8 contiguous nucleobases of any of SEQ ID NOs: 36-2646 or 2664-2813. In certain embodiments, one of the modified oligonucleotides has a nucleobase sequence comprising at least 8 contiguous nucleobases of any of SEQ ID NOs: 2-10.

In certain embodiments, antisense compounds are double-stranded. Such double-stranded antisense compounds comprise a first oligomeric compound having a region complementary to a target nucleic acid and a second oligomeric compound having a region complementary to the first oligomeric compound. The first oligomeric compound of such double stranded antisense compounds typically comprises or consists of a modified oligonucleotide and optionally a conjugate group. The oligonucleotide of the second oligomeric compound of such double-stranded antisense compound may be modified or unmodified. Either or both oligomeric compounds of a double-stranded antisense compound may comprise a conjugate group. The oligomeric compounds of double-stranded antisense compounds may include non-complementary overhanging nucleosides.

Examples of single-stranded and double-stranded compounds include but are not limited to oligonucleotides, siRNAs, microRNA targeting oligonucleotides, and single-stranded RNAi compounds, such as small hairpin RNAs (shRNAs), single-stranded siRNAs (ssRNAs), and microRNA mimics.

In certain embodiments, a compound described herein has a nucleobase sequence that, when written in the 5' to 3' direction, comprises the reverse complement of the target segment of a target nucleic acid to which it is targeted.

In certain embodiments, a compound described herein comprises an oligonucleotide consisting of 10 to 30 linked subunits. In certain embodiments, a compound described herein comprises an oligonucleotide consisting of 12 to 30 linked subunits. In certain embodiments, a compound described herein comprises an oligonucleotide consisting of 12 to 22 linked subunits. In certain embodiments, a compound described herein comprises an oligonucleotide consisting of 14 to 30 linked subunits. In certain embodiments, compound described herein comprises an oligonucleotide consisting of 14 to 20 linked subunits. In certain embodiments, a compound described herein comprises an oligonucleotide consisting of 15 to 30 linked subunits. In certain embodiments, a compound described herein comprises an oligonucleotide consisting of 15 to 20 linked subunits. In certain embodiments, a compound described herein comprises an oligonucleotide consisting of 16 to 30 linked subunits. In certain embodiments, a compound described herein comprises an oligonucleotide consisting of 16 to 20 linked subunits. In certain embodiments, a compound described herein comprises an oligonucleotide consisting of 17 to 30 linked subunits. In certain embodiments, a compound described herein comprises an oligonucleotide consisting of 17 to 20 linked subunits. In certain embodiments, a compound described herein comprises an oligonucleotide consisting of 18 to 30 linked subunits. In certain embodiments, a compound described herein comprises an oligonucleotide consisting of 18 to 21 linked subunits. In certain embodiments, a compound described herein comprises an oligonucleotide consisting of 18 to 20 linked subunits. In certain embodiments, a compound described herein comprises an oligonucleotide consisting of 20 to 30 linked subunits. In other words, such oligonucleotides consist of 12 to 30 linked subunits, 14 to 30 linked subunits, 14 to 20 subunits, 15 to 30 subunits, 15 to 20 subunits, 16 to 30 subunits, 16 to 20 subunits, 17 to 30 subunits, 17 to 20 subunits, 18 to 30 subunits, 18 to 20 subunits, 18 to 21 subunits, 20 to 30 subunits, or 12 to 22 linked subunits, respectively. In certain embodiments, a compound described herein comprises an oligonucleotide consisting of 14 linked subunits. In certain embodiments, a compound described herein comprises an oligonucleotide consisting of 16 linked subunits. In certain embodiments, a compound described herein comprises an oligonucleotide consisting of 17 linked subunits. In certain embodiments, compound described herein comprises an oligonucleotide consisting of 18 linked subunits. In certain embodiments, a compound described herein comprises an oligonucleotide consisting of 19 linked subunits. In certain embodiments, a compound described herein comprises an oligonucleotide consisting of 20 linked subunits. In other embodiments, a compound described herein comprises an oligonucleotide consisting of 8 to 80, 12 to 50, 13 to 30, 13 to 50, 14 to 30, 14 to 50, 15 to 30, 15 to 50, 16 to 30, 16 to 50, 17 to 30, 17 to 50, 18 to 22, 18 to 24, 18 to 30, 18 to 50, 19 to 22, 19 to 30, 19 to 50, or 20 to 30 linked subunits. In certain such embodiments, the compound described herein comprises an oligonucleotide consisting of 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75,

76, 77, 78, 79, or 80 linked subunits, or a range defined by any two of the above values. In some embodiments the linked subunits are nucleotides, nucleosides, or nucleobases.

In certain embodiments, the compound may further comprise additional features or elements, such as a conjugate group, that are attached to the oligonucleotide. In certain embodiments, such compounds are antisense compounds. In certain embodiments, such compounds are oligomeric compounds. In embodiments where a conjugate group comprises a nucleoside (*i.e.* a nucleoside that links the conjugate group to the oligonucleotide), the nucleoside of the conjugate group is not counted in the length of the oligonucleotide.

In certain embodiments, compounds may be shortened or truncated. For example, a single subunit may be deleted from the 5' end (5' truncation), or alternatively from the 3' end (3' truncation). A shortened or truncated compound targeted to an MALAT1 nucleic acid may have two subunits deleted from the 5' end, or alternatively may have two subunits deleted from the 3' end, of the compound. Alternatively, the deleted nucleosides may be dispersed throughout the compound.

When a single additional subunit is present in a lengthened compound, the additional subunit may be located at the 5' or 3' end of the compound. When two or more additional subunits are present, the added subunits may be adjacent to each other, for example, in a compound having two subunits added to the 5' end (5' addition), or alternatively to the 3' end (3' addition), of the compound. Alternatively, the added subunits may be dispersed throughout the compound.

It is possible to increase or decrease the length of a compound, such as an oligonucleotide, and/or introduce mismatch bases without eliminating activity (Woolf et al. *Proc. Natl. Acad. Sci. USA* 1992, 89:7305-7309; Gautschi *et al. J. Natl. Cancer Inst.* March 2001, 93:463-471; Maher and Dolnick *Nuc. Acid. Res.* 1998, 16:3341-3358). However, seemingly small changes in oligonucleotide sequence, chemistry and motif can make large differences in one or more of the many properties required for clinical development (Seth et al. *J. Med. Chem.* 2009, 52, 10; Egli et al. *J. Am. Chem. Soc.* 2011, 133, 16642).

In certain embodiments, compounds described herein are interfering RNA compounds (RNAi), which include double-stranded RNA compounds (also referred to as short-interfering RNA or siRNA) and single-stranded RNAi compounds (or ssRNA). Such compounds work at least in part through the RISC pathway to degrade and/or sequester a target nucleic acid (thus, include microRNA/microRNA-mimic compounds). As used herein, the term siRNA is meant to be equivalent to other terms used to describe nucleic acid molecules that are capable of mediating sequence specific RNAi, for example short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), short hairpin RNA (shRNA), short interfering oligonucleotide, short interfering nucleic acid, short interfering modified oligonucleotide, chemically modified siRNA, post-transcriptional gene silencing RNA (ptgsRNA), and others. In addition, as used herein, the term "RNAi" is meant to be equivalent to other terms used to describe sequence specific RNA interference, such as post transcriptional gene silencing, translational inhibition, or epigenetics.

In certain embodiments, a compound described herein can comprise any of the oligonucleotide sequences targeted to MALAT1 described herein. In certain embodiments, the compound can be double-

stranded. In certain embodiments, the compound comprises a first strand comprising at least an 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 contiguous nucleobase portion of any one of SEQ ID NOs: 2-10 or 36-2813 and a second strand. In certain embodiments, the compound comprises a first strand comprising the nucleobase sequence of any one of SEQ ID NOs: 2-10 or 36-2813 and a second strand. In certain embodiments, the compound comprises ribonucleotides in which the first strand has uracil (U) in place of thymine (T) in any one of SEQ ID NOs: 2-10 or 36-2813. In certain embodiments, the compound comprises (i) a first strand comprising a nucleobase sequence complementary to the site on MALAT1 to which any of SEQ ID NOs: 2-10 or 36-2813 is targeted, and (ii) a second strand. In certain embodiments, the compound comprises a first strand comprising at least an 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 contiguous nucleobase portion of any one of SEQ ID NOs: 2-10 and a second strand. In certain embodiments, the compound comprises a first strand comprising the nucleobase sequence of any one of SEQ ID NOs: 2-10 and a second strand. In certain embodiments, the compound comprises ribonucleotides in which the first strand has uracil (U) in place of thymine (T) in any one of SEQ ID NOs: 2-10. In certain embodiments, the compound comprises (i) a first strand comprising a nucleobase sequence complementary to the site on MALAT1 to which any of SEQ ID NOs: 2-10 is targeted, and (ii) a second strand. In certain embodiments, the compound comprises one or more modified nucleotides in which the 2' position in the sugar contains a halogen (such as fluorine group; 2'-F) or contains an alkoxy group (such as a methoxy group; 2'-OMe). In certain embodiments, the compound comprises at least one 2'-F sugar modification and at least one 2'-OMe sugar modification. In certain embodiments, the at least one 2'-F sugar modification and at least one 2'-OMe sugar modification are arranged in an alternating pattern for at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 contiguous nucleobases along a strand of the dsRNA compound. In certain embodiments, the compound comprises one or more linkages between adjacent nucleotides other than a naturally-occurring phosphodiester linkage. Examples of such linkages include phosphoramide, phosphorothioate, and phosphorodithioate linkages. The compounds may also be chemically modified nucleic acid molecules as taught in U.S. Pat. No. 6,673,661. In other embodiments, the compound contains one or two capped strands, as disclosed, for example, by WO 00/63364, filed Apr. 19, 2000.

In certain embodiments, the first strand of the compound is an siRNA guide strand and the second strand of the compound is an siRNA passenger strand. In certain embodiments, the second strand of the compound is complementary to the first strand. In certain embodiments, each strand of the compound consisting of 16, 17, 18, 19, 20, 21, 22, or 23 linked nucleosides. In certain embodiments, the first or second strand of the compound can comprise a conjugate group.

In certain embodiments, a compound described herein can comprise any of the oligonucleotide sequences targeted to MALAT1 described herein. In certain embodiments, the compound is single stranded. In certain embodiments, such a compound is a single-stranded RNAi (ssRNAi) compound. In certain embodiments, the compound comprises at least an 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 contiguous nucleobase portion of any one of SEQ ID NOs: 2-10 or 36-2813. In certain embodiments, the compound

comprises the nucleobase sequence of any one of SEQ ID NOs: 2-10 or 36-2813. In certain embodiments, the compound comprises ribonucleotides in which uracil (U) is in place of thymine (T) in any one of SEQ ID NOs: 2-10 or 36-2813. In certain embodiments, the compound comprises a nucleobase sequence complementary to the site on MALAT1 to which any of SEQ ID NOs: 2-10 or 36-2813 is targeted. In certain embodiments, the compound comprises at least an 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 contiguous nucleobase portion of any one of SEQ ID NOs: 2-10. In certain embodiments, the compound comprises the nucleobase sequence of any one of SEQ ID NOs: 2-10. In certain embodiments, the compound comprises ribonucleotides in which uracil (U) is in place of thymine (T) in any one of SEQ ID NOs: 2-10. In certain embodiments, the compound comprises a nucleobase sequence complementary to the site on MALAT1 to which any of SEQ ID NOs: 2-10 is targeted. In certain embodiments, the compound comprises one or more modified nucleotides in which the 2' position in the sugar contains a halogen (such as fluorine group; 2'-F) or contains an alkoxy group (such as a methoxy group; 2'-OMe). In certain embodiments, the compound comprises at least one 2'-F sugar modification and at least one 2'-OMe sugar modification. In certain embodiments, the at least one 2'-F sugar modification and at least one 2'-OMe sugar modification are arranged in an alternating pattern for at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 contiguous nucleobases along a strand of the compound. In certain embodiments, the compound comprises one or more linkages between adjacent nucleotides other than a naturally-occurring phosphodiester linkage. Examples of such linkages include phosphoramide, phosphorothioate, and phosphorodithioate linkages. The compounds may also be chemically modified nucleic acid molecules as taught in U.S. Pat. No. 6,673,661. In other embodiments, the compound contains a capped strand, as disclosed, for example, by WO 00/63364, filed Apr. 19, 2000. In certain embodiments, the compound consists of 16, 17, 18, 19, 20, 21, 22, or 23 linked nucleosides. In certain embodiments, the compound can comprise a conjugate group.

In certain embodiments, compounds described herein comprise modified oligonucleotides. Certain modified oligonucleotides have one or more asymmetric center and thus give rise to enantiomers, diastereomers, and other stereoisomeric configurations that may be defined, in terms of absolute stereochemistry, as (R) or (S), as α or β such as for sugar anomers, or as (D) or (L) such as for amino acids etc. Included in the modified oligonucleotides provided herein are all such possible isomers, including their racemic and optically pure forms, unless specified otherwise. Likewise, all cis- and trans-isomers and tautomeric forms are also included.

The compounds described herein include variations in which one or more atoms are replaced with a non-radioactive isotope or radioactive isotope of the indicated element. For example, compounds herein that comprise hydrogen atoms encompass all possible deuterium substitutions for each of the ^{1}H hydrogen atoms. Isotopic substitutions encompassed by the compounds herein include but are not limited to: ^{2}H or ^{3}H in place of ^{1}H, ^{13}C or ^{14}C in place of ^{12}C, ^{15}N in place of ^{14}N, ^{17}O or ^{18}O in place of ^{16}O, and ^{33}S, ^{34}S, ^{35}S, or ^{36}S in place of ^{32}S. In certain embodiments, non-radioactive isotopic substitutions may impart new properties on the compound that are beneficial for use as a therapeutic or research tool. In certain embodiments, radioactive

isotopic substitutions may make the compound suitable for research or diagnostic purposes, such as an imaging assay.

Certain Mechanisms

In certain embodiments, compounds described herein comprise or consist of modified oligonucleotides. In certain embodiments, compounds described herein are antisense compounds. In certain embodiments, compounds comprise oligomeric compounds. In certain embodiments, compounds described herein are capable of hybridizing to a target nucleic acid, resulting in at least one antisense activity. In certain embodiments, compounds described herein selectively affect one or more target nucleic acid. Such compounds comprise a nucleobase sequence that hybridizes to one or more target nucleic acid, resulting in one or more desired antisense activity and does not hybridize to one or more non-target nucleic acid or does not hybridize to one or more non-target nucleic acid in such a way that results in a significant undesired antisense activity.

In certain antisense activities, hybridization of a compound described herein to a target nucleic acid results in recruitment of a protein that cleaves the target nucleic acid. For example, certain compounds described herein result in RNase H mediated cleavage of the target nucleic acid. RNase H is a cellular endonuclease that cleaves the RNA strand of an RNA:DNA duplex. The DNA in such an RNA:DNA duplex need not be unmodified DNA. In certain embodiments, compounds described herein are sufficiently "DNA-like" to elicit RNase H activity. Further, in certain embodiments, one or more non-DNA-like nucleoside in the gap of a gapmer is tolerated.

In certain antisense activities, compounds described herein or a portion of the compound is loaded into an RNA-induced silencing complex (RISC), ultimately resulting in cleavage of the target nucleic acid. For example, certain compounds described herein result in cleavage of the target nucleic acid by Argonaute. Compounds that are loaded into RISC are RNAi compounds. RNAi compounds may be double-stranded (siRNA) or single-stranded (ssRNA).

In certain embodiments, hybridization of compounds described herein to a target nucleic acid does not result in recruitment of a protein that cleaves that target nucleic acid. In certain such embodiments, hybridization of the compound to the target nucleic acid results in alteration of splicing of the target nucleic acid. In certain embodiments, hybridization of the compound to a target nucleic acid results in inhibition of a binding interaction between the target nucleic acid and a protein or other nucleic acid. In certain such embodiments, hybridization of the compound to a target nucleic acid results in alteration of translation of the target nucleic acid.

Antisense activities may be observed directly or indirectly. In certain embodiments, observation or detection of an antisense activity involves observation or detection of a change in an amount of a target nucleic acid or protein encoded by such target nucleic acid, a change in the ratio of splice variants of a nucleic acid or protein, and/or a phenotypic change in a cell or animal.

Target Nucleic Acids, Target Regions and Nucleotide Sequences

In certain embodiments, compounds described herein comprise or consist of an oligonucleotide comprising a region that is complementary to a target nucleic acid. In certain embodiments, the target nucleic acid is an endogenous RNA molecule. In certain embodiments, the target nucleic acid encodes a protein. In certain such embodiments, the target nucleic acid is selected from: an mRNA and a pre-mRNA, including intronic, exonic and untranslated regions. In certain embodiments, the target RNA is an mRNA. In certain embodiments, the target nucleic acid is a pre-mRNA. In certain such embodiments, the target region is entirely within an intron. In certain embodiments, the target region spans an intron/exon junction. In certain embodiments, the target region is at least 50% within an intron.

Nucleotide sequences that encode MALAT1 include, without limitation, the following: RefSEQ No. XR_001309.1 (SEQ ID NO: 1), which is incorporated by reference in its entirety.

Hybridization

In some embodiments, hybridization occurs between a compound disclosed herein and a MALAT1 nucleic acid. The most common mechanism of hybridization involves hydrogen bonding (e.g., Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding) between complementary nucleobases of the nucleic acid molecules.

Hybridization can occur under varying conditions. Hybridization conditions are sequence-dependent and are determined by the nature and composition of the nucleic acid molecules to be hybridized.

Methods of determining whether a sequence is specifically hybridizable to a target nucleic acid are well known in the art. In certain embodiments, the compounds provided herein are specifically hybridizable with a MALAT1 nucleic acid.

Complementarity

An oligonucleotide is said to be complementary to another nucleic acid when the nucleobase sequence of such oligonucleotide or one or more regions thereof matches the nucleobase sequence of another oligonucleotide or nucleic acid or one or more regions thereof when the two nucleobase sequences are aligned in opposing directions. Nucleobase matches or complementary nucleobases, as described herein, are limited to the following pairs: adenine (A) and thymine (T), adenine (A) and uracil (U), cytosine (C) and guanine (G), and 5-methyl cytosine (mC) and guanine (G) unless otherwise specified. Complementary oligonucleotides and/or nucleic acids need not have nucleobase complementarity at each nucleoside and may include one or more nucleobase mismatches. An oligonucleotide is fully complementary or 100% complementary when such oligonucleotides have nucleobase matches at each nucleoside without any nucleobase mismatches.

In certain embodiments, compounds described herein comprise or consist of modified oligonucleotides. In certain embodiments, compounds described herein are antisense compounds. In certain embodiments, compounds comprise oligomeric compounds. Non-complementary nucleobases between a compound and a MALAT1 nucleic acid may be tolerated provided that the compound remains able to specifically hybridize to a target nucleic acid. Moreover, a compound may hybridize over one or more segments of a MALAT1 nucleic acid such that intervening or adjacent segments are not involved in the hybridization event (e.g., a loop structure, mismatch or hairpin structure).

In certain embodiments, the compounds provided herein, or a specified portion thereof, are, are at least, or are up to 70%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% complementary to a MALAT1 nucleic acid, a target region, target segment, or specified portion thereof. In certain embodiments, the compounds provided herein, or a specified portion thereof, are 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95%, 95% to 100%, or any number in between these ranges, complementary to a MALAT1 nucleic acid, a target region, target segment, or specified portion thereof. Percent complementarity of a compound with a target nucleic acid can be determined using routine methods.

For example, a compound in which 18 of 20 nucleobases of the compound are complementary to a target region, and would therefore specifically hybridize, would represent 90 percent complementarity. In this example, the remaining non-complementary nucleobases may be clustered or interspersed with complementary nucleobases and need not be contiguous to each other or to complementary nucleobases. As such, a compound which consisting of 18 nucleobases having four non-complementary nucleobases which are flanked by two regions of complete complementarity with the target nucleic acid would have 77.8% overall complementarity with the target nucleic acid. Percent complementarity of a compound with a region of a target nucleic acid can be determined routinely using BLAST programs (basic local alignment search tools) and PowerBLAST programs known in the art (Altschul *et al.*, *J. Mol. Biol.*, 1990, 215, 403 410; Zhang and Madden, Genome Res., 1997, 7, 649 656). Percent homology, sequence identity or complementarity, can be determined by, for example, the Gap program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, Madison Wis.), using default settings, which uses the algorithm of Smith and Waterman (Adv. Appl. Math., 1981, 2, 482 489).

In certain embodiments, compounds described herein, or specified portions thereof, are fully complementary (i.e. 100% complementary) to a target nucleic acid, or specified portion thereof. For example, a compound may be fully complementary to a MALAT1 nucleic acid, or a target region, or a target segment or target sequence thereof. As used herein, "fully complementary" means each nucleobase of a compound is complementary to the corresponding nucleobase of a target nucleic acid. For example, a 20 nucleobase compound is fully complementary to a target sequence that is 400 nucleobases long, so long as there is a corresponding 20 nucleobase portion of the target nucleic acid that is fully complementary to the compound. Fully complementary can also be used in reference to a specified portion of the first and /or the second nucleic acid. For example, a 20 nucleobase portion of a 30 nucleobase compound can be "fully complementary" to a

target sequence that is 400 nucleobases long. The 20 nucleobase portion of the 30 nucleobase compound is fully complementary to the target sequence if the target sequence has a corresponding 20 nucleobase portion wherein each nucleobase is complementary to the 20 nucleobase portion of the compound. At the same time, the entire 30 nucleobase compound may or may not be fully complementary to the target sequence, depending on whether the remaining 10 nucleobases of the compound are also complementary to the target sequence.

In certain embodiments, compounds described herein comprise one or more mismatched nucleobases relative to the target nucleic acid. In certain such embodiments, antisense activity against the target is reduced by such mismatch, but activity against a non-target is reduced by a greater amount. Thus, in certain such embodiments selectivity of the compound is improved. In certain embodiments, the mismatch is specifically positioned within an oligonucleotide having a gapmer motif. In certain such embodiments, the mismatch is at position 1, 2, 3, 4, 5, 6, 7, or 8 from the 5'-end of the gap region. In certain such embodiments, the mismatch is at position 9, 8, 7, 6, 5, 4, 3, 2, 1 from the 3'-end of the gap region. In certain such embodiments, the mismatch is at position 1, 2, 3, or 4 from the 5'-end of the wing region. In certain such embodiments, the mismatch is at position 4, 3, 2, or 1 from the 3'-end of the wing region. In certain embodiments, the mismatch is specifically positioned within an oligonucleotide not having a gapmer motif. In certain such embodiments, the mismatch is at position 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 from the 5'-end of the oligonucleotide. In certain such embodiments, the mismatch is at position , 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 from the 3'-end of the oligonucleotide.

The location of a non-complementary nucleobase may be at the 5' end or 3' end of the compound. Alternatively, the non-complementary nucleobase or nucleobases may be at an internal position of the compound. When two or more non-complementary nucleobases are present, they may be contiguous (i.e. linked) or non-contiguous. In one embodiment, a non-complementary nucleobase is located in the wing segment of a gapmer oligonucleotide.

In certain embodiments, compounds described herein that are, or are up to 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleobases in length comprise no more than 4, no more than 3, no more than 2, or no more than 1 non-complementary nucleobase(s) relative to a target nucleic acid, such as a MALAT1 nucleic acid, or specified portion thereof.

In certain embodiments, compounds described herein that are, or are up to 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleobases in length comprise no more than 6, no more than 5, no more than 4, no more than 3, no more than 2, or no more than 1 non-complementary nucleobase(s) relative to a target nucleic acid, such as a MALAT1 nucleic acid, or specified portion thereof.

In certain embodiments, compounds described herein also include those which are complementary to a portion of a target nucleic acid. As used herein, "portion" refers to a defined number of contiguous (i.e. linked) nucleobases within a region or segment of a target nucleic acid. A "portion" can also refer to a defined number of contiguous nucleobases of a compound. In certain embodiments, the–compounds, are complementary to at least an 8 nucleobase portion of a target segment. In certain embodiments, the compounds

are complementary to at least a 9 nucleobase portion of a target segment. In certain embodiments, the compounds are complementary to at least a 10 nucleobase portion of a target segment. In certain embodiments, the compounds are complementary to at least an 11 nucleobase portion of a target segment. In certain embodiments, the compounds are complementary to at least a 12 nucleobase portion of a target segment. In certain embodiments, the compounds are complementary to at least a 13 nucleobase portion of a target segment. In certain embodiments, the compounds are complementary to at least a 14 nucleobase portion of a target segment. In certain embodiments, the compounds are complementary to at least a 15 nucleobase portion of a target segment. In certain embodiments, the compounds are complementary to at least a 16 nucleobase portion of a target segment. Also contemplated are compounds that are complementary to at least a 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more nucleobase portion of a target segment, or a range defined by any two of these values.

Identity

The compounds provided herein may also have a defined percent identity to a particular nucleotide sequence, SEQ ID NO, or compound represented by a specific ION number, or portion thereof. In certain embodiments, compounds described herein are antisense compounds or oligomeric compounds. In certain embodiments, compounds described herein are modified oligonucleotides. As used herein, a compound is identical to the sequence disclosed herein if it has the same nucleobase pairing ability. For example, a RNA which contains uracil in place of thymidine in a disclosed DNA sequence would be considered identical to the DNA sequence since both uracil and thymidine pair with adenine. Shortened and lengthened versions of the compounds described herein as well as compounds having non-identical bases relative to the compounds provided herein also are contemplated. The non-identical bases may be adjacent to each other or dispersed throughout the compound. Percent identity of an compound is calculated according to the number of bases that have identical base pairing relative to the sequence to which it is being compared.

In certain embodiments, compounds described herein, or portions thereof, are, or are at least, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to one or more of the compounds or SEQ ID NOs, or a portion thereof, disclosed herein. In certain embodiments, compounds described herein are about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical, or any percentage between such values, to a particular nucleotide sequence, SEQ ID NO, or compound represented by a specific ION number, or portion thereof, in which the compounds comprise an oligonucleotide having one or more mismatched nucleobases. In certain such embodiments, the mismatch is at position 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 from the 5'-end of the oligonucleotide. In certain such embodiments, the mismatch is at position , 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 from the 3'-end of the oligonucleotide.

In certain embodiments, compounds described herein comprise or consist of antisense compounds. In certain embodiments, a portion of the antisense compound is compared to an equal length portion of the target

nucleic acid. In certain embodiments, an 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleobase portion is compared to an equal length portion of the target nucleic acid.

In certain embodiments, compounds described herein comprise or consist of oligonucleotides. In certain embodiments, a portion of the oligonucleotide is compared to an equal length portion of the target nucleic acid. In certain embodiments, an 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleobase portion is compared to an equal length portion of the target nucleic acid.

Certain Modified Compounds

In certain embodiments, compounds described herein comprise or consist of oligonucleotides consisting of linked nucleosides. Oligonucleotides may be unmodified oligonucleotides (RNA or DNA) or may be modified oligonucleotides. Modified oligonucleotides comprise at least one modification relative to unmodified RNA or DNA (i.e., comprise at least one modified nucleoside (comprising a modified sugar moiety and/or a modified nucleobase) and/or at least one modified internucleoside linkage).

A. Modified Nucleosides

Modified nucleosides comprise a modified sugar moiety or a modified nucleobase or both a modifed sugar moiety and a modified nucleobase.

1. Modified Sugar Moieties

In certain embodiments, sugar moieties are non-bicyclic modified sugar moieties. In certain embodiments, modified sugar moieties are bicyclic or tricyclic sugar moieties. In certain embodiments, modified sugar moieties are sugar surrogates. Such sugar surrogates may comprise one or more substitutions corresponding to those of other types of modified sugar moieties.

In certain embodiments, modified sugar moieties are non-bicyclic modified sugar moieties comprising a furanosyl ring with one or more acyclic substituent, including but not limited to substituents at the 2', 4', and/or 5' positions. In certain embodiments one or more acyclic substituent of non-bicyclic modified sugar moieties is branched. Examples of 2'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to: 2'-F, 2'-OCH_3 ("OMe" or "O-methyl"), and 2'-$O(CH_2)_2OCH_3$ ("MOE"). In certain embodiments, 2'-substituent groups are selected from among: halo, allyl, amino, azido, SH, CN, OCN, CF_3, OCF_3, O-C_1-C_{10} alkoxy, O-C_1-C_{10} substituted alkoxy, O-C_1-C_{10} alkyl, O-C_1-C_{10} substituted alkyl, S-alkyl, N(R_m)-alkyl, O-alkenyl, S-alkenyl, N(R_m)-alkenyl, O-alkynyl, S-alkynyl, N(R_m)-alkynyl, O-alkylenyl-O-alkyl, alkynyl, alkaryl, aralkyl, O-alkaryl, O-aralkyl, $O(CH_2)_2SCH_3$, $O(CH_2)_2ON(R_m)(R_n)$ or $OCH_2C(=O)$-$N(R_m)(R_n)$, where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C_1-C_{10} alkyl, and the 2'-substituent groups described in Cook et al., U.S. 6,531,584; Cook et al., U.S. 5,859,221; and Cook et al., U.S. 6,005,087. Certain embodiments of these 2'-substituent groups can be further substituted with one or more substituent groups independently selected from among: hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro (NO_2), thiol, thioalkoxy, thioalkyl, halogen, alkyl, aryl, alkenyl and alkynyl. Examples of 4'-

substituent groups suitable for linearly non-bicyclic modified sugar moieties include but are not limited to alkoxy (*e.g.*, methoxy), alkyl, and those described in Manoharan et al., WO 2015/106128. Examples of 5'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to: 5'-methyl (R or S), 5'-vinyl, and 5'-methoxy. In certain embodiments, non-bicyclic modified sugars comprise more than one non-bridging sugar substituent, for example, 2'-F-5'-methyl sugar moieties and the modified sugar moieties and modified nucleosides described in Migawa et al., US2010/190837 and Rajeev et al., US2013/0203836.

In certain embodiments, a 2'-substituted nucleoside or 2'- non-bicyclic modified nucleoside comprises a sugar moiety comprising a linear 2'-substituent group selected from: F, NH_2, N_3, OCF_3, OCH_3, $O(CH_2)_3NH_2$, $CH_2CH{=}CH_2$, $OCH_2CH{=}CH_2$, $OCH_2CH_2OCH_3$, $O(CH_2)_2SCH_3$, $O(CH_2)_2ON(R_m)(R_n)$, $O(CH_2)_2O(CH_2)_2N(CH_3)_2$, and N-substituted acetamide ($OCH_2C(=O)$-$N(R_m)(R_n)$), where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C_1-C_{10} alkyl.

In certain embodiments, a 2'-substituted nucleoside or 2'- non-bicyclic modified nucleoside comprises a sugar moiety comprising a linear 2'-substituent group selected from: F, OCF_3, OCH_3, $OCH_2CH_2OCH_3$, $O(CH_2)_2SCH_3$, $O(CH_2)_2ON(CH_3)_2$, $O(CH_2)_2O(CH_2)_2N(CH_3)_2$, and $OCH_2C(=O)$-$N(H)CH_3$ ("NMA").

In certain embodiments, a 2'-substituted nucleoside or 2'- non-bicyclic modified nucleoside comprises a sugar moiety comprising a linear 2'-substituent group selected from: F, OCH_3, and $OCH_2CH_2OCH_3$.

Nucleosides comprising modified sugar moieties, such as non-bicyclic modified sugar moieties, are referred to by the position(s) of the substitution(s) on the sugar moiety of the nucleoside. For example, nucleosides comprising 2'-substituted or 2-modified sugar moieties are referred to as 2'-substituted nucleosides or 2-modified nucleosides.

Certain modifed sugar moieties comprise a bridging sugar substituent that forms a second ring resulting in a bicyclic sugar moiety. In certain such embodiments, the bicyclic sugar moiety comprises a bridge between the 4' and the 2' furanose ring atoms. Examples of such 4' to 2' bridging sugar substituents include but are not limited to: 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2-O-2' ("LNA"), 4'-CH_2-S-2', 4'-$(CH_2)_2$-O-2' ("ENA"), 4'-$CH(CH_3)$-O-2' (referred to as "constrained ethyl" or "cEt" when in the *S* configuration), 4'-CH_2-O-CH_2-2', 4'-CH_2-N(R)-2', 4'-$CH(CH_2OCH_3)$-O-2' ("constrained MOE" or "cMOE") and analogs thereof (*see, e.g.*, Seth et al., U.S. 7,399,845, Bhat et al., U.S. 7,569,686, Swayze et al., U.S. 7,741,457, and Swayze et al., U.S. 8,022,193), 4'-$C(CH_3)(CH_3)$-O-2' and analogs thereof (*see, e.g.*, Seth et al., U.S. 8,278,283), 4'-CH_2-$N(OCH_3)$-2' and analogs thereof (*see, e.g.*, Prakash et al., U.S. 8,278,425), 4'-CH_2-O-$N(CH_3)$-2' (*see, e.g.*, Allerson et al., U.S. 7,696,345 and Allerson et al., U.S. 8,124,745), 4'-CH_2-$C(H)(CH_3)$-2' (*see, e.g.*, Zhou, *et al., J. Org. Chem.*,2009, *74*, 118-134), 4'-CH_2-$C(=CH_2)$-2' and analogs thereof (*see e.g.*,, Seth et al., U.S. 8,278,426), 4'-$C(R_aR_b)$-N(R)-O-2', 4'-$C(R_aR_b)$-O-N(R)-2', 4'-CH_2-O-N(R)-2', and 4'-CH_2-N(R)-O-2', wherein each R, R_a, and R_b is, independently, H, a protecting group, or C_1-C_{12} alkyl (*see, e.g.* Imanishi et al., U.S. 7,427,672).

In certain embodiments, such 4' to 2' bridges independently comprise from 1 to 4 linked groups independently selected from: $-[C(R_a)(R_b)]_n-$, $-[C(R_a)(R_b)]_n-O-$, $-C(R_a)=C(R_b)-$, $-C(R_a)=N-$, $-C(=NR_a)-$, $-C(=O)-$, $-C(=S)-$, $-O-$, $-Si(R_a)_2-$, $-S(=O)_x-$, and $-N(R_a)-$;

wherein:

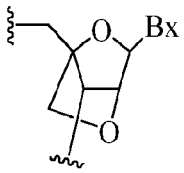
x is 0, 1, or 2;

n is 1, 2, 3, or 4;

each R_a and R_b is, independently, H, a protecting group, hydroxyl, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C_5-C_7 alicyclic radical, substituted C_5-C_7 alicyclic radical, halogen, OJ_1, NJ_1J_2, SJ_1, N_3, $COOJ_1$, acyl (C(=O)-H), substituted acyl, CN, sulfonyl ($S(=O)_2-J_1$), or sulfoxyl ($S(=O)-J_1$); and each J_1 and J_2 is, independently, H, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, acyl (C(=O)-H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C_1-C_{12} aminoalkyl, substituted C_1-C_{12} aminoalkyl, or a protecting group.

Additional bicyclic sugar moieties are known in the art, see, for example: Freier *et al., Nucleic Acids Research*, 1997, *25*(*22*), 4429-4443, Albaek *et al., J. Org. Chem.*, 2006, *71*, 7731-7740, Singh et al., *Chem. Commun.*, 1998, *4*, 455-456; Koshkin et al., *Tetrahedron*, 1998, *54*, 3607-3630; Wahlestedt et al., *Proc. Natl. Acad. Sci. U. S. A.*, 2000, *97*, 5633-5638; Kumar et al., *Bioorg. Med. Chem. Lett.*, 1998, *8*, 2219-2222; Singh et al., *J. Org. Chem.*, 1998, *63*, 10035-10039; Srivastava et al., *J. Am. Chem. Soc.*, 2007, *129*, 8362-8379; Elayadi *et al., Curr. Opinion Invens. Drugs*, 2001, *2*, 558-561; Braasch *et al., Chem. Biol.*, 2001, *8*, 1-7; Orum *et al., Curr. Opinion Mol. Ther.*, 2001, *3*, 239-243; Wengel et al.,U.S. 7,053,207, Imanishi et al., U.S. 6,268,490, Imanishi et al. U.S. 6,770,748, Imanishi et al., U.S. RE44,779; Wengel et al., U.S. 6,794,499, Wengel et al., U.S. 6,670,461; Wengel et al., U.S. 7,034,133, Wengel et al., U.S. 8,080,644; Wengel et al., U.S. 8,034,909; Wengel et al., U.S. 8,153,365; Wengel et al., U.S. 7,572,582; and Ramasamy et al., U.S. 6,525,191, Torsten et al., WO 2004/106356, Wengel et al., WO 1999/014226; Seth et al.,WO 2007/134181; Seth et al., U.S. 7,547,684; Seth et al., U.S. 7,666,854; Seth et al., U.S. 8,088,746; Seth et al., U.S. 7,750,131; Seth et al., U.S. 8,030,467; Seth et al., U.S. 8,268,980; Seth et al., U.S. 8,546,556; Seth et al., U.S. 8,530,640; Migawa et al., U.S. 9,012,421; Seth et al., U.S. 8,501,805; Allerson et al., US2008/0039618; and Migawa et al., US2015/0191727.

In certain embodiments, bicyclic sugar moieties and nucleosides incorporating such bicyclic sugar moieties are further defined by isomeric configuration. For example, an LNA nucleoside (described herein) may be in the α-L configuration or in the β-D configuration.



LNA (β-D-configuration)
bridge = 4'-CH_2-O-2'



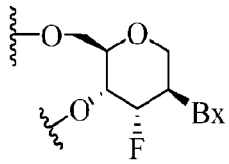
α-*L*-LNA (α-*L*-configuration)
bridge = 4'-CH_2-O-2'

α-L-methyleneoxy (4'-CH_2-O-2') or α-L-LNA bicyclic nucleosides have been incorporated into oligonucleotides that showed antisense activity (Frieden et al., *Nucleic Acids Research,* 2003, *21*, 6365-6372). Herein, general descriptions of bicyclic nucleosides include both isomeric configurations. When the positions of specific bicyclic nucleosides (*e.g.*, LNA or cEt) are identified in exemplified embodiments herein, they are in the β-D configuration, unless otherwise specified.

In certain embodiments, modified sugar moieties comprise one or more non-bridging sugar substituent and one or more bridging sugar substituent (e.g., 5'-substituted and 4'-2' bridged sugars).

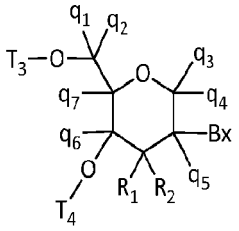
In certain embodiments, modified sugar moieties are sugar surrogates. In certain such embodiments, the oxygen atom of the sugar moiety is replaced, *e.g.*, with a sulfur, carbon or nitrogen atom. In certain such embodiments, such modified sugar moieties also comprise bridging and/or non-bridging substituents as described herein. For example, certain sugar surrogates comprise a 4'-sulfur atom and a substitution at the 2'-position (*see*, *e.g.*, Bhat et al., U.S. 7,875,733 and Bhat et al., U.S. 7,939,677) and/or the 5' position.

In certain embodiments, sugar surrogates comprise rings having other than 5 atoms. For example, in certain embodiments, a sugar surrogate comprises a six-membered tetrahydropyran ("THP"). Such tetrahydropyrans may be further modified or substituted. Nucleosides comprising such modified tetrahydropyrans include but are not limited to hexitol nucleic acid ("HNA"), anitol nucleic acid ("ANA"), manitol nucleic acid ("MNA") (*see* e.g., Leumann, CJ. *Bioorg. & Med. Chem.* 2002, *10*, 841-854), fluoro HNA:



F-HNA

("F-HNA", *see e.g.*, Swayze et al., U.S. 8,088,904; Swayze et al., U.S. 8,440,803; and Swayze et al., U.S. 9,005,906, F-HNA can also be referred to as a F-THP or 3'-fluoro tetrahydropyran), and nucleosides comprising additional modified THP compounds having the formula:



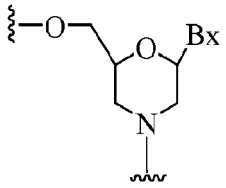
wherein, independently, for each of said modified THP nucleoside:

Bx is a nucleobase moiety;

T_3 and T_4 are each, independently, an internucleoside linking group linking the modified THP nucleoside to the remainder of an oligonucleotide or one of T_3 and T_4 is an internucleoside linking group linking the modified THP nucleoside to the remainder of an oligonucleotide and the other of T_3 and T_4 is H, a hydroxyl protecting group, a linked conjugate group, or a 5' or 3'-terminal group; q_1, q_2, q_3, q_4, q_5, q_6 and q_7 are each, independently, H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, or substituted C_2-C_6 alkynyl; and each of R_1 and R_2 is independently selected from among: hydrogen, halogen, substituted or unsubstituted alkoxy, NJ_1J_2, SJ_1, N_3, $OC(=X)J_1$, $OC(=X)NJ_1J_2$, $NJ_3C(=X)NJ_1J_2$, and CN, wherein X is O, S or NJ_1, and each J_1, J_2, and J_3 is, independently, H or C_1-C_6 alkyl.

In certain embodiments, modified THP nucleosides are provided wherein q_1, q_2, q_3, q_4, q_5, q_6 and q_7 are each H. In certain embodiments, at least one of q_1, q_2, q_3, q_4, q_5, q_6 and q_7 is other than H. In certain embodiments, at least one of q_1, q_2, q_3, q_4, q_5, q_6 and q_7 is methyl. In certain embodiments, modified THP nucleosides are provided wherein one of R_1 and R_2 is F. In certain embodiments, R_1 is F and R_2 is H, in certain embodiments, R_1 is methoxy and R_2 is H, and in certain embodiments, R_1 is methoxyethoxy and R_2 is H.

In certain embodiments, sugar surrogates comprise rings having more than 5 atoms and more than one heteroatom. For example, nucleosides comprising morpholino sugar moieties and their use in oligonucleotides have been reported (*see, e.g.*, Braasch et al., Biochemistry, 2002, *41*, 4503-4510 and Summerton et al., U.S. 5,698,685; Summerton et al., U.S. 5,166,315; Summerton et al., U.S. 5,185,444; and Summerton et al., U.S. 5,034,506). As used here, the term "morpholino" means a sugar surrogate having the following structure:



In certain embodiments, morpholinos may be modified, for example by adding or altering various substituent groups from the above morpholino structure. Such sugar surrogates are refered to herein as "modifed morpholinos."

In certain embodiments, sugar surrogates comprise acyclic moieites. Examples of nucleosides and oligonucleotides comprising such acyclic sugar surrogates include but are not limited to: peptide nucleic acid

("PNA"), acyclic butyl nucleic acid (*see, e.g.,* Kumar et al., *Org. Biomol. Chem.*, 2013, *11*, 5853-5865), and nucleosides and oligonucleotides described in Manoharan et al., US2013/130378.

Many other bicyclic and tricyclic sugar and sugar surrogate ring systems are known in the art that can be used in modified nucleosides.

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2. Modified Nucleobases

Nucleobase (or base) modifications or substitutions are structurally distinguishable from, yet functionally interchangeable with, naturally occurring or synthetic unmodified nucleobases. Both natural and modified nucleobases are capable of participating in hydrogen bonding. Such nucleobase modifications can 10 impart nuclease stability, binding affinity or some other beneficial biological property to antisense compounds.

In certain embodiments, compounds described herein comprise modified oligonucleotides. In certain embodiments, modified oligonucleotides comprise one or more nucleoside comprising an unmodified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more nucleoside comprising a modified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more nucleoside 15 that does not comprise a nucleobase, referred to as an abasic nucleoside.

In certain embodiments, modified nucleobases are selected from: 5-substituted pyrimidines, 6-azapyrimi¬dines, alkyl or alkynyl substituted pyrimidines, alkyl substituted purines, and N-2, N-6 and O-6 substituted purines. In certain embodiments, modified nucleobases are selected from: 2-aminopropyladenine, 5-hydroxymethyl cytosine, 5-methylcytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-N-methylguanine, 20 6-N-methyladenine, 2-propyladenine , 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-propynyl (C≡C-CH3) uracil, 5-propynylcytosine, 6-azouracil, 6-azocytosine, 6-azothymine, 5-ribosyluracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl, 8-aza and other 8-substituted purines, 5-halo, particularly 5-bromo, 5-trifluoromethyl, 5-halouracil, and 5-halocytosine, 7-methylguanine, 7-methyladenine, 2-F-adenine, 2-aminoadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine, 3-deazaadenine, 6-N-25 benzoyladenine, 2-N-isobutyrylguanine, 4-N-benzoylcytosine, 4-N-benzoyluracil, 5-methyl 4-N-benzoylcytosine, 5-methyl 4-N-benzoyluracil, universal bases, hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases. Further modified nucleobases include tricyclic pyrimidines, such as 1,3-diazaphenoxazine-2-one, 1,3-diazaphenothiazine-2-one and 9-(2-aminoethoxy)-1,3-diazaphenoxazine-2-one (G-clamp). Modified nucleobases may also include those in which the purine or pyrimidine base is replaced 30 with other heterocycles, for example 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone. Further nucleobases include those disclosed in Merigan et al., U.S. 3,687,808, those disclosed in The Concise Encyclopedia Of Polymer Science And Engineering, Kroschwitz, J.I., Ed., John Wiley & Sons, 1990, 858-859; Englisch et al., Angewandte Chemie, International Edition, 1991, 30, 613; Sanghvi, Y.S., Chapter 15, Antisense Research and Applications, Crooke, S.T. and Lebleu, B., Eds., CRC Press, 1993, 273-288; and those disclosed 35 in Chapters 6 and 15, Antisense Drug Technology, Crooke S.T., Ed., CRC Press, 2008, 163-166 and 442-443.

Publications that teach the preparation of certain of the above noted modified nucleobases as well as

other modified nucleobases include without limitation, Manoharan et al., US2003/0158403, Manoharan et al., US2003/0175906; Dinh et al., U.S. 4,845,205; Spielvogel et al., U.S. 5,130,302; Rogers et al., U.S. 5,134,066; Bischofberger et al., U.S. 5,175,273; Urdea et al., U.S. 5,367,066; Benner et al., U.S. 5,432,272; Matteucci et al., U.S. 5,434,257; Gmeiner et al., U.S. 5,457,187; Cook et al., U.S. 5,459,255; Froehler et al., U.S. 5,484,908; Matteucci et al., U.S. 5,502,177; Hawkins et al., U.S. 5,525,711; Haralambidis et al., U.S. 5,552,540; Cook et al., U.S. 5,587,469; Froehler et al., U.S. 5,594,121; Switzer et al., U.S. 5,596,091; Cook et al., U.S. 5,614,617; Froehler et al., U.S. 5,645,985; Cook et al., U.S. 5,681,941; Cook et al., U.S. 5,811,534; Cook et al., U.S. 5,750,692; Cook et al., U.S. 5,948,903; Cook et al., U.S. 5,587,470; Cook et al., U.S. 5,457,191; Matteucci et al., U.S. 5,763,588; Froehler et al., U.S. 5,830,653; Cook et al., U.S. 5,808,027; Cook et al., U.S. 6,166,199; and Matteucci et al., U.S. 6,005,096.

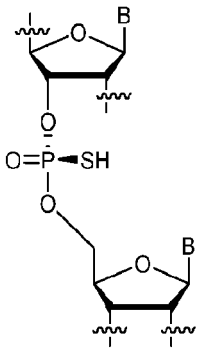
In certain embodiments, compounds targeted to a MALAT1 nucleic acid comprise one or more modified nucleobases. In certain embodiments, the modified nucleobase is 5-methylcytosine. In certain embodiments, each cytosine is a 5-methylcytosine.

3. Modified Internucleoside Linkages

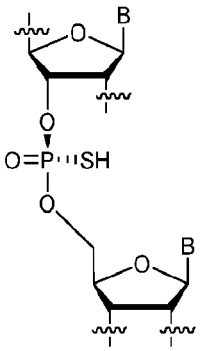
The naturally occuring internucleoside linkage of RNA and DNA is a 3' to 5' phosphodiester linkageIn certain embodiments, compounds described herein having one or more modified, i.e. non-naturally occurring, internucleoside linkages are often selected over compounds having naturally occurring internucleoside linkages because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for target nucleic acids, and increased stability in the presence of nucleases.

Representative internucleoside linkages having a chiral center include but are not limited to alkylphosphonates and phosphorothioates. Modified oligonucleotides comprising internucleoside linkages having a chiral center can be prepared as populations of modified oligonucleotides comprising stereorandom internucleoside linkages, or as populations of modified oligonucleotides comprising phosphorothioate linkages in particular stereochemical configurations. In certain embodiments, populations of modified oligonucleotides comprise phosphorothioate internucleoside linkages wherein all of the phosphorothioate internucleoside linkages are stereorandom. Such modified oligonucleotides can be generated using synthetic methods that result in random selection of the stereochemical configuration of each phosphorothioate linkage. Nonetheless, as is well understood by those of skill in the art, each individual phosphorothioate of each individual oligonucleotide molecule has a defined stereoconfiguration. In certain embodiments, populations of modified oligonucleotides are enriched for modified oligonucleotides comprising one or more particular phosphorothioate internucleoside linkages in a particular, independently selected stereochemical configuration. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 65% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 70% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 80%

of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 90% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 99% of the molecules in the population. Such chirally enriched populations of modified oligonucleotides can be generated using synthetic methods known in the art, *e.g.*, methods described in Oka et al., *JACS* 125, 8307 (2003), Wan et al. *Nuc. Acid. Res.* 42, 13456 (2014), and WO 2017/015555. In certain embodiments, a population of modified oligonucleotides is enriched for modified oligonucleotides having at least one indicated phosphorothioate in the (*S*p) configuration. In certain embodiments, a population of modified oligonucleotides is enriched for modified oligonucleotides having at least one phosphorothioate in the (*R*p) configuration. In certain embodiments, modified oligonucleotides comprising (*R*p) and/or (*S*p) phosphorothioates comprise one or more of the following formulas, respectively, wherein "B" indicates a nucleobase:



(R_p)



(S_p)

Unless otherwise indicated, chiral internucleoside linkages of modified oligonucleotides described herein can be stereorandom or in a particular stereochemical configuration.

In certain embodiments, compounds targeted to an MALAT1 nucleic acid comprise one or more modified internucleoside linkages. In certain embodiments, the modified internucleoside linkages are phosphorothioate linkages. In certain embodiments, each internucleoside linkage of an antisense compound is a phosphorothioate internucleoside linkage.

In certain embodiments, compounds described herein comprise oligonucleotides. Oligonucleotides having modified internucleoside linkages include internucleoside linkages that retain a phosphorus atom as well as internucleoside linkages that do not have a phosphorus atom. Representative phosphorus containing internucleoside linkages include, but are not limited to, phosphodiesters, phosphotriesters, methylphosphonates, phosphoramidate, and phosphorothioates. Methods of preparation of phosphorous-containing and non-phosphorous-containing linkages are well known.

In certain embodiments, nucleosides of modified oligonucleotides may be linked together using any internucleoside linkage. The two main classes of internucleoside linking groups are defined by the presence or absence of a phosphorus atom. Representative phosphorus-containing internucleoside linkages include but are not limited to phosphates, which contain a phosphodiester bond ("P=O") (also referred to as unmodified or

naturally occurring linkages), phosphotriesters, methylphosphonates, phosphoramidates, and phosphorothioates ("P=S"), and phosphorodithioates ("HS-P=S"). Representative non-phosphorus containing internucleoside linking groups include but are not limited to methylenemethylimino (-CH2-N(CH3)-O-CH2-), thiodiester, thionocarbamate (-O-C(=O)(NH)-S-); siloxane (-O-SiH2-O-); and N,N'-dimethylhydrazine (-CH2-N(CH3)-N(CH3)-). Modified internucleoside linkages, compared to naturally occurring phosphate linkages, can be used to alter, typically increase, nuclease resistance of the oligonucleotide. In certain embodiments, internucleoside linkages having a chiral atom can be prepared as a racemic mixture, or as separate enantiomers. Representative chiral internucleoside linkages include but are not limited to alkylphosphonates and phosphorothioates. Methods of preparation of phosphorous-containing and non-phosphorous-containing internucleoside linkages are well known to those skilled in the art.

Neutral internucleoside linkages include, without limitation, phosphotriesters, methylphosphonates, MMI (3'-CH2-N(CH3)-O-5'), amide-3 (3'-CH2-C(=O)-N(H)-5'), amide-4 (3'-CH2-N(H)-C(=O)-5'), formacetal (3'-O-CH2-O-5'), methoxypropyl, and thioformacetal (3'-S-CH2-O-5'). Further neutral internucleoside linkages include nonionic linkages comprising siloxane (dialkylsiloxane), carboxylate ester, carboxamide, sulfide, sulfonate ester and amides (See for example: Carbohydrate Modifications in Antisense Research; Y.S. Sanghvi and P.D. Cook, Eds., ACS Symposium Series 580; Chapters 3 and 4, 40-65). Further neutral internucleoside linkages include nonionic linkages comprising mixed N, O, S and CH2 component parts.

In certain embodiments, oligonucleotides comprise modified internucleoside linkages arranged along the oligonucleotide or region thereof in a defined pattern or modified internucleoside linkage motif. In certain embodiments, internucleoside linkages are arranged in a gapped motif. In such embodiments, the internucleoside linkages in each of two wing regions are different from the internucleoside linkages in the gap region. In certain embodiments the internucleoside linkages in the wings are phosphodiester and the internucleoside linkages in the gap are phosphorothioate. The nucleoside motif is independently selected, so such oligonucleotides having a gapped internucleoside linkage motif may or may not have a gapped nucleoside motif and if it does have a gapped nucleoside motif, the wing and gap lengths may or may not be the same.

In certain embodiments, oligonucleotides comprise a region having an alternating internucleoside linkage motif. In certain embodiments, oligonucleotides comprise a region of uniformly modified internucleoside linkages. In certain such embodiments, the oligonucleotide comprises a region that is uniformly linked by phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide is uniformly linked by phosphorothioate. In certain embodiments, each internucleoside linkage of the oligonucleotide is selected from phosphodiester and phosphorothioate. In certain embodiments, each internucleoside linkage of the oligonucleotide is selected from phosphodiester and phosphorothioate and at least one internucleoside linkage is phosphorothioate.

In certain embodiments, the oligonucleotide comprises at least 6 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least 8 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least 10 phosphorothioate internucleoside

linkages. In certain embodiments, the oligonucleotide comprises at least one block of at least 6 consecutive phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least one block of at least 8 consecutive phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least one block of at least 10 consecutive phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least block of at least one 12 consecutive phosphorothioate internucleoside linkages. In certain such embodiments, at least one such block is located at the 3' end of the oligonucleotide. In certain such embodiments, at least one such block is located within 3 nucleosides of the 3' end of the oligonucleotide.

In certain embodiments, oligonucleotides comprise one or more methylphosponate linkages. In certain embodiments, oligonucleotides having a gapmer nucleoside motif comprise a linkage motif comprising all phosphorothioate linkages except for one or two methylphosponate linkages. In certain embodiments, one methylphosponate linkage is in the central gap of an oligonucleotide having a gapmer nucleoside motif.

In certain embodiments, it is desirable to arrange the number of phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages to maintain nuclease resistance. In certain embodiments, it is desirable to arrange the number and position of phosphorothioate internucleoside linkages and the number and position of phosphodiester internucleoside linkages to maintain nuclease resistance. In certain embodiments, the number of phosphorothioate internucleoside linkages may be decreased and the number of phosphodiester internucleoside linkages may be increased. In certain embodiments, the number of phosphorothioate internucleoside linkages may be decreased and the number of phosphodiester internucleoside linkages may be increased while still maintaining nuclease resistance. In certain embodiments it is desirable to decrease the number of phosphorothioate internucleoside linkages while retaining nuclease resistance. In certain embodiments it is desirable to increase the number of phosphodiester internucleoside linkages while retaining nuclease resistance.

Certain Motifs

In certain embodiments, compounds described herein comprise oligonucleotides. Oligonucleotides can have a motif, *e.g.* a pattern of unmodified and/or modified sugar moieties, nucleobases, and/or internucleoside linkages. In certain embodiments, modified oligonucleotides comprise one or more modified nucleoside comprising a modified sugar. In certain embodiments, modified oligonucleotides comprise one or more modified nucleosides comprising a modified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more modified internucleoside linkage. In such embodiments, the modified, unmodified, and differently modified sugar moieties, nucleobases, and/or internucleoside linkages of a modified oligonucleotide define a pattern or motif. In certain embodiments, the patterns of sugar moieties, nucleobases, and internucleoside linkages are each independent of one another. Thus, a modified oligonucleotide may be described by its sugar motif, nucleobase motif and/or internucleoside linkage motif (as used herein, nucleobase motif describes the modifications to the nucleobases independent of the sequence of nucleobases).

a. Certain Sugar Motifs

In certain embodiments, compounds described herein comprise oligonucleotides. In certain embodiments, oligonucleotides comprise one or more type of modified sugar and/or unmodified sugar moiety arranged along the oligonucleotide or region thereof in a defined pattern or sugar motif. In certain instances, such sugar motifs include but are not limited to any of the sugar modifications discussed herein.

In certain embodiments, modified oligonucleotides comprise or consist of a region having a gapmer motif, which comprises two external regions or "wings" and a central or internal region or "gap." The three regions of a gapmer motif (the 5'-wing, the gap, and the 3'-wing) form a contiguous sequence of nucleosides wherein at least some of the sugar moieties of the nucleosides of each of the wings differ from at least some of the sugar moieties of the nucleosides of the gap. Specifically, at least the sugar moieties of the nucleosides of each wing that are closest to the gap (the 3'-most nucleoside of the 5'-wing and the 5'-most nucleoside of the 3'-wing) differ from the sugar moiety of the neighboring gap nucleosides, thus defining the boundary between the wings and the gap (i.e., the wing/gap junction). In certain embodiments, the sugar moieties within the gap are the same as one another. In certain embodiments, the gap includes one or more nucleoside having a sugar moiety that differs from the sugar moiety of one or more other nucleosides of the gap. In certain embodiments, the sugar motifs of the two wings are the same as one another (symmetric gapmer). In certain embodiments, the sugar motif of the 5'-wing differs from the sugar motif of the 3'-wing (asymmetric gapmer).

In certain embodiments, the wings of a gapmer comprise 1-5 nucleosides. In certain embodiments, the wings of a gapmer comprise 2-5 nucleosides. In certain embodiments, the wings of a gapmer comprise 3-5 nucleosides. In certain embodiments, the nucleosides of a gapmer are all modified nucleosides.

In certain embodiments, the gap of a gapmer comprises 7-12 nucleosides. In certain embodiments, the gap of a gapmer comprises 7-10 nucleosides. In certain embodiments, the gap of a gapmer comprises 8-10 nucleosides. In certain embodiments, the gap of a gapmer comprises 10 nucleosides. In certain embodiment, each nucleoside of the gap of a gapmer is an unmodified 2'-deoxy nucleoside.

In certain embodiments, the gapmer is a deoxy gapmer. In such embodiments, the nucleosides on the gap side of each wing/gap junction are unmodified 2'-deoxy nucleosides and the nucleosides on the wing sides of each wing/gap junction are modified nucleosides. In certain such embodiments, each nucleoside of the gap is an unmodified 2'-deoxy nucleoside. In certain such embodiments, each nucleoside of each wing is a modified nucleoside.

In certain embodiments, a modified oligonucleotide has a fully modified sugar motif wherein each nucleoside of the modified oligonucleotide comprises a modified sugar moiety. In certain embodiments, modified oligonucleotides comprise or consist of a region having a fully modified sugar motif wherein each nucleoside of the region comprises a modified sugar moiety. In certain embodiments, modified oligonucleotides comprise or consist of a region having a fully modified sugar motif, wherein each nucleoside within the fully modified region comprises the same modified sugar moiety, referred to herein as a uniformly modified sugar motif. In certain embodiments, a fully modified oligonucleotide is a uniformly modified

oligonucleotide. In certain embodiments, each nucleoside of a uniformly modified comprises the same 2'-modification.

In certain embodiments, a modified oligonucleotide can comprise a sugar motif described in Swayze et al., US2010/0197762; Freier et al., US2014/0107330; Freier et al., US2015/0184153; and Seth et al., US2015/0267195, each of which is incorporated by reference in its entirety herein.

Certain embodiments provided herein are directed to modified oligomeric compounds useful for inhibiting target nucleic acid expression, which can be useful for treating, preventing, ameliorating, or slowing progression of a disease associated with such a target nucleic acid. In certain embodiments, the modified oligomeric compounds comprise antisense oligonucleotides that are gapmers having certain sugar motifs. In certain embodiments, the gapmer sugar motifs provided herein can be combined with any nucleobase sequence and any internucleoside linkage motif to form potent antisense oligonucleotides.

In certain embodiments, a method comprises contacting a cell or administering to a subject a compound comprising a modified oligonucleotide consisting of 16 linked nucleosides and having the motif: ekk-d9-kkee, wherein 'd' represents a 2'-deoxyribose sugar, 'k' represents a cEt nucleoside, and 'e' represents a 2'-MOE nucleoside. In certain embodiments, the cell is a cancer cell. In certain embodiments, the subject has cancer. In certain embodiments, administering the compound to the subject treats the subject's cancer.

In certain embodiments, a method comprises contacting a cell or administering to a subject a compound comprising a modified oligonucleotide consisting of 16 linked nucleosides and having the motif: k-d9-kekeke, wherein 'd' represents a 2'-deoxyribose sugar, 'k' represents a cEt nucleoside, and 'e' represents a 2'-MOE nucleoside. In certain embodiments, the cell is a cancer cell. In certain embodiments, the subject has cancer. In certain embodiments, administering the compound to the subject treats the subject's cancer.

In certain embodiments, a method comprises contacting a cell or administering to a subject a compound comprising a modified oligonucleotide consisting of 16 linked nucleosides and having the motif: kkk-d8-kekek, wherein 'd' represents a 2'-deoxyribose sugar, 'k' represents a cEt nucleoside, and 'e' represents a 2'-MOE nucleoside. In certain embodiments, the cell is a cancer cell. In certain embodiments, the subject has cancer. In certain embodiments, administering the compound to the subject treats the subject's cancer.

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In certain embodiments, a method comprises contacting a cell or administering to a subject a compound comprising a modified oligonucleotide consisting of 16 linked nucleosides and having the motif: kk-d9-kdkdk, wherein 'd' represents a 2'-deoxyribose sugar, 'k' represents a cEt nucleoside, and 'e' represents a 2'-MOE nucleoside. In certain embodiments, the cell is a cancer cell. In certain embodiments, the subject has cancer. In certain embodiments, administering the compound to the subject treats the subject's cancer.

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b. Certain Nucleobase Motifs

In certain embodiments, compounds described herein comprise oligonucleotides. In certain embodiments, oligonucleotides comprise modified and/or unmodified nucleobases arranged along the oligonucleotide or region thereof in a defined pattern or motif. In certain embodiments, each nucleobase is modified. In certain embodiments, none of the nucleobases are modified. In certain embodiments, each purine or each pyrimidine is modified. In certain embodiments, each adenine is modified. In certain embodiments, each guanine is modified. In certain embodiments, each thymine is modified. In certain embodiments, each uracil is modified. In certain embodiments, each cytosine is modified. In certain embodiments, some or all of the cytosine nucleobases in a modified oligonucleotide are 5-methylcytosines.

In certain embodiments, modified oligonucleotides comprise a block of modified nucleobases. In certain such embodiments, the block is at the 3'-end of the oligonucleotide. In certain embodiments the block is within 3 nucleosides of the 3'-end of the oligonucleotide. In certain embodiments, the block is at the 5'-end of the oligonucleotide. In certain embodiments the block is within 3 nucleosides of the 5'-end of the oligonucleotide.

In certain embodiments, oligonucleotides having a gapmer motif comprise a nucleoside comprising a modified nucleobase. In certain such embodiments, one nucleoside comprising a modified nucleobase is in the central gap of an oligonucleotide having a gapmer motif. In certain such embodiments, the sugar moiety of said nucleoside is a 2'-deoxyribosyl moiety. In certain embodiments, the modified nucleobase is selected from: a 2-thiopyrimidine and a 5-propynepyrimidine.

c. Certain Internucleoside Linkage Motifs

In certain embodiments, compounds described herein comprise oligonucleotides. In certain embodiments, oligonucleotides comprise modified and/or unmodified internucleoside linkages arranged along

the oligonucleotide or region thereof in a defined pattern or motif. In certain embodiments, essentially each internucleoside linking group is a phosphate internucleoside linkage (P=O). In certain embodiments, each internucleoside linking group of a modified oligonucleotide is a phosphorothioate (P=S). In certain embodiments, each internucleoside linking group of a modified oligonucleotide is independently selected from a phosphorothioate and phosphate internucleoside linkage. In certain embodiments, the sugar motif of a modified oligonucleotide is a gapmer and the internucleoside linkages within the gap are all modified. In certain such embodiments, some or all of the internucleoside linkages in the wings are unmodified phosphate linkages. In certain embodiments, the terminal internucleoside linkages are modified.

4. Certain Modified Oligonucleotides

In certain embodiments, compounds described herein comprise modified oligonucleotides. In certain embodiments, the above modifications (sugar, nucleobase, internucleoside linkage) are incorporated into a modified oligonucleotide. In certain embodiments, modified oligonucleotides are characterized by their modification, motifs, and overall lengths. In certain embodiments, such parameters are each independent of one another. Thus, unless otherwise indicated, each internucleoside linkage of an oligonucleotide having a gapmer sugar motif may be modified or unmodified and may or may not follow the gapmer modification pattern of the sugar modifications. For example, the internucleoside linkages within the wing regions of a sugar gapmer may be the same or different from one another and may be the same or different from the internucleoside linkages of the gap region of the sugar motif. Likewise, such gapmer oligonucleotides may comprise one or more modified nucleobase independent of the gapmer pattern of the sugar modifications. Furthermore, in certain instances, an oligonucleotide is described by an overall length or range and by lengths or length ranges of two or more regions (e.g., a regions of nucleosides having specified sugar modifications), in such circumstances it may be possible to select numbers for each range that result in an oligonucleotide having an overall length falling outside the specified range. In such circumstances, both elements must be satisfied. For example, in certain embodiments, a modified oligonucleotide consists of 15-20 linked nucleosides and has a sugar motif consisting of three regions, A, B, and C, wherein region A consists of 2-6 linked nucleosides having a specified sugar motif, region B consists of 6-10 linked nucleosides having a specified sugar motif, and region C consists of 2-6 linked nucleosides having a specified sugar motif. Such embodiments do not include modified oligonucleotides where A and C each consist of 6 linked nucleosides and B consists of 10 linked nucleosides (even though those numbers of nucleosides are permitted within the requirements for A, B, and C) because the overall length of such oligonucleotide is 22, which exceeds the upper limit of the overall length of the modified oligonucleotide (20). Herein, if a description of an oligonucleotide is silent with respect to one or more parameter, such parameter is not limited. Thus, a modified oligonucleotide described only as having a gapmer sugar motif without further description may have any length, internucleoside linkage motif, and nucleobase motif. Unless otherwise indicated, all modifications are independent of nucleobase sequence.

Certain Conjugated Compounds

In certain embodiments, the compounds described herein comprise or consist of an oligonucleotide (modified or unmodified) and optionally one or more conjugate groups and/or terminal groups. Conjugate groups consist of one or more conjugate moiety and a conjugate linker which links the conjugate moiety to the oligonucleotide. Conjugate groups may be attached to either or both ends of an oligonucleotide and/or at any internal position. In certain embodiments, conjugate groups are attached to the 2'-position of a nucleoside of a modified oligonucleotide. In certain embodiments, conjugate groups that are attached to either or both ends of an oligonucleotide are terminal groups. In certain such embodiments, conjugate groups or terminal groups are attached at the 3' and/or 5'-end of oligonucleotides. In certain such embodiments, conjugate groups (or terminal groups) are attached at the 3'-end of oligonucleotides. In certain embodiments, conjugate groups are attached near the 3'-end of oligonucleotides. In certain embodiments, conjugate groups (or terminal groups) are attached at the 5'-end of oligonucleotides. In certain embodiments, conjugate groups are attached near the 5'-end of oligonucleotides.

In certain embodiments, the oligonucleotide is modified. In certain embodiments, the oligonucleotide of a compound has a nucleobase sequence that is complementary to a target nucleic acid. In certain embodiments, oligonucleotides are complementary to a messenger RNA (mRNA). In certain embodiments, oligonucleotides are complementary to a sense transcript.

Examples of terminal groups include but are not limited to conjugate groups, capping groups, phosphate moieties, protecting groups, modified or unmodified nucleosides, and two or more nucleosides that are independently modified or unmodified.

A. Certain Conjugate Groups

In certain embodiments, oligonucleotides are covalently attached to one or more conjugate groups. In certain embodiments, conjugate groups modify one or more properties of the attached oligonucleotide, including but not limited to pharmacodynamics, pharmacokinetics, stability, binding, absorption, tissue distribution, cellular distribution, cellular uptake, charge and clearanceIn certain embodiments, conjugate groups impart a new property on the attached oligonucleotide, *e.g.*, fluorophores or reporter groups that enable detection of the oligonucleotide.

Certain conjugate groups and conjugate moieties have been described previously, for example: cholesterol moiety (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86, 6553-6556), cholic acid (Manoharan et al., *Bioorg. Med. Chem. Lett.*, 1994, *4*, 1053-1060), a thioether, *e.g.*, hexyl-S-tritylthiol (Manoharan et al., *Ann. N.Y. Acad. Sci.*, 1992, *660*, 306-309; Manoharan et al., *Bioorg. Med. Chem. Lett.*, 1993, *3*, 2765-2770), a thiocholesterol (Oberhauser et al., *Nucl. Acids Res.*, 1992, *20*, 533-538), an aliphatic chain, *e.g.*, do-decan-diol or undecyl residues (Saison-Behmoaras et al., *EMBO J.*, 1991, 10, 1111-1118; Kabanov et al., *FEBS Lett.*, 1990, 259, 327-330; Svinarchuk et al., *Biochimie*, 1993, *75*, 49-54), a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan et al.,

Tetrahedron Lett., 1995, *36*, 3651-3654; Shea et al., *Nucl. Acids Res.*, 1990, 18, 3777-3783), a polyamine or a polyethylene glycol chain (Manoharan et al., *Nucleosides & Nucleotides*, 1995, 14, 969-973), or adamantane acetic, a palmityl moiety (Mishra et al., *Biochim. Biophys. Acta*, 1995, 1264, 229-237), an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke et al., *J. Pharmacol. Exp. Ther.*, 1996, *i*, 923-937), a tocopherol group (Nishina et al., *Molecular Therapy Nucleic Acids*, 2015, *4*, e220; doi:10.1038/mtna.2014.72 and Nishina et al., *Molecular Therapy*, 2008, 16, 734-740), or a GalNAc cluster (*e.g.*, WO2014/179620).

1. Conjugate Moieties

Conjugate moieties include, without limitation, intercalators, reporter molecules, polyamines, polyamides, peptides, carbohydrates (e.g., GalNAc), vitamin moieties, polyethylene glycols, thioethers, polyethers, cholesterols, thiocholesterols, cholic acid moieties, folate, lipids, phospholipids, biotin, phenazine, phenanthridine, anthraquinone, adamantane, acridine, fluoresceins, rhodamines, coumarins, fluorophores, and dyes.

In certain embodiments, a conjugate moiety comprises an active drug substance, for example, aspirin, warfarin, phenylbutazone, ibuprofen, suprofen, fen-bufen, ketoprofen, (*S*)-(+)-pranoprofen, carprofen, dansylsarcosine, 2,3,5-triiodobenzoic acid, fingolimod, flufenamic acid, folinic acid, a benzothiadiazide, chlorothiazide, a diazepine, indo-methicin, a barbiturate, a cephalosporin, a sulfa drug, an antidiabetic, an antibacterial or an antibiotic.

2. Conjugate linkers

Conjugate moieties are attached to oligonucleotides through conjugate linkers. In certain compounds, a conjugate group is a single chemical bond (i.e. conjugate moiety is attached to an oligonucleotide via a conjugate linker through a single bond). In certain embodiments, the conjugate linker comprises a chain structure, such as a hydrocarbyl chain, or an oligomer of repeating units such as ethylene glycol, nucleosides, or amino acid units.

In certain embodiments, a conjugate linker comprises one or more groups selected from alkyl, amino, oxo, amide, disulfide, polyethylene glycol, ether, thioether, and hydroxylamino. In certain such embodiments, the conjugate linker comprises groups selected from alkyl, amino, oxo, amide and ether groups. In certain embodiments, the conjugate linker comprises groups selected from alkyl and amide groups. In certain embodiments, the conjugate linker comprises groups selected from alkyl and ether groups. In certain embodiments, the conjugate linker comprises at least one phosphorus moiety. In certain embodiments, the conjugate linker comprises at least one phosphate group. In certain embodiments, the conjugate linker includes at least one neutral linking group.

In certain embodiments, conjugate linkers, including the conjugate linkers described above, are bifunctional linking moieties, *e.g.*, those known in the art to be useful for attaching conjugate groups to parent compounds, such as the oligonucleotides provided herein. In general, a bifunctional linking moiety comprises at least two functional groups. One of the functional groups is selected to bind to a particular site on a compound

and the other is selected to bind to a conjugate group. Examples of functional groups used in a bifunctional linking moiety include but are not limited to electrophiles for reacting with nucleophilic groups and nucleophiles for reacting with electrophilic groups. In certain embodiments, bifunctional linking moieties comprise one or more groups selected from amino, hydroxyl, carboxylic acid, thiol, alkyl, alkenyl, and alkynyl.

Examples of conjugate linkers include but are not limited to pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) and 6-aminohexanoic acid (AHEX or AHA). Other conjugate linkers include but are not limited to substituted or unsubstituted C_1-C_{10} alkyl, substituted or unsubstituted C_2-C_{10} alkenyl or substituted or unsubstituted C_2-C_{10} alkynyl, wherein a nonlimiting list of preferred substituent groups includes hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl.

In certain embodiments, conjugate linkers comprise 1-10 linker-nucleosides. In certain embodiments, such linker-nucleosides are modified nucleosides. In certain embodiments such linker-nucleosides comprise a modified sugar moiety. In certain embodiments, linker-nucleosides are unmodified. In certain embodiments, linker-nucleosides comprise an optionally protected heterocyclic base selected from a purine, substituted purine, pyrimidine or substituted pyrimidine. In certain embodiments, a cleavable moiety is a nucleoside selected from uracil, thymine, cytosine, 4-N-benzoylcytosine, 5-methylcytosine, 4-N-benzoyl-5-methylcytosine, adenine, 6-N-benzoyladenine, guanine and 2-N-isobutyrylguanine. It is typically desirable for linker-nucleosides to be cleaved from the compound after it reaches a target tissue. Accordingly, linker-nucleosides are typically linked to one another and to the remainder of the compound through cleavable bonds. In certain embodiments, such cleavable bonds are phosphodiester bonds.

Herein, linker-nucleosides are not considered to be part of the oligonucleotide. Accordingly, in embodiments in which a compound comprises an oligonucleotide consisting of a specified number or range of linked nucleosides and/or a specified percent complementarity to a reference nucleic acid and the compound also comprises a conjugate group comprising a conjugate linker comprising linker-nucleosides, those linker-nucleosides are not counted toward the length of the oligonucleotide and are not used in determining the percent complementarity of the oligonucleotide for the reference nucleic acid. For example, a compound may comprise (1) a modified oligonucleotide consisting of 8-30 nucleosides and (2) a conjugate group comprising 1-10 linker-nucleosides that are contiguous with the nucleosides of the modified oligonucleotide. The total number of contiguous linked nucleosides in such a compound is more than 30. Alternatively, an compound may comprise a modified oligonucleotide consisting of 8-30 nucleosides and no conjugate group. The total number of contiguous linked nucleosides in such a compound is no more than 30. Unless otherwise indicated conjugate linkers comprise no more than 10 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 5 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 3 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 2 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 1 linker-nucleoside.

In certain embodiments, it is desirable for a conjugate group to be cleaved from the oligonucleotide.

For example, in certain circumstances compounds comprising a particular conjugate moiety are better taken up by a particular cell type, but once the compound has been taken up, it is desirable that the conjugate group be cleaved to release the unconjugated or parent oligonucleotide. Thus, certain conjugate may comprise one or more cleavable moieties, typically within the conjugate linker. In certain embodiments, a cleavable moiety is a cleavable bond. In certain embodiments, a cleavable moiety is a group of atoms comprising at least one cleavable bond. In certain embodiments, a cleavable moiety comprises a group of atoms having one, two, three, four, or more than four cleavable bonds. In certain embodiments, a cleavable moiety is selectively cleaved inside a cell or subcellular compartment, such as a lysosome. In certain embodiments, a cleavable moiety is selectively cleaved by endogenous enzymes, such as nucleases.

In certain embodiments, a cleavable bond is selected from among: an amide, an ester, an ether, one or both esters of a phosphodiester, a phosphate ester, a carbamate, or a disulfide. In certain embodiments, a cleavable bond is one or both of the esters of a phosphodiester. In certain embodiments, a cleavable moiety comprises a phosphate or phosphodiester. In certain embodiments, the cleavable moiety is a phosphate linkage between an oligonucleotide and a conjugate moiety or conjugate group.

In certain embodiments, a cleavable moiety comprises or consists of one or more linker-nucleosides. In certain such embodiments, one or more linker-nucleosides are linked to one another and/or to the remainder of the compound through cleavable bonds. In certain embodiments, such cleavable bonds are unmodified phosphodiester bonds. In certain embodiments, a cleavable moiety is 2'-deoxy nucleoside that is attached to either the 3' or 5'-terminal nucleoside of an oligonucleotide by a phosphate internucleoside linkage and covalently attached to the remainder of the conjugate linker or conjugate moiety by a phosphate or phosphorothioate linkage. In certain such embodiments, the cleavable moiety is 2'-deoxyadenosine.

Compositions and Methods for Formulating Pharmaceutical Compositions

Compounds described herein may be admixed with pharmaceutically acceptable active or inert substances for the preparation of pharmaceutical compositions or formulations. Compositions and methods for the formulation of pharmaceutical compositions are dependent upon a number of criteria, including, but not limited to, route of administration, extent of disease, or dose to be administered.

Certain embodiments provide pharmaceutical compositions comprising one or more compounds or a salt thereof. In certain embodiments, the compounds are antisense compounds or oligomeric compounds. In certain embodiments, the compounds comprise or consist of a modified oligonucleotide. In certain such embodiments, the pharmaceutical composition comprises a suitable pharmaceutically acceptable diluent or carrier. In certain embodiments, a pharmaceutical composition comprises a sterile saline solution and one or more compound. In certain embodiments, such pharmaceutical composition consists of a sterile saline solution and one or more compound. In certain embodiments, the sterile saline is pharmaceutical grade saline. In certain embodiments, a pharmaceutical composition comprises one or more compound and sterile water. In certain embodiments, a pharmaceutical composition consists of one compound and sterile water. In certain

embodiments, the sterile water is pharmaceutical grade water. In certain embodiments, a pharmaceutical composition comprises one or more compound and phosphate-buffered saline (PBS). In certain embodiments, a pharmaceutical composition consists of one or more compound and sterile PBS. In certain embodiments, the sterile PBS is pharmaceutical grade PBS. Compositions and methods for the formulation of pharmaceutical compositions are dependent upon a number of criteria, including, but not limited to, route of administration, extent of disease, or dose to be administered.

A compound described herein targeted to MALAT1 nucleic acid can be utilized in pharmaceutical compositions by combining the compound with a suitable pharmaceutically acceptable diluent or carrier. In certain embodiments, a pharmaceutically acceptable diluent is water, such as sterile water suitable for injection. Accordingly, in one embodiment, employed in the methods described herein is a pharmaceutical composition comprising a compound targeted to MALAT1 nucleic acid and a pharmaceutically acceptable diluent. In certain embodiments, the pharmaceutically acceptable diluent is water. In certain embodiments, the compound comprises or consists of a modified oligonucleotide provided herein.

Pharmaceutical compositions comprising compounds provided herein encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other oligonucleotide which, upon administration to an animal, including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. In certain embodiments, the compounds are antisense compounds or oligomeric compounds. In certain embodiments, the compound comprises or consists of a modified oligonucleotide. Accordingly, for example, the disclosure is also drawn to pharmaceutically acceptable salts of compounds, prodrugs, pharmaceutically acceptable salts of such prodrugs, and other bioequivalents. Suitable pharmaceutically acceptable salts include, but are not limited to, sodium and potassium salts.

A prodrug can include the incorporation of additional nucleosides at one or both ends of a compound which are cleaved by endogenous nucleases within the body, to form the active compound.

In certain embodiments, the compounds or compositions further comprise a pharmaceutically acceptable carrier or diluent.

EXAMPLES

Non-limiting disclosure and incorporation by reference

Although the sequence listing accompanying this filing identifies each sequence as either "RNA" or "DNA" as required, in reality, those sequences may be modified with any combination of chemical modifications. One of skill in the art will readily appreciate that such designation as "RNA" or "DNA" to describe modified oligonucleotides is, in certain instances, arbitrary. For example, an oligonucleotide comprising a nucleoside comprising a 2'-OH sugar moiety and a thymine base could be described as a DNA having a modified sugar (2'-OH for the natural 2'-H of DNA) or as an RNA having a modified base (thymine (methylated uracil) for natural uracil of RNA).

Accordingly, nucleic acid sequences provided herein, including, but not limited to those in the sequence listing, are intended to encompass nucleic acids containing any combination of natural or modified RNA and/or DNA, including, but not limited to such nucleic acids having modified nucleobases. By way of further example and without limitation, an oligonucleotide having the nucleobase sequence "ATCGATCG" encompasses any oligonucleotides having such nucleobase sequence, whether modified or unmodified, including, but not limited to, such compounds comprising RNA bases, such as those having sequence "AUCGAUCG" and those having some DNA bases and some RNA bases such as "AUCGATCG" and compounds having other modified nucleobases, such as "AT^{m}CGAUCG," wherein ^{m}C indicates a cytosine base comprising a methyl group at the 5-position.

While certain compounds, compositions and methods described herein have been described with specificity in accordance with certain embodiments, the following examples serve only to illustrate the compounds described herein and are not intended to limit the same. Each of the references recited in the present application is incorporated herein by reference in its entirety.

Example 1: Design of gapmers with PS internucleoside linkages complementary to human MALAT1 RNA

Modified oligonucleotides complementary to human a MALAT1 nucleic acid were designed. The modified oligonucleotides in the table below are 3-10-3 cET gapmers. The gapmers are 16 nucleosides in length, wherein the central gap segment comprises of either ten 2'-deoxynucleosides, or of a combination of one 2'-O-methyl nucleoside and nine 2'-deoxynucleosides. The central gap segment is flanked by wing segments on the 5' direction and the 3' direction comprising three nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a cEt sugar modification. The internucleoside linkages throughout each gapmer are phosphorothioate (P=S) linkages. Each cytosine residue is a 5-methylcytosine. The sequence and chemical notation column specifies the sequence, including 5-methylcytosines, sugar chemistry, and the internucleoside linkage chemistry; wherein subscript 'd' represents a 2'-β-D-deoxyribosyl sugar moiety, subscript 'k' represents a cET sugar moiety, subscript 's' represents to a phosphorothioate internucleoside linkage, superscript 'm' before the cytosine residue represents a 5-methylcytosine, and subscript 'y' represents a 2'-O-methyl ribose sugar. "Start site" indicates the 5'-most nucleoside to which the gapmer is complementary in the human nucleic acid sequence. "Stop site" indicates the 3'-most nucleoside to which the gapmer is complementary in the human nucleic acid sequence.

Each modified oligonucleotide listed in the table below is complementary to human MALAT1 nucleic acid sequence SEQ ID NO: 1 (GENBANK Accession No: XR_001309.1).

Table 1

cET gapmers with PS internucleoside linkages complementary to human MALAT1

Compound Number	Sequence (5' to 3')	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Chemistry Notation (5' to 3')	SEQ ID NO
1157034	TTCGGTTTAATCTCTT	1535	1550	$T_{ks}T_{ks}{}^{m}C_{ks}G_{ds}G_{ds}T_{ds}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ks}T_{ks}T_{k}$	2
1157111	GGTTACCAATAATTTC	2034	2049	$G_{ks}G_{ks}T_{ks}T_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}A_{ds}T_{ds}A_{ds}A_{ds}T_{ds}T_{ks}T_{ks}{}^{m}C_{k}$	3
1157190	TGGTAATTACTCTTGA	2341	2356	$T_{ks}G_{ks}G_{ks}T_{ds}A_{ds}A_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ks}G_{ks}A_{k}$	4

1157929	GTAGTAAGAATCTCAG	4821	4836	$G_{ks}T_{ks}A_{ks}G_{ds}T_{ds}A_{ds}A_{ds}G_{ds}A_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ks}A_{ks}G_{k}$	5
1158161	CCTTAGTTGGCATCAA	5494	5509	$^{m}C_{ks}{}^{m}C_{ks}T_{ks}T_{ds}A_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ds}{}^{m}C_{ds}A_{ds}T_{ds}{}^{m}C_{ks}A_{ks}A_{k}$	6
1158162	TCCTTAGTTGGCATCA	5495	5510	$T_{ks}{}^{m}C_{ks}{}^{m}C_{ks}T_{ds}T_{ds}A_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ds}{}^{m}C_{ds}A_{ds}T_{ks}{}^{m}C_{ks}A_{k}$	7
1304884	GGATUAATGTAGTGTA	5049	5064	$G_{ks}G_{ks}A_{ks}T_{ds}U_{ys}A_{ds}A_{ds}T_{ds}G_{ds}T_{ds}A_{ds}G_{ds}T_{ds}G_{ks}T_{ks}A_{k}$	8
1304890	GGTTATAGCTTGACAA	4931	4946	$G_{ks}G_{ks}T_{ks}T_{ds}A_{ys}T_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ks}A_{ks}A_{k}$	9
1304906	GCAGATAATGTTCTCA	4840	4855	$G_{ks}{}^{m}C_{ks}A_{ks}G_{ds}A_{ys}T_{ds}A_{ds}A_{ds}T_{ds}G_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{ks}{}^{m}C_{ks}A_{k}$	10

Example 2: Antisense inhibition of human MALAT1 in A-431 cells by modified oligonucleotides

The modified oligonucleotides were tested in a series of experiments that had similar culture conditions. The results for each experiment are presented in a single table shown below. Cultured A-431 cells at a density of 10,000 cells per well were treated using free uptake with 5 nM of modified oligonucleotide. After a treatment period of approximately 48 hours, RNA was isolated from the cells and MALAT1 RNA levels were measured by quantitative real-time RTPCR. Human primer probe set RTS2736 (forward sequence AAAGCAAGGTCTCCCCACAAG, designated herein as SEQ ID NO.: 2814; reverse sequence TGAAGGGTCTGTGCTAGATCAAAA, designated herein as SEQ ID NO.: 2815; probe sequence TGCCACATCGCCACCCCGT, designated herein as SEQ ID NO.: 2816) was used to measure RNA levels. MALAT1 RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Results are presented in the tables below as percent control of the amount of MALAT1 RNA relative to untreated control cells (%UTC).

Table 2

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers targeting SEQ ID NO.: 1

Compound Number	%UTC
1157034	25
1157111	11
1157190	19
1157929	20
1158161	18
1158162	24

Example 3: Dose-dependent inhibition of human MALAT1 in A-431 cells by cEt gapmers

Modified oligonucleotides described in the studies above were tested at various doses in A-431 cells. Cultured A-431 cells at a density of 10,000 cells per well were treated using free uptake with modified oligonucleotides diluted to concentrations described in the tables below. After approximately 48 hours, MALAT1 RNA levels were measured as previously described using the Human MALAT1 primer-probe set RTS2736. MALAT1 RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Results are presented in the tables below as percent control of the amount of MALAT1 RNA relative to untreated control cells (%UTC). IC50s were calculated using a linear regression on a log/linear plot of the data in excel.

Table 3

Dose-dependent inhibition of human MALAT1 mRNA expression by modified oligonucleotides in A-431

Compound Number	%control				IC50 (nM)
	0.3 nM	1.25 nM	5.0 nM	20.0 nM	
1157034	72	57	26	6	1
1157111	108	73	6	7	2
1157190	89	93	58	18	6
1157929	81	76	29	10	2
1158161	83	77	37	9	3
1158162	82	78	32	10	3

Example 4: Dose-dependent inhibition of human MALAT1 in MDA-MB-436 cells by cEt gapmers

Modified oligonucleotides described in the studies above were tested at various doses in MDA-MB-436 cells. Cultured MDA-MB-436 cells at a density of 5,000-12,000 cells per well were treated using free uptake with modified oligonucleotides diluted to concentrations described in the tables below. After approximately 48 hours, MALAT1 RNA levels were measured as previously described using the Human MALAT1 primer-probe set RTS2736. MALAT1 RNA levels were normalized to b-actin, measured using human primer-probe set HTS5002 (forward sequence CGGACTATGACTTAGTTGCGTTACA, designated herein as SEQ ID NO.: 2817; reverse sequence GCCATGCCAATCTCATCTTGT, designated herein as SEQ ID NO.: 2818; probe sequence CCTTTCTTGACAAAACCTAACTTGCGCAGA, designated herein as SEQ ID NO.: 2819). Results are presented in the tables below as percent control of the amount of MALAT1 RNA relative to untreated control cells (%UTC). Each table below represents a separate experiment. IC50s for table 4 were calculated using the "log(inhibitor) vs. response – variable slope (4 parameters)" formula using Prism6 software. IC50s for tables 5 and 6 were calculated using the "log(inhibitor) vs. response – variable slope (3 parameters)" formula using Prism7 software.

Table 4

Dose-dependent inhibition of human MALAT1 RNA expression by modified oligonucleotides in MDA-MB-436 cells

Compound Number	%control				IC50 (nM)
	0.8 nM	4.0 nM	20.0 nM	100.0 nM	
1157034	50	25	17	5	0.7
1157111	98	30	13	8	2.9
1157190	56	39	15	5	1.4
1157929	58	51	33	5	2.6
1158161	36	48	27	3	0.5
1158162	57	37	22	6	1.5

Table 5

Dose-dependent inhibition of human MALAT1 RNA expression by modified oligonucleotides in MDA-MB-436 cells

Compound Number	%control				IC50 (nM)
	8 nM	40 nM	200 nM	1000 nM	
1304906	68	23	6	2	8
1304890	68	20	5	3	5
1304884	68	25	5	2	10

Table 6

Dose-dependent inhibition of human MALAT1 RNA expression by modified oligonucleotides in MDA-MB-436 cells

Compound Number	%control				IC50 (nM)
	0.4 nM	2 nM	10 nM	50 nM	
1304906	98	88	47	17	9
1304890	109	88	52	17	8
1304884	98	75	55	23	8

Example 5: Tolerability of modified oligonucleotides targeting human MALAT1 in CD-1 mice

CD-1 mice were treated with modified oligonucleotides selected from studies described above and evaluated for changes in the levels of various plasma chemistry markers.

Treatment

Groups of male CD-1 mice at 4-6 weeks of age (obtained from Charles River) were injected subcutaneously twice a week for four weeks (for a total of 8 treatments) with 50 mg/kg of modified oligonucleotides. One group of male CD-1 mice was injected with PBS. Mice were euthanized 25 days post start of treatment (24 hours post final administration).

Plasma chemistry markers

To evaluate the effect of modified oligonucleotides on liver function, plasma levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), total bilirubin (TBIL), and albumin (ALB) were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400c, Melville, NY). The results are presented in the tables below.

Table 7

Plasma chemistry markers in CD-1 mice

ION NO.	ALT (IU/L)	AST (IU/L)	BUN (mg/dL)	TBIL (mg/dL)	Albumin (g/dL)
PBS	20	46	24	0.2	2.5

1157929	330	225	24	0.2	2.3
1158161	86	128	29	0.2	2.3

Body and organ weights

Body weights of CD-1 mice were measured at the end of the study, and the average body weight for each group is presented in the table below. Kidney, spleen, and liver weights were measured at the end of the study and are presented in the table below.

Table 8

Body and organ weights

ION No.	Body Weight (g)	Liver (g)	Kidney (g)	Spleen (g)
PBS	32	1.7	0.5	0.1
1157929	34	2.3	0.5	0.2
1158161	34	2.3	0.5	0.2

Example 6: Tolerability of modified oligonucleotides targeting human MALAT1 in CD-1 mice

CD-1 mice were treated with modified oligonucleotides selected from studies described above and evaluated for changes in the levels of various plasma chemistry markers.

Treatment

Groups of male CD-1 mice at 4-6 weeks of age (obtained from Charles River) were injected subcutaneously twice a week for four weeks (for a total of 8 treatments) with 50 mg/kg of modified oligonucleotides. One group of male CD-1 mice was injected with PBS. Mice were euthanized 24 days post start of treatment (24 hours post final administration).

Plasma chemistry markers

To evaluate the effect of modified oligonucleotides on liver function, plasma levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), and total bilirubin (TBIL), were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400c, Melville, NY). The results are presented in the tables below.

Table 9

Plasma chemistry markers in CD-1 mice

ION NO.	ALT (IU/L)	AST (IU/L)	BUN (mg/dL)	TBIL (mg/dL)
PBS	43	71	26	0.2
1157111	341	200	22	0.2

Body and organ weights

Body weights of CD-1 mice were measured at the end of the study, and the average body weight for each group is presented in the table below. Kidney, spleen, and liver weights were measured at the end of the study and are presented in the table below.

Table 10

Body and organ weights

ION No.	Body Weight (g)	Liver (g)	Kidney (g)	Spleen (g)
PBS	37	2.0	0.6	0.1
1157111	38	2.8	0.5	0.2

Example 7: Tolerability of modified oligonucleotides targeting human MALAT1 in CD-1 mice

CD-1 mice were treated with modified oligonucleotides selected from studies described above and evaluated for changes in the levels of various plasma chemistry markers.

Treatment

Groups of male CD-1 mice at 4-6 weeks of age (obtained from Charles River) were injected subcutaneously twice a week for four weeks (for a total of 8 treatments) with 50 mg/kg of modified oligonucleotides. One group of male CD-1 mice was injected with PBS. Mice were euthanized 26 days post start of treatment (24 hours post final administration).

Plasma chemistry markers

To evaluate the effect of modified oligonucleotides on liver function, plasma levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), and total bilirubin (TBIL), were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400c, Melville, NY). The results are presented in the tables below.

Table 11

Plasma chemistry markers in CD-1 mice

ION NO.	ALT (IU/L)	AST (IU/L)	BUN (mg/dL)	TBIL (mg/dL)
PBS	22	46	22	0.3
1157034	608	480	21	0.2
1157190	41	83	23	0.2
1158162	435	325	24	0.2

Body and organ weights

Body weights of CD-1 mice were measured at the end of the study, and the average body weight for each group is presented in the table below. Kidney, spleen, and liver weights were measured at the end of the study and are presented in the table below.

Table 12

Body and organ weights

ION No.	Body Weight (g)	Liver (g)	Kidney (g)	Spleen (g)
PBS	33	1.8	0.5	0.1
1157034	37	2.3	0.5	0.2
1157190	35	1.9	0.4	0.2
1158162	36	2.6	0.5	0.2

Example 8: Tolerability of modified oligonucleotides targeting human MALAT1 in CD-1 mice

CD-1 mice were treated with modified oligonucleotides selected from studies described above and evaluated for changes in the levels of various plasma chemistry markers.

Treatment

Groups of male CD-1 mice at 4-6 weeks of age (obtained from Charles River) were injected subcutaneously twice a week for four weeks (for a total of 8 treatments) with 50 mg/kg of modified oligonucleotides. One group of male CD-1 mice was injected with PBS. Mice were euthanized 25 days post start of treatment (24 hours following the final administration).

Plasma chemistry markers

To evaluate the effect of modified oligonucleotides on liver function, plasma levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), and total bilirubin (TBIL), were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400c, Melville, NY). The results are presented in the tables below.

Table 13

Plasma chemistry markers in CD-1 mice

ION NO.	ALT (IU/L)	AST (IU/L)	BUN (mg/dL)	TBIL (mg/dL)
PBS	20	51	21	0.2
1304890	33	51	21	0.2
1304906	59	78	22	0.2

Body and organ weights

Body weights of CD-1 mice were measured at the end of the study, and the average body weight for each group is presented in the table below. Kidney, spleen, and liver weights were measured at the end of the study and are presented in the table below.

Table 14

Body and organ weights

ION No.	Body Weight (g)	Liver (g)	Kidney (g)	Spleen (g)
PBS	32	1.6	0.5	0.1
1304890	36	2.0	0.5	0.2
1304906	34	1.8	0.5	0.1

Example 9: Tolerability of modified oligonucleotides targeting human MALAT1 in CD-1 mice

CD-1 mice were treated with modified oligonucleotides selected from studies described above and evaluated for changes in the levels of various plasma chemistry markers.

Treatment

Groups of male CD-1 mice at 4-6 weeks of age (obtained from Charles River) were injected subcutaneously twice a week for four weeks (for a total of 8 treatments) with 50 mg/kg of modified oligonucleotides. One group of male CD-1 mice was injected with PBS. Mice were euthanized 25 days post start of treatment (24 hours following the final administration).

Plasma chemistry markers

To evaluate the effect of modified oligonucleotides on liver function, plasma levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), and total bilirubin (TBIL), were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400c, Melville, NY). The results are presented in the tables below.

Table 15

Plasma chemistry markers in CD-1 mice

ION NO.	ALT (IU/L)	AST (IU/L)	BUN (mg/dL)	TBIL (mg/dL)
PBS	19	56	16	0.2
1304884	33	55	15	0.1

Body and organ weights

Body weights of CD-1 mice were measured at the end of the study, and the average body weight for each group is presented in the table below. Kidney, spleen, and liver weights were measured at the end of the study and are presented in the table below.

Table 16

Body and organ weights

ION No.	Body Weight (g)	Liver (g)	Kidney (g)	Spleen (g)
PBS	34	2.0	0.5	0.1
1304884	37	2.2	0.5	0.2

Example 10: Effect of modified oligonucleotides targeting human MALAT1 in cynomolgus monkeys

Cynomolgus monkeys were treated with certain Ionis modified oligonucleotides selected from studies described in the Examples above. Modified oligonucleotide tolerability was evaluated.

STUDY 1

Treatment

Prior to the study, the monkeys were kept in quarantine during which the animals were observed daily for general health. The monkeys were 2-4 years old and weighed 2-4 kg. Seven groups of 4 randomly assigned male cynomolgus monkeys each were injected subcutaneously with Ionis oligonucleotide or saline in a clockwise rotation between four different sites on the back. Following loading doses on days 1, 3, 5 and 7, the monkeys were dosed once per week for 6 weeks (on days 14, 21, 28, 35, and 41) with 35 mg/kg of Ionis oligonucleotide. A control group of 4 cynomolgus monkeys was injected with 0.9% saline in a similar manner and served as the control group.

During the study period, the monkeys were observed at least once daily for signs of illness or distress. Any animal experiencing illness or distress was promptly reported to the veterinarian and Study Director. Any animal in poor health or in a possible moribund condition was identified for further monitoring and possible euthanasia. Scheduled euthanasia of the animals was conducted on day 43 approximately 48 hours after the last dose by exsanguination while under deep anesthesia. The protocols described in the Example were approved by the Institutional Animal Care and Use Committee (IACUC).

Body and organ weight measurements

To evaluate the effect of modified oligonucleotides on the overall health of the animals, body and organ weights were measured. Terminal body weight was measured prior to necropsy. Organ weights were measured as well.

Table 17

Body and organ weights (g)

Compound No.	Body Weight (g) Day 43	Heart	kidney	spleen	liver
Saline	2565	10	12	3	49

1157034	2748	10	16	5	67
1157111	2524	9	13	3	62
1157190	2663	10	15	5	63
1157929	2655	10	14	3	59
1158161	2418	9	14	3	53
1158162	2499	9	18	3	55

Kidney and Liver function

To evaluate the effect of modified oligonucleotides on hepatic and kidney function, blood samples were collected from all the study groups on day 43. The monkeys were fasted overnight prior to blood collection. Blood was collected in tubes without anticoagulant for serum separation. The tubes were kept at room temperature for a minimum of 90 minutes and then centrifuged at 3000 rpm for 10 minutes to obtain serum. Levels of various liver function markers were measured using a Toshiba 120FR NEO chemistry analyzer (Toshiba Co., Japan). Plasma levels of blood urea nitrogen (BUN), creatinine (CREA), total protein (TP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBIL) were measured.

Table 18

Liver function markers in cynomolgus monkey plasma

Compound No.	ALT (IU/L)	AST (IU/L)	BUN (mg/dL)	CREA (mg/dL)	TP (g/dL)	TBIL (mg/dL)
Saline	49	59	21	0.9	7.3	0.3
1157034	40	55	18	0.8	6.8	0.2
1157111	41	72	23	0.8	7.1	0.3
1157190	59	67	21	0.9	7.1	0.3
1157929	63	71	21	0.9	7.1	0.2
1158161	58	59	18	0.8	7.3	0.3
1158162	53	81	17	0.8	7.5	0.3

Pro-inflammatory proteins analysis

To evaluate any inflammatory effect of modified oligonucleotides in cynomolgus monkeys, blood samples were taken for analysis. The monkeys were fasted overnight prior to blood collection. On day 41 (pre-dose and 24hours post-dose), approximately 0.8 mL of blood was collected from each animal and put into tubes without anticoagulant for serum separation. The tubes were kept at room temperature for a minimum of 90 min and then centrifuged at 3,000 rpm for 10 min at room temperature to obtain serum. Complement C3 were measured using a Toshiba 120 FR NEO chemistry analyzer (Toshiba Co., Japan). Another marker of inflammation, C-Reactive Protein (CRP) was tested together with the clinical chemistry parameters tested for liver function above.

Table 19

Pro-inflammatory protein analysis in cynomolgus monkeys

Compound No.	Complement C3 (mg/dL)		CRP (mg/L)
	Day 41 (pre-dose)	Day 41 (24hr post-dose)	day 43
Saline	95	92	5
1157034	115	100	3
1157111	105	87	9
1157190	106	90	4
1157929	115	105	7
1158161	107	99	5
1158162	111	100	6

Hematology

To evaluate any effect of modified oligonucleotides in cynomolgus monkeys on hematologic parameters, blood samples of approximately 0.5 mL of blood was collected from each of the available study animals on day 43. The samples were collected in tubes containing K_2-EDTA. Samples were analyzed for red blood cell (RBC) count, Hemoglobin (HGB), Hematocrit (HCT), platelet count (PLT), total white blood cell count (WBC), neutrophil counts (NEU), lymphocyte counts (LYM), and monocyte counts (MON) using an ADVIA2120i hematology analyzer (Siemens, USA).

Table 20

Hematological marker analysis in cynomolgus monkeys

Compound No.	RBC (x106/µL)	HGB (g/dL)	HCT (%)	PLT (10^3/µL)	WBC (x10^3/µL)	NEU (%)	LYM (%)	MON (%)
Saline	5	12	43	320	8	47	49	3
1157034	6	13	45	329	11	34	61	4
1157111	5	13	43	419	13	50	45	3
1157190	6	13	44	383	10	38	56	4
1157929	6	13	45	309	8	37	57	3
1158161	6	13	43	332	11	31	63	3
1158162	5	12	43	453	9	41	52	5

Urine Analysis

Food was removed overnight the day before fresh urine collection, but water was supplied. Fresh urine samples for urinalysis and urine chemistry were collected from all animals using a clean cage pan on wet ice (first in the morning) on day 43. Urinalysis/Urine Chemistry parameters creatinine (UCRE), microprotein (UTP), urine microalbumin (UALB),

and protein/creatinine (P/C) ratio were measured using a Toshiba 120FR automated chemistry analyzer (Toshiba Co., Japan).

Table 21

Urine analysis in cynomolgus monkeys

Compound No.	UCRE (mg/dL)	UTP (mg/dL)	UALB (mg/dL)	P/C ratio
Saline	98	14	0.75	0.15
1157034	44	16	0.34	0.39
1157111	46	13	0.30	0.29
1157190	64	17	0.29	0.28
1157929	83	13	0.56	0.17
1158161	111	18	0.70	0.17
1158162	45	26	5.10	0.65

STUDY 2

Treatment

Prior to the study, the monkeys were kept in quarantine during which the animals were observed daily for general health. The monkeys were 2-4 years old and weighed 2-4 kg. Four groups of 4 randomly assigned male cynomolgus monkeys each were injected subcutaneously with Ionis oligonucleotide or saline in a clockwise rotation between four different sites on the back. Following loading doses on days 1, 3, 5 and 7, the monkeys were dosed once per week for 6 weeks (on days 14, 21, 28, 35, and 41) with 35 mg/kg of Ionis oligonucleotide. A control group of 4 cynomolgus monkeys was injected with 0.9% saline in a similar manner and served as the control group.

During the study period, the monkeys were observed at least once daily for signs of illness or distress. Any animal experiencing illness or distress was promptly reported to the veterinarian and Study Director. Any animal in poor health or in a possible moribund condition was identified for further monitoring and possible euthanasia. Scheduled euthanasia of the animals was conducted on day 43 approximately 48 hours after the last dose by exsanguination while under deep anesthesia. The protocols described in the Example were approved by the Institutional Animal Care and Use Committee (IACUC).

Body and organ weight measurements

To evaluate the effect of modified oligonucleotides on the overall health of the animals, body and organ weights were measured. Terminal body weight was measured prior to necropsy. Organ weights were measured as well.

Table 22

Body and organ weights (g)

Compound No.	Body Weight (g) Day 43	Heart	kidney	spleen	liver
Saline	2843	9	12	3	57
1304884	2643	9	14	4	65
1304890	2788	9	14	3	61
1304906	2678	10	13	3	60

Kidney and Liver function

To evaluate the effect of modified oligonucleotides on hepatic and kidney function, blood samples were collected from all the study groups on day 43. The monkeys were fasted overnight prior to blood collection. Blood was collected in tubes without anticoagulant for serum separation. The tubes were kept at room temperature for a minimum of 90 minutes and then centrifuged at 3000 rpm for 10 minutes to obtain serum. Levels of various liver function markers were measured using a Toshiba 120FR NEO chemistry analyzer (Toshiba Co., Japan). Plasma levels of blood urea nitrogen (BUN), creatinine (CREA), total protein (TP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBIL) were measured.

Table 23

Liver function markers in cynomolgus monkey plasma

Compound No.	ALT (IU/L)	AST (IU/L)	BUN (mg/dL)	CREA (mg/dL)	TP (g/dL)	TBIL (mg/dL)
Saline	52	74	28	1.0	7.0	0.3
1304884	64	47	23	0.9	7.0	0.2
1304890	52	62	25	0.9	7.0	0.2
1304906	75	73	24	0.9	7.2	0.3

Pro-inflammatory proteins analysis

To evaluate any inflammatory effect of modified oligonucleotides in cynomolgus monkeys, blood samples were taken for analysis. The monkeys were fasted overnight prior to blood collection. On day 41 (pre-dose and 24hours post-dose), approximately 0.8 mL of blood was collected from each animal and put into tubes without anticoagulant for serum separation. The tubes were kept at room temperature for a minimum of 90 min and then centrifuged at 3,000 rpm for 10 min at room temperature to obtain serum. Complement C3 were measured using a Toshiba 120 FR NEO chemistry analyzer (Toshiba Co., Japan). Another marker of inflammation, C-Reactive Protein (CRP) was tested together with the clinical chemistry parameters tested for liver function above.

Table 24

Pro-inflammatory protein analysis in cynomolgus monkeys

Compound No.	Complement C3 (mg/dL)		CRP (mg/L)
	Day 43 (pre-dose)	Day 43 (24hr post-dose)	day 43
Saline	127	127	5
1304884	112	98	3
1304890	102	98	3
1304906	108	88	3

Hematology

To evaluate any effect of modified oligonucleotides in cynomolgus monkeys on hematologic parameters, blood samples of approximately 0.5 mL of blood was collected from each of the available study animals on day 43. The samples were collected in tubes containing K_2-EDTA. Samples were analyzed for red blood cell (RBC) count, Hemoglobin (HGB), Hematocrit (HCT), platelet count (PLT), total white blood cell count (WBC), neutrophil counts (NEU), lymphocyte counts (LYM), and monocyte counts (MON) using an ADVIA2120i hematology analyzer (Siemens, USA).

Table 25

Hematological marker analysis in cynomolgus monkeys

Compound No.	RBC (x106/µL)	HGB (g/dL)	HCT (%)	PLT (10^3/µL)	WBC (x10^3/µL)	NEU (%)	LYM (%)	MON (%)
Saline	5	12	43	352	12	29	64	3
1304884	5	13	41	386	9	30	62	3
1304890	5	13	42	460	12	33	62	2
1304906	6	13	42	413	13	48	46	4

Urine Analysis

Food was removed overnight the day before fresh urine collection, but water was supplied. Fresh urine samples for urinalysis and urine chemistry were collected from all animals using a clean cage pan on wet ice (first in the morning) on day 43. Urinalysis/Urine Chemistry parameters creatinine (UCRE), microprotein (UTP), urine microalbumin (UALB), and protein/creatinine (P/C) ratio were measured using a Toshiba 120FR automated chemistry analyzer (Toshiba Co., Japan).

Table 26

Urine analysis in cynomolgus monkeys

Compound No.	UCRE (mg/dL)	UTP (mg/dL)	UALB (mg/dL)	P/C ratio
Saline	73	10	0.5	0.1

1304884	45	12	0.7	0.3
1304890	81	15	0.9	0.2
1304906	70	11	0.5	0.2

Example 11: Dose-dependent inhibition of human MALAT1 in A431 cells by comparator compounds

Certain modified oligonucleotides described in the art were tested at various doses in A431 cells and used as comparator compounds in other Examples below. The following modified oligonucleotides described in the art were compared: 395240, 395243, 395244, 395248, 395251, 395252, 395253, 395254, 395255, 395256, 395257, 395259, 395267, 395269, 395272, 395275, 395280, 395283, 395287, 395290, 556089, 559497, and 626112. The chemical notation column in the table below specifies the sequence and chemistry information, including 5-methylcytosines, sugar chemistry, and the internucleoside linkage chemistry; wherein subscript 'd' represents a 2'-β-D-deoxyribosyl sugar moiety, subscript 'k' represents a cET sugar moiety, subscript 'e' represents a 2'-MOE sugar moiety, subscript, 's' represents to a phosphorothioate internucleoside linkage, superscript 'm' before the cytosine residue represents a 5-methylcytosine, and subscript 'o' represents a phosphodiester internucleoside linkage. "Start site" indicates the 5'-most nucleoside to which the gapmer is complementary in the human nucleic acid sequence. "Stop site" indicates the 3'-most nucleoside to which the gapmer is complementary in the human nucleic acid sequence. Each modified oligonucleotide listed in the table below is complementary to human MALAT1 nucleic acid sequence SEQ ID NO: 1 (GENBANK Accession No: XR_001309.1).

Table 27

Certain Comparator Compounds

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	Chemistry Notation (5' to 3')	Reference Number	SEQ ID No.
395240	3320	3339	TGCCTTTAGGAT TCTAGACA	$T_{es}G_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{ds}T_{ds}A_{ds}G_{ds}G_{ds}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{ds}A_{es}G_{es}A_{es}{}^{m}C_{es}A_{e}$	WO 2012/012467	11
395243	3885	3904	TAATTGCCAATA TTTGCCCC	$T_{es}A_{es}A_{es}T_{es}T_{es}G_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}A_{ds}T_{ds}A_{ds}T_{ds}T_{ds}T_{ds}G_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{e}$	WO 2012/012467	12
395244	4036	4055	GGGAGTTACTTG CCAACTTG	$G_{es}G_{es}G_{es}A_{es}G_{es}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}A_{es}{}^{m}C_{es}T_{es}T_{es}G_{e}$	WO 2012/012467	13
395248	4493	4512	TTGCAGTTAAAC AATGGAAA	$T_{es}T_{es}G_{es}{}^{m}C_{es}A_{es}G_{ds}T_{ds}T_{ds}A_{ds}A_{ds}A_{ds}{}^{m}C_{ds}A_{ds}A_{ds}T_{ds}G_{es}G_{es}A_{es}A_{es}A_{e}$	WO 2012/012467	14
395251	4698	4717	CCAGGCTGGTTA TGACTCAG	$^{m}C_{es}{}^{m}C_{es}A_{es}G_{es}G_{es}{}^{m}C_{ds}T_{ds}G_{ds}G_{ds}T_{ds}T_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{es}T_{es}{}^{m}C_{es}A_{es}G_{e}$	WO 2012/012467	15
395252	4748	4767	TTATCAATTCAC CAAGGAGC	$T_{es}T_{es}A_{es}T_{es}{}^{m}C_{es}A_{ds}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}A_{ds}G_{es}G_{es}A_{es}G_{es}{}^{m}C_{e}$	WO 2012/012467	16
395253	4783	4802	ATGGAGGTATGA CATATAAT	$A_{es}T_{es}G_{es}G_{es}A_{es}G_{ds}G_{ds}T_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}A_{es}T_{es}A_{es}A_{es}T_{e}$	WO 2012/012467	17

395254	4843	4862	GGCATATGCAGA TAATGTTC	$G_{es}G_{es}{}^{m}C_{es}A_{es}T_{es}A_{ds}T_{ds}G_{ds}{}^{m}C_{ds}A_{ds}G_{ds}$ $A_{ds}T_{ds}A_{ds}A_{ds}T_{es}G_{es}T_{es}T_{es}{}^{m}C_{e}$	WO 2012/012467	18
395255	5123	5142	ACATTGGCACAC AGCACAGC	$A_{es}{}^{m}C_{es}A_{es}T_{es}T_{es}G_{ds}G_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}A_{ds}$ $^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}A_{es}{}^{m}C_{es}A_{es}G_{es}{}^{m}C_{e}$	WO 2012/012467	19
395256	5134	5153	AGGCAAACGAA ACATTGGCA	$A_{es}G_{es}G_{es}{}^{m}C_{es}A_{es}A_{ds}A_{ds}{}^{m}C_{ds}G_{ds}A_{ds}A_{ds}$ $A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}T_{es}G_{es}G_{es}{}^{m}C_{es}A_{e}$	WO 2012/012467	20
395257	5248	5267	CTAACATGCAAT ACTGCAGA	$^{m}C_{es}T_{es}A_{es}A_{es}{}^{m}C_{es}A_{ds}T_{ds}G_{ds}{}^{m}C_{ds}A_{ds}A_{ds}$ $T_{ds}A_{ds}{}^{m}C_{ds}T_{ds}G_{es}{}^{m}C_{es}A_{es}G_{es}A_{e}$	WO 2012/012467	21
395259	5393	5412	AAGCCCACAGG AACAAGTCC	$A_{es}A_{es}G_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}A_{ds}G_{ds}G$ $_{ds}A_{ds}A_{ds}{}^{m}C_{ds}A_{ds}A_{es}G_{es}T_{es}{}^{m}C_{es}{}^{m}C_{e}$	WO 2012/012467	22
395267	6098	6117	GGTCAATAGTGT AAAACATT	$G_{es}G_{es}T_{es}{}^{m}C_{es}A_{es}A_{ds}T_{ds}A_{ds}G_{ds}T_{ds}G_{ds}T_{ds}$ $A_{ds}A_{ds}A_{ds}A_{es}{}^{m}C_{es}A_{es}T_{es}T_{e}$	WO 2012/012467	23
395269	6174	6193	TTCATGAAGGAT GAAATGCC	$T_{es}T_{es}{}^{m}C_{es}A_{es}T_{es}G_{ds}A_{ds}A_{ds}G_{ds}G_{ds}A_{ds}T_{ds}$ $G_{ds}A_{ds}A_{ds}A_{es}T_{es}G_{es}{}^{m}C_{es}{}^{m}C_{e}$	WO 2012/012467	24
395272	6445	6464	CAATGCATTCTA ATAGCAGC	$^{m}C_{es}A_{es}A_{es}T_{es}G_{es}{}^{m}C_{ds}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{ds}$ $A_{ds}A_{ds}T_{ds}A_{ds}G_{es}{}^{m}C_{es}A_{es}G_{es}{}^{m}C_{e}$	WO 2012/012467	25
395275	6759	6778	AACATTTCCACT TGCCAGTT	$A_{es}A_{es}{}^{m}C_{es}A_{es}T_{es}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{d}$ $_{s}T_{ds}T_{ds}G_{ds}{}^{m}C_{ds}{}^{m}C_{es}A_{es}G_{es}T_{es}T_{e}$	WO 2012/012467	26
395280	6958	6977	GGTTCCCAATCC CCACATTT	$G_{es}G_{es}T_{es}T_{es}{}^{m}C_{es}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}A_{ds}T_{ds}{}^{m}C_{d}$ $_{s}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{es}A_{es}T_{es}T_{es}T_{e}$	WO 2012/012467	27
395283	7335	7354	TAATAAAAATCA GGTGAGGC	$T_{es}A_{es}A_{es}T_{es}A_{es}A_{ds}A_{ds}A_{ds}A_{ds}T_{ds}{}^{m}C_{ds}A_{d}$ $_{s}G_{ds}G_{ds}T_{ds}G_{es}A_{es}G_{es}G_{es}{}^{m}C_{e}$	WO 2012/012467	28
395287	7878	7897	TCCCACCCAGCA TTACAGTT	$T_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{es}A_{es}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}G_{ds}$ $^{m}C_{ds}A_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{es}A_{es}G_{es}T_{es}T_{e}$	WO 2012/012467	29
395290	8007	8026	TAAGATGCTAGC TTGGCCAA	$T_{es}A_{es}A_{es}G_{es}A_{es}T_{ds}G_{ds}{}^{m}C_{ds}T_{ds}A_{ds}G_{ds}{}^{m}C$ $_{ds}T_{ds}T_{ds}G_{ds}G_{es}{}^{m}C_{es}{}^{m}C_{es}A_{es}A_{e}$	WO 2012/012467	30
556089	6445	6460	GCATTCTAATAG CAGC	$G_{ks}{}^{m}C_{ks}A_{ks}T_{ds}T_{ds}{}^{m}C_{ds}T_{ds}A_{ds}A_{ds}T_{ds}A_{ds}$ $G_{ds}{}^{m}C_{ds}A_{ks}G_{ks}{}^{m}C_{k}$	WO 2017/192820; St-Pierre et al., Bioorg Med Chem. 2016; 24(11):2397-409	31
559497	3629	3644	AGTACTATAGCA TCTG	$A_{ks}G_{ks}T_{ks}A_{ds}{}^{m}C_{ds}T_{ds}A_{ds}T_{ds}A_{ds}G_{ds}{}^{m}C_{ds}$ $A_{ds}T_{ds}{}^{m}C_{ks}T_{ks}G_{k}$	Hung et al., Nucleic Acid Ther. 2013; 23(6):369-78.	32
626112	4699	4718	GCCAGGCTGGTT ATGACTCA	$G_{es}{}^{m}C_{eo}{}^{m}C_{eo}A_{eo}G_{eo}G_{ds}{}^{m}C_{ds}T_{ds}G_{ds}G_{ds}T_{d}$ $_{s}T_{ds}A_{ds}T_{ds}G_{ds}A_{eo}{}^{m}C_{eo}T_{es}{}^{m}C_{es}A_{e}$	WO 2016/073828	33

Compounds 1058667 and 1058668 have been described in the art. The chemical notation column in the table below specifies the sequence and chemistry information of certain comparator compounds, including 5-methylcytosines, sugar chemistry, and the internucleoside linkage chemistry; wherein subscript 'd' represents a 2'-β-D-deoxyribosyl sugar moiety, subscript 'l' represents an LNA sugar moiety, subscript 's' represents to a phosphorothioate internucleoside linkage, and superscript 'm' before the cytosine residue represents a 5-methylcytosine. Compounds 1058667 and 1058668

are complementary to mouse MALAT1 nucleic acid sequence and mismatched with human MALAT1 nucleic acid sequence. "Start site" indicates the 5'-most nucleoside to which the gapmer is complementary in the mouse nucleic acid sequence. "Stop site" indicates the 3'-most nucleoside to which the gapmer is complementary in the mouse nucleic acid sequence. Each modified oligonucleotide listed in the table below is complementary to mouse MALAT1 nucleic acid sequence SEQ ID NO: 2823 (complement of GENBANK Accession No: NC_000085.6 truncated from nucleotides 5793001 to 5806000)

Table 28

Certain Comparator Compounds

Compound Number	SEQ ID NO: 2823 Start Site	SEQ ID NO: 2823 Stop Site	Sequence (5' to 3')	Chemistry Notation (5' to 3')	Reference Number	SEQ ID No.
1058668	8368	8383	GTCACAATGCATTCTA	$G_{ls}T_{ls}{}^{m}C_{ls}A_{ds}{}^{m}C_{ds}A_{ds}A_{ds}T_{ds}G_{ds}{}^{m}C_{ds}A_{ds}T_{ds}T_{ds}{}^{m}C_{ls}T_{ls}A_{l}$	Michalik et al., Circ Res. 2014; 114(9):1389-97 and WO 2019/161364	34
1058667	6043	6061	TTTAAGTTCTCTGGTATGA	$T_{ls}T_{ls}T_{ls}A_{ds}A_{ds}G_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}G_{ds}G_{ds}T_{ds}A_{ds}T_{ls}G_{ls}A_{l}$	Bernard et al.EMBO J 2010 29(18):3082-93	35

The modified oligonucleotides below were tested in a series of experiments using the same culture conditions. The results for each experiment are presented in separate tables shown below. Cultured A431 cells at a density of 10,000 cells per well were transfected using free uptake with modified oligonucleotides diluted to different concentrations as specified in the tables below. After a treatment period of approximately 48 hours, RNA levels were measured as previously described using the Human primer-probe set RTS2738 (described herein above). MALAT1 RNA levels were normalized to total RNA, as measured by RIBOGREEN®. Results are presented as percent change of MALAT1 RNA, relative to PBS control.

The half maximal inhibitory concentration (IC_{50}) of each modified oligonucleotide was calculated using a linear regression on a log/linear plot of the data in excel and is also presented in the tables below.

Table 29

Dose-dependent percent reduction of human MALAT1 RNA in A431 cells by modified oligonucleotides

Compound Number	MALAT1 (% UTC)					
	0.4 nM	2 nM	10 nM	50 nM	250 nM	IC_{50} nM
395240	98	72	37	10	4	7
395243	97	101	101	48	10	46
395244	91	84	58	12	7	10
395248	92	97	49	20	6	12
395255	126	121	88	35	13	39
395256	111	108	77	19	4	21

395257	80	94	74	40	16	26
395259	121	97	101	52	23	68
395280	103	115	73	32	14	29
395283	107	89	84	25	10	23
395287	93	78	63	51	31	41
395290	113	90	101	34	18	40
626112	92	93	76	34	14	24

Table 30

Dose-dependent percent reduction of human MALAT1 RNA in A431 cells by modified oligonucleotides

Compound Number	MALAT1 (% UTC)					
	0.4 nM	2 nM	10 nM	50 nM	250 nM	IC_{50} nM
395251	103	88	54	11	4	11
395252	100	117	68	22	6	20
395253	110	87	73	14	4	15
395254	106	73	32	10	5	7
395267	143	126	71	22	6	27
395269	97	112	123	61	26	168
395272	89	87	78	68	19	63
395275	83	81	69	29	14	16
556089	106	107	79	37	11	30
559497	88	102	59	23	6	14
1058667	131	118	99	30	11	39
1058668	105	95	74	27	7	20

Example 12: Antisense inhibition of human MALAT1 in A431 cells by 3-10-3 cEt gapmers

Modified oligonucleotides complementary to a MALAT1 nucleic acid were synthesized and tested for their effect on MALAT1 RNA levels *in vitro* in comparison with comparator compounds 395240, 395253, 395254, 395256, 556089, and 559497 described above. The modified oligonucleotides were tested in a series of experiments using the same culture conditions. The results for each separate experiment are presented in separate tables below.

Except for the comparator compounds 395240, 395253, 395254, and 395256, which are 5-10-5 MOE gapmers (i.e., they have a central gap segment of ten 2'-deoxynucleosides flanked on each side by wing segments, each comprising five 2'-O-methoxyethyl modified nucleosides), the modified oligonucleotides are all 3-10-3 cEt gapmers (i.e., they have a central gap segment of ten 2'-deoxynucleosides flanked on each side by wing segments, each comprising three cEt modified nucleosides). The internucleoside linkages throughout each modified oligonucleotide are phosphorothioate (P=S) linkages. All cytosine nucleobases throughout each modified oligonucleotide are 5-methylcytosines.

"Start site" indicates the 5'-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. "Stop site" indicates the 3'-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. As shown in the tables below, the modified oligonucleotides are 100% complementary to either the human MALAT1 RNA transcript, designated herein as SEQ ID NO: 1 (GENBANK Accession No. XR_001309.1) or the

human MALAT1 RNA transcript designated here in as SEQ ID NO: 2824 (GENBANK Accession No. EF177381.1). 'N/A' indicates that the modified oligonucleotide is not complementary to that particular target sequence with 100% complementarity.

Cultured A431 cells at a density of 10,000 cells per well were transfected using free uptake with 5 nM of modified oligonucleotide. After a treatment period of 48 hours, RNA was isolated from the cells and MALAT1 RNA levels were measured by quantitative real-time RTPCR. Human MALAT1 primer probe set RTS2736 (described herein above) was used to measure RNA levels. MALAT1 RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Results are presented as percent change of MALAT1 RNA, relative to PBS control (%UTC). The symbol "ǂ" indicates that the modified oligonucleotide is complementary to the target transcript within the amplicon region of the primer probe set, and so the associated data is not reliable. In such instances, additional assays using alternative primer probes must be performed to accurately assess the potency and efficacy of such modified oligonucleotides. In some cases, %UTC values are not available. This is indicated as N.D. (Not Defined) and additional assays will be performed to accurately assess the potency and efficacy of such modified oligonucleotides.

Modified oligonucleotides marked with a triple asterisk (⁂) have been previously described in Example 1. The %UTC data for modified oligonucleotides marked with a triple asterisk (⁂) in the tables below is identical to the data described in Example 2 as the data is from the same experiments.

Table 31

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395240	3320	3339	3520	3539	TGCCTTTAGGATTCTAGACA	61	11
395253	4783	4802	4982	5001	ATGGAGGTATGACATATAAT	78	17
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	61	18
395256	5134	5153	5333	5352	AGGCAAACGAAACATTGGCA	97	20
556089	6445	6460	6644	6659	GCATTCTAATAGCAGC	90	31
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	124	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	42	36
1156449	11	26	N/A	N/A	CGGGCTGCAGGCTGCG	86	37
1156482	157	172	123	138	ACCTGGGCTCCCGGAG	81	38
1156515	252	267	218	233	GGTTTTATCTAAATAC	75	39
1156549	348	363	314	329	CCTGGTTAGGTATGAG	81	40
1156583	483	498	449	464	GACCAACTAAGCGAAT	61	41
1156617	529	544	495	510	AAGGCAAATCGCCATG	86	42
1156651	598	613	564	579	GCCCCCCACGGCCCGC	90	43
1156685	720	735	686	701	CGTGAAAACCCACTCT	106	44
1156718	829	844	795	810	CCCCAACTGCTTGCAG	87	45
1156752	892	907	858	873	TTACGCAACTGAGCCC	89	46
1156786	957	972	923	938	GTAGGTATAGTTTACC	61	47

1156820	N/A	N/A	1006	1021	AAACGGGTCATCAAAC	81	48
1156854	N/A	N/A	1119	1134	ACAGCTTATGGAACTT	73	49
1156888	1015	1030	1215	1230	GGAATTCGATCACCTT	71	50
1156922	1068	1083	1268	1283	ACCGCACAGCTCGGGC	95	51
1156956	1172	1187	1372	1387	TGTATTAATCTCTATC	59	52
1156990	1331	1346	1531	1546	ACCTCCGTCATGTTTT	57	53
1157023	1513	1528	1713	1728	AGATCGCCTTCAAATT	59	54
1157057	1588	1603	1788	1803	TTTAAATGACGCAATT	85	55
1157090	1846	1861	2046	2061	TGCCCTTAGCTTTTTG	44	56
1157124	2094	2109	2294	2309	GCTTTACCTTCTAACT	31	57
1157158	2278	2293	2478	2493	GCTACTATATTTAAGG	71	58
1157190⁂	2341	2356	2541	2556	TGGTAATTACTCTTGA	19	4
1157224	2434	2449	2634	2649	TCTGTGTAGCACCTGG	37	59
1157258	2546	2561	2746	2761	TATCTTCACCACGAAC	100	60
1157292	2671	2686	2871	2886	CATCACCAAATTGCAC	72	61
1157325	2744	2759	2944	2959	GTCTAGGATCCTCTAC	86	62
1157359	2814	2829	3014	3029	CATATTGCCGACCTCA	57	63
1157393	2893	2908	3093	3108	TTTACACCTCAGTACG	65	64
1157426	2971	2986	3171	3186	ACAAGATTCATGAGTA	73	65
1157458	3122	3137	3322	3337	CATACAAACTGCTTAC	71	66
1157492	3234	3249	3434	3449	CCCCGCCTCAGTTACA	65	67
1157525	3335	3350	3535	3550	CTTGAGTCATTTGCCT	35	68
1157559	3447	3462	3647	3662	ATGGACATCTCTTCCA	70	69
1157591	3628	3643	3828	3843	GTACTATAGCATCTGT	55	70
1157624	3697	3712	3897	3912	TCCAGTCCCTGAAGGT	88	71
1157658	3824	3839	4024	4039	AACTTCAACATTTGGC	44	72
1157691	3941	3956	4141	4156	CAATTACCTAAACCCA	80	73
1157725	4050	4065	4250	4265	CTAAATCATTGGGAGT	52	74
1157758	4184	4199	4384	4399	GCTCTATACTTTGAAG	49	75
1157791	4274	4289	4474	4489	CCAAACAACTTTTGCA	56	76
1157825	4428	4443	4628	4643	TAGAATCTTACTTGAT	66	77
1157858	4614	4629	4813	4828	CCTCTAAGAGACATTC	71	78
1157890	4747	4762	4946	4961	AATTCACCAAGGAGCT	65	79
1157924	4815	4830	5014	5029	AGAATCTCAGGGTTAT	36	80
1157958	4903	4918	5102	5117	AAAATGGTAGATTCCG	19	81
1157992	5050	5065	5249	5264	AGGATTAATGTAGTGT	13	82
1158025	5137	5152	5336	5351	GGCAAACGAAACATTG	65	83
1158058	5220	5235	5419	5434	TTATCTGTTAACAGCT	69	84
1158091	5286	5301	5485	5500	GAACTCCACAGCTCTT	67	85
1158123	5388	5403	5587	5602	GGAACAAGTCCTACAA	77	86
1158156	5487	5502	5686	5701	TGGCATCAAGGCACTG	51	87
1158190	5577	5592	5776	5791	TTTTAGCAGTAACATC	66	88
1158223	5773	5788	5972	5987	AGTGTTCGCAGACAAA	66	89

1158256	5896	5911	6095	6110	GCCTCTATTGCCATGT	70	90
1158289	5993	6008	6192	6207	AGACCCCTGACTTTCT	78	91
1158323	6081	6096	6280	6295	CCTACCACTCTAAGAT	73	92
1158357	6195	6210	6394	6409	TCAAAATCCTGAATGG	62	93
1158390	6324	6339	6523	6538	AGTAAGCCCCACCCCC	71	94
1158423	6436	6451	6635	6650	TAGCAGCGGGATCAGA	68	95
1158455	6537	6552	6736	6751	CTTTATCACTCAGCTG	63	96
1158488	6695	6710	6894	6909	TTTAAGGTTGCATCTG	59	97
1158519	6968	6983	7167	7182	ACTAGTGGTTCCCAAT	67	98
1158552	7062	7077	7261	7276	CAGAAAAAGCTTGTTC	63	99
1158586	7159	7174	7358	7373	GCCAACACAGTTTGCT	70	100
1158618	7306	7321	7505	7520	GACCTTAGGATAATAG	20	101
1158652	7399	7414	7598	7613	TCAAGCATTCCTTCGG	27	102
1158685	7522	7537	7721	7736	AAAAGTGGTTGCCCGC	72	103
1158719	7654	7669	7853	7868	TCCAAGCTACTGGCTG	80	104
1158753	7708	7723	7907	7922	AGACCTCGACACCATC	54	105
1158785	7775	7790	7974	7989	TAATACCCTTCTGTTA	81	106
1158819	7872	7887	8071	8086	CATTACAGTTCTTGAA	59	107
1158852	7949	7964	8148	8163	GCATTCCCACCCAAAA	66	108
1158885	8040	8055	8239	8254	ACTGAAGAGCATTGGA	66	109
1158916	8196	8211	8395	8410	CGCCGCAGGGATTTGA	81	110
1158950	8328	8343	8527	8542	CAAGGATGTATATAGT	100	111
1158984ǂ	8424	8439	8623	8638	CTGCAGGCTATTACCT	106	112

Table 32

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395240	3320	3339	3520	3539	TGCCTTTAGGATTCTAGACA	49	11
395253	4783	4802	4982	5001	ATGGAGGTATGACATATAAT	75	17
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	49	18
395256	5134	5153	5333	5352	AGGCAAACGAAACATTGGCA	88	20
556089	6445	6460	6644	6659	GCATTCTAATAGCAGC	79	31
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	117	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	27	36
946417	6325	6340	6524	6539	AAGTAAGCCCCACCCC	63	113
946420	7160	7175	7359	7374	CGCCAACACAGTTTGC	88	114
1156450	13	28	N/A	N/A	CTCGGGCTGCAGGCTG	81	115
1156483	158	173	124	139	AACCTGGGCTCCCGGA	70	116
1156516	256	271	222	237	GAGTGGTTTTATCTAA	69	117
1156550	349	364	315	330	GCCTGGTTAGGTATGA	79	118

1156584	484	499	450	465	AGACCAACTAAGCGAA	62	119
1156618	530	545	496	511	CAAGGCAAATCGCCAT	58	120
1156652	599	614	565	580	AGCCCCCCACGGCCCG	73	121
1156686	734	749	700	715	GGAAATCTTAGAAACG	64	122
1156719	830	845	796	811	CCCCCAACTGCTTGCA	71	123
1156753	893	908	859	874	ATTACGCAACTGAGCC	84	124
1156787	958	973	924	939	AGTAGGTATAGTTTAC	90	125
1156821	N/A	N/A	1007	1022	TAAACGGGTCATCAAA	66	126
1156855	N/A	N/A	1123	1138	CTTAACAGCTTATGGA	70	127
1156889	1016	1031	1216	1231	CGGAATTCGATCACCT	81	128
1156923	1069	1084	1269	1284	TACCGCACAGCTCGGG	80	129
1156957	1174	1189	1374	1389	GTTGTATTAATCTCTA	24	130
1156991	1333	1348	1533	1548	CAACCTCCGTCATGTT	65	131
1157024	1514	1529	1714	1729	AAGATCGCCTTCAAAT	51	132
1157058	1589	1604	1789	1804	CTTTAAATGACGCAAT	65	133
1157091	1851	1866	2051	2066	CATTTTGCCCTTAGCT	46	134
1157125	2095	2110	2295	2310	AGCTTTACCTTCTAAC	53	135
1157159	2283	2298	2483	2498	ACTAAGCTACTATATT	61	136
1157191	2342	2357	2542	2557	TTGGTAATTACTCTTG	32	137
1157225	2441	2456	2641	2656	ATCCACTTCTGTGTAG	62	138
1157259	2547	2562	2747	2762	CTATCTTCACCACGAA	60	139
1157293	2676	2691	2876	2891	ACCTTCATCACCAAAT	78	140
1157326	2745	2760	2945	2960	GGTCTAGGATCCTCTA	77	141
1157360	2815	2830	3015	3030	ACATATTGCCGACCTC	57	142
1157394	2894	2909	3094	3109	CTTTACACCTCAGTAC	62	143
1157427	2972	2987	3172	3187	GACAAGATTCATGAGT	53	144
1157459	3133	3148	3333	3348	CCCCAACTAAACATAC	74	145
1157493	3235	3250	3435	3450	CCCCCGCCTCAGTTAC	72	146
1157526	3337	3352	3537	3552	ACCTTGAGTCATTTGC	34	147
1157560	3448	3463	3648	3663	AATGGACATCTCTTCC	73	148
1157592	3630	3645	3830	3845	TAGTACTATAGCATCT	51	149
1157625	3709	3724	3909	3924	GATAAAAGCAGCTCCA	70	150
1157659	3837	3852	4037	4052	TATTGGAAAACTTAAC	74	151
1157692	3942	3957	4142	4157	ACAATTACCTAAACCC	67	152
1157726	4051	4066	4251	4266	ACTAAATCATTGGGAG	41	153
1157759	4185	4200	4385	4400	AGCTCTATACTTTGAA	36	154
1157792	4282	4297	4482	4497	TACCATATCCAAACAA	89	155
1157826	4429	4444	4629	4644	ATAGAATCTTACTTGA	34	156
1157859	4615	4630	4814	4829	CCCTCTAAGAGACATT	68	157
1157891	4751	4766	4950	4965	TATCAATTCACCAAGG	99	158
1157925	4817	4832	5016	5031	TAAGAATCTCAGGGTT	31	159
1157959	4904	4919	5103	5118	TAAAATGGTAGATTCC	12	160
1157993	5051	5066	5250	5265	CAGGATTAATGTAGTG	15	161

1158026	5138	5153	5337	5352	AGGCAAACGAAACATT	65	162
1158059	5221	5236	5420	5435	CTTATCTGTTAACAGC	57	163
1158092	5289	5304	5488	5503	TAAGAACTCCACAGCT	59	164
1158124	5389	5404	5588	5603	AGGAACAAGTCCTACA	64	165
1158157	5488	5503	5687	5702	TTGGCATCAAGGCACT	28	166
1158191	5600	5615	5799	5814	CAATTTACATCACAAC	55	167
1158224	5775	5790	5974	5989	AGAGTGTTCGCAGACA	43	168
1158257	5900	5915	6099	6114	GAGGGCCTCTATTGCC	86	169
1158290	5995	6010	6194	6209	ATAGACCCCTGACTTT	66	170
1158324	6082	6097	6281	6296	GCCTACCACTCTAAGA	71	171
1158358	6200	6215	6399	6414	GCAATTCAAAATCCTG	49	172
1158424	6437	6452	6636	6651	ATAGCAGCGGGATCAG	43	173
1158456	6538	6553	6737	6752	CCTTTATCACTCAGCT	46	174
1158489	6697	6712	6896	6911	ATTTTAAGGTTGCATC	63	175
1158520	6970	6985	7169	7184	GAACTAGTGGTTCCCA	54	176
1158553	7081	7096	7280	7295	CTGACTTTGTATGTAA	49	177
1158619	7307	7322	7506	7521	TGACCTTAGGATAATA	38	178
1158653	7400	7415	7599	7614	TTCAAGCATTCCTTCG	38	179
1158686	7523	7538	7722	7737	GAAAAGTGGTTGCCCG	68	180
1158720	7655	7670	7854	7869	ATCCAAGCTACTGGCT	60	181
1158754	7709	7724	7908	7923	AAGACCTCGACACCAT	56	182
1158786	7780	7795	7979	7994	GGTTTTAATACCCTTC	49	183
1158820	7873	7888	8072	8087	GCATTACAGTTCTTGA	28	184
1158853	7968	7983	8167	8182	GTCTTAGCAGAGAATT	53	185
1158886	8041	8056	8240	8255	TACTGAAGAGCATTGG	29	186
1158917	8210	8225	8409	8424	AGTCAAAGCAAAGACG	65	187
1158951	8329	8344	8528	8543	TCAAGGATGTATATAG	94	188
1158985	8426	8441	8625	8640	AGCTGCAGGCTATTAC	61	189

Example 13: Antisense inhibition of human MALAT1 in A431 cells by 3-10-3 cEt gapmers

Modified oligonucleotides complementary to a MALAT1 nucleic acid were synthesized and tested for their effect on MALAT1 RNA levels *in vitro* in comparison with comparator compounds 395254 and 559497 described above. The modified oligonucleotides were tested in a series of experiments using the same culture conditions. The results for each separate experiment are presented in separate tables below.

Except for the comparator compound 395254, which is a 5-10-5 MOE gapmer (i.e., it has a central gap segment of ten 2'-deoxynucleosides flanked on each side by wing segments, each comprising five 2'-O-methoxyethyl modified nucleosides), the modified oligonucleotides are all 3-10-3 cEt gapmers (i.e., they have a central gap segment of ten 2'-deoxynucleosides flanked on each side by wing segments, each comprising three cEt modified nucleosides). The internucleoside linkages throughout each modified oligonucleotide are phosphorothioate (P=S) linkages. All cytosine nucleobases throughout each modified oligonucleotide are 5-methylcytosines.

"Start site" indicates the 5'-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. "Stop site" indicates the 3'-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. As shown in the tables below, the modified oligonucleotides are 100% complementary to either the human MALAT1 RNA transcript, designated herein as SEQ ID NO: 1 (GENBANK Accession No. XR_001309.1) or the human MALAT1 RNA transcript designated here in as SEQ ID NO: 2824 (GENBANK Accession No. EF177381.1). 'N/A' indicates that the modified oligonucleotide is not complementary to that particular target sequence with 100% complementarity.

Table 33

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	107	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	130	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	38	36
568439	1590	1605	1790	1805	GCTTTAAATGACGCAA	122	190
1156451	14	29	N/A	N/A	TCTCGGGCTGCAGGCT	80	191
1156484	159	174	125	140	AAACCTGGGCTCCCGG	80	192
1156517	257	272	223	238	TGAGTGGTTTTATCTA	93	193
1156551	354	369	320	335	GTTATGCCTGGTTAGG	84	194
1156585	485	500	451	466	TAGACCAACTAAGCGA	109	195
1156619	531	546	497	512	ACAAGGCAAATCGCCA	83	196
1156653	603	618	569	584	CGCCAGCCCCCCACGG	145	197
1156687	738	753	704	719	CTTGGGAAATCTTAGA	111	198
1156720	831	846	797	812	TCCCCCAACTGCTTGC	89	199
1156754	894	909	860	875	CATTACGCAACTGAGC	101	200
1156788	959	974	925	940	CAGTAGGTATAGTTTA	117	201
1156822	N/A	N/A	1008	1023	TTAAACGGGTCATCAA	100	202
1156856	N/A	N/A	1124	1139	TCTTAACAGCTTATGG	69	203
1156890	1017	1032	1217	1232	CCGGAATTCGATCACC	91	204
1156924	1071	1086	1271	1286	CCTACCGCACAGCTCG	97	205
1156958	1176	1191	1376	1391	TAGTTGTATTAATCTC	62	206
1156992	1334	1349	1534	1549	TCAACCTCCGTCATGT	68	207
1157025	1515	1530	1715	1730	AAAGATCGCCTTCAAA	68	208
1157092	1853	1868	2053	2068	TACATTTTGCCCTTAG	30	209
1157126	2117	2132	2317	2332	CGTAAACACCCTCATC	68	210
1157160	2284	2299	2484	2499	AACTAAGCTACTATAT	102	211
1157192	2344	2359	2544	2559	AGTTGGTAATTACTCT	60	212
1157226	2446	2461	2646	2661	ACTGAATCCACTTCTG	65	213
1157260	2548	2563	2748	2763	CCTATCTTCACCACGA	94	214
1157294	2678	2693	2878	2893	CTACCTTCATCACCAA	98	215

1157327	2746	2761	2946	2961	TGGTCTAGGATCCTCT	115	216
1157361	2816	2831	3016	3031	AACATATTGCCGACCT	55	217
1157395	2895	2910	3095	3110	CCTTTACACCTCAGTA	87	218
1157428	2973	2988	3173	3188	AGACAAGATTCATGAG	50	219
1157460	3134	3149	3334	3349	ACCCCAACTAAACATA	74	220
1157494	3236	3251	3436	3451	CCCCCCGCCTCAGTTA	107	221
1157527	3338	3353	3538	3553	CACCTTGAGTCATTTG	63	222
1157561	3449	3464	3649	3664	CAATGGACATCTCTTC	51	223
1157593	3631	3646	3831	3846	ATAGTACTATAGCATC	70	224
1157626	3710	3725	3910	3925	GGATAAAAGCAGCTCC	68	225
1157660	3872	3887	4072	4087	CCCTCCCCTTTAATAA	117	226
1157693	3943	3958	4143	4158	AACAATTACCTAAACC	84	227
1157727	4052	4067	4252	4267	AACTAAATCATTGGGA	101	228
1157760	4190	4205	4390	4405	CCAAAAGCTCTATACT	88	229
1157793	4283	4298	4483	4498	CTACCATATCCAAACA	79	230
1157827	4447	4462	4647	4662	GCTTACACACAACTGA	50	231
1157860	4616	4631	4815	4830	ACCCTCTAAGAGACAT	65	232
1157892	4752	4767	4951	4966	TTATCAATTCACCAAG	75	233
1157926	4818	4833	5017	5032	GTAAGAATCTCAGGGT	22	234
1157960	4920	4935	5119	5134	GACAAGCAATTAACTT	34	235
1157994	5052	5067	5251	5266	CCAGGATTAATGTAGT	29	236
1158027	5139	5154	5338	5353	GAGGCAAACGAAACAT	99	237
1158060	5222	5237	5421	5436	ACTTATCTGTTAACAG	75	238
1158093	5290	5305	5489	5504	TTAAGAACTCCACAGC	54	239
1158125	5390	5405	5589	5604	CAGGAACAAGTCCTAC	81	240
1158158	5491	5506	5690	5705	TAGTTGGCATCAAGGC	28	241
1158192	5605	5620	5804	5819	CTACACAATTTACATC	78	242
1158225	5777	5792	5976	5991	AAAGAGTGTTCGCAGA	46	243
1158258	5901	5916	6100	6115	AGAGGGCCTCTATTGC	67	244
1158291	5996	6011	6195	6210	TATAGACCCCTGACTT	58	245
1158325	6083	6098	6282	6297	TGCCTACCACTCTAAG	110	246
1158359	6208	6223	6407	6422	ACTCATATGCAATTCA	39	247
1158391	6326	6341	6525	6540	CAAGTAAGCCCCACCC	74	248
1158425	6438	6453	6637	6652	AATAGCAGCGGGATCA	66	249
1158457	6539	6554	6738	6753	GCCTTTATCACTCAGC	71	250
1158490	6698	6713	6897	6912	GATTTTAAGGTTGCAT	45	251
1158521	6971	6986	7170	7185	AGAACTAGTGGTTCCC	103	252
1158554	7082	7097	7281	7296	TCTGACTTTGTATGTA	52	253
1158587	7161	7176	7360	7375	ACGCCAACACAGTTTG	52	254
1158620	7308	7323	7507	7522	TTGACCTTAGGATAAT	53	255
1158654	7405	7420	7604	7619	GGTACTTCAAGCATTC	56	256
1158687	7524	7539	7723	7738	GGAAAAGTGGTTGCCC	76	257
1158721	7656	7671	7855	7870	GATCCAAGCTACTGGC	82	258

1158755	7710	7725	7909	7924	AAAGACCTCGACACCA	85	259
1158787	7781	7796	7980	7995	TGGTTTTAATACCCTT	89	260
1158821	7874	7889	8073	8088	AGCATTACAGTTCTTG	22	261
1158854	7977	7992	8176	8191	CCTGAAAAAGTCTTAG	72	262
1158887	8042	8057	8241	8256	CTACTGAAGAGCATTG	78	263
1158918	8216	8231	8415	8430	ATTAGTAGTCAAAGCA	80	264
1158952	8330	8345	8529	8544	ATCAAGGATGTATATA	100	265
1158986	8445	8460	8644	8659	TAGGGCTTCTCAAAAC	96	266

Table 34

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	96	18
556064	5140	5155	5339	5354	TGAGGCAAACGAAACA	84	267
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	123	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	33	36
1156452	15	30	N/A	N/A	GTCTCGGGCTGCAGGC	106	268
1156485	160	175	126	141	GAAACCTGGGCTCCCG	87	269
1156518	262	277	228	243	GAGTTTGAGTGGTTTT	74	270
1156552	356	371	322	337	GTGTTATGCCTGGTTA	98	271
1156586	486	501	452	467	GTAGACCAACTAAGCG	74	272
1156620	532	547	498	513	CACAAGGCAAATCGCC	80	273
1156654	610	625	576	591	CAGTTGCCGCCAGCCC	103	274
1156688	739	754	705	720	GCTTGGGAAATCTTAG	93	275
1156721	832	847	798	813	CTCCCCCAACTGCTTG	78	276
1156755	895	910	861	876	CCATTACGCAACTGAG	88	277
1156789	960	975	926	941	ACAGTAGGTATAGTTT	76	278
1156823	N/A	N/A	1009	1024	TTTAAACGGGTCATCA	90	279
1156857	N/A	N/A	1125	1140	TTCTTAACAGCTTATG	79	280
1156891	1018	1033	1218	1233	ACCGGAATTCGATCAC	65	281
1156925	1072	1087	1272	1287	GCCTACCGCACAGCTC	74	282
1156959	1177	1192	1377	1392	GTAGTTGTATTAATCT	32	283
1156993	1335	1350	1535	1550	CTCAACCTCCGTCATG	41	284
1157026	1516	1531	1716	1731	AAAAGATCGCCTTCAA	66	285
1157059	1591	1606	1791	1806	GGCTTTAAATGACGCA	83	286
1157093	1854	1869	2054	2069	GTACATTTTGCCCTTA	36	287
1157127	2133	2148	2333	2348	AATTGGTTCTGGTCTA	42	288
1157161	2285	2300	2485	2500	AAACTAAGCTACTATA	117	289
1157193	2345	2360	2545	2560	AAGTTGGTAATTACTC	78	290
1157227	2451	2466	2651	2666	GATTCACTGAATCCAC	92	291

1157261	2549	2564	2749	2764	TCCTATCTTCACCACG	60	292
1157295	2681	2696	2881	2896	CTGCTACCTTCATCAC	61	293
1157328	2755	2770	2955	2970	CTGGCATGCTGGTCTA	81	294
1157362	2817	2832	3017	3032	CAACATATTGCCGACC	126	295
1157396	2896	2911	3096	3111	CCCTTTACACCTCAGT	75	296
1157429	2974	2989	3174	3189	CAGACAAGATTCATGA	81	297
1157461	3135	3150	3335	3350	TACCCCAACTAAACAT	82	298
1157495	3237	3252	3437	3452	CCCCCCCGCCTCAGTT	85	299
1157528	3339	3354	3539	3554	ACACCTTGAGTCATTT	50	300
1157562	3450	3465	3650	3665	CCAATGGACATCTCTT	60	301
1157594	3632	3647	3832	3847	AATAGTACTATAGCAT	85	302
1157627	3722	3737	3922	3937	ATACTCTTCCAAGGAT	65	303
1157661	3876	3891	4076	4091	TTGCCCCTCCCCTTTA	58	304
1157694	3946	3961	4146	4161	CTAAACAATTACCTAA	97	305
1157728	4053	4068	4253	4268	AAACTAAATCATTGGG	57	306
1157761	4191	4206	4391	4406	CCCAAAAGCTCTATAC	94	307
1157794	4284	4299	4484	4499	ACTACCATATCCAAAC	73	308
1157828	4448	4463	4648	4663	TGCTTACACACAACTG	65	309
1157861	4617	4632	4816	4831	CACCCTCTAAGAGACA	99	310
1157893	4753	4768	4952	4967	CTTATCAATTCACCAA	53	311
1157927	4819	4834	5018	5033	AGTAAGAATCTCAGGG	55	312
1157961	4921	4936	5120	5135	TGACAAGCAATTAACT	72	313
1157995	5053	5068	5252	5267	TCCAGGATTAATGTAG	52	314
1158061	5223	5238	5422	5437	AACTTATCTGTTAACA	70	315
1158094	5293	5308	5492	5507	TATTTAAGAACTCCAC	74	316
1158126	5391	5406	5590	5605	ACAGGAACAAGTCCTA	90	317
1158159	5492	5507	5691	5706	TTAGTTGGCATCAAGG	26	318
1158193	5615	5630	5814	5829	TAATGGTTTTCTACAC	60	319
1158226	5778	5793	5977	5992	TAAAGAGTGTTCGCAG	49	320
1158259	5902	5917	6101	6116	TAGAGGGCCTCTATTG	61	321
1158292	5997	6012	6196	6211	TTATAGACCCCTGACT	90	322
1158326	6084	6099	6283	6298	TTGCCTACCACTCTAA	100	323
1158360	6209	6224	6408	6423	CACTCATATGCAATTC	63	324
1158392	6328	6343	6527	6542	AACAAGTAAGCCCCAC	89	325
1158426	6439	6454	6638	6653	TAATAGCAGCGGGATC	70	326
1158458	6540	6555	6739	6754	AGCCTTTATCACTCAG	65	327
1158491	6699	6714	6898	6913	TGATTTTAAGGTTGCA	30	328
1158522	6972	6987	7171	7186	AAGAACTAGTGGTTCC	70	329
1158555	7085	7100	7284	7299	TGATCTGACTTTGTAT	53	330
1158588	7162	7177	7361	7376	CACGCCAACACAGTTT	64	331
1158621	7309	7324	7508	7523	CTTGACCTTAGGATAA	56	332
1158655	7406	7421	7605	7620	GGGTACTTCAAGCATT	57	333
1158688	7525	7540	7724	7739	GGGAAAAGTGGTTGCC	91	334

1158722	7657	7672	7856	7871	GGATCCAAGCTACTGG	82	335
1158756	7711	7726	7910	7925	CAAAGACCTCGACACC	82	336
1158788	7784	7799	7983	7998	CTGTGGTTTTAATACC	49	337
1158822	7876	7891	8075	8090	CCAGCATTACAGTTCT	58	338
1158855	7987	8002	8186	8201	GTTATGTTCACCTGAA	39	339
1158888	8043	8058	8242	8257	CCTACTGAAGAGCATT	75	340
1158919	8217	8232	8416	8431	GATTAGTAGTCAAAGC	76	341
1158953	8331	8346	8530	8545	CATCAAGGATGTATAT	104	342
1158987	8448	8463	8647	8662	CAGTAGGGCTTCTCAA	90	343

Table 35

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	77	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	102	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	45	36
1156453	16	31	N/A	N/A	AGTCTCGGGCTGCAGG	97	344
1156486	168	183	134	149	GACTCTGGGAAACCTG	99	345
1156519	264	279	230	245	CAGAGTTTGAGTGGTT	84	346
1156553	357	372	323	338	TGTGTTATGCCTGGTT	99	347
1156587	487	502	453	468	AGTAGACCAACTAAGC	75	348
1156621	533	548	499	514	TCACAAGGCAAATCGC	93	349
1156655	613	628	579	594	CCCCAGTTGCCGCCAG	118	350
1156689	740	755	706	721	TGCTTGGGAAATCTTA	77	351
1156722	838	853	804	819	GACTTTCTCCCCCAAC	94	352
1156756	896	911	862	877	TCCATTACGCAACTGA	91	353
1156790	961	976	927	942	GACAGTAGGTATAGTT	113	354
1156824	N/A	N/A	1010	1025	TTTTAAACGGGTCATC	83	355
1156858	N/A	N/A	1152	1167	AGGTTCTAGTTTTACT	84	356
1156892	1019	1034	1219	1234	CACCGGAATTCGATCA	80	357
1156926	1073	1088	1273	1288	TGCCTACCGCACAGCT	81	358
1156960	1178	1193	1378	1393	AGTAGTTGTATTAATC	36	359
1156994	1336	1351	1536	1551	TCTCAACCTCCGTCAT	73	360
1157027	1517	1532	1717	1732	TAAAAGATCGCCTTCA	59	361
1157060	1592	1607	1792	1807	AGGCTTTAAATGACGC	111	362
1157094	1865	1880	2065	2080	CTTCTAAGTTTGTACA	53	363
1157128	2134	2149	2334	2349	AAATTGGTTCTGGTCT	52	364
1157162	2286	2301	2486	2501	CAAACTAAGCTACTAT	85	365
1157194	2346	2361	2546	2561	TAAGTTGGTAATTACT	83	366
1157228	2452	2467	2652	2667	AGATTCACTGAATCCA	94	367

1157262	2558	2573	2758	2773	GGACTCTTTTCCTATC	104	368
1157296	2682	2697	2882	2897	CCTGCTACCTTCATCA	78	369
1157329	2759	2774	2959	2974	CACACTGGCATGCTGG	91	370
1157363	2818	2833	3018	3033	ACAACATATTGCCGAC	90	371
1157397	2897	2912	3097	3112	TCCCTTTACACCTCAG	75	372
1157430	2975	2990	3175	3190	TCAGACAAGATTCATG	69	373
1157462	3136	3151	3336	3351	TTACCCCAACTAAACA	104	374
1157496	3238	3253	3438	3453	TCCCCCCCGCCTCAGT	84	375
1157529	3340	3355	3540	3555	TACACCTTGAGTCATT	62	376
1157563	3451	3466	3651	3666	TCCAATGGACATCTCT	75	377
1157595	3633	3648	3833	3848	CAATAGTACTATAGCA	93	378
1157628	3723	3738	3923	3938	AATACTCTTCCAAGGA	85	379
1157662	3880	3895	4080	4095	ATATTTGCCCCTCCCC	73	380
1157695	3947	3962	4147	4162	ACTAAACAATTACCTA	91	381
1157729	4092	4107	4292	4307	TAACTTCCCCCAGCTT	80	382
1157762	4192	4207	4392	4407	CCCCAAAAGCTCTATA	92	383
1157795	4285	4300	4485	4500	CACTACCATATCCAAA	77	384
1157829	4449	4464	4649	4664	TTGCTTACACACAACT	82	385
1157862	4618	4633	4817	4832	CCACCCTCTAAGAGAC	117	386
1157894	4754	4769	4953	4968	ACTTATCAATTCACCA	72	387
1157928	4820	4835	5019	5034	TAGTAAGAATCTCAGG	40	388
1157962	4922	4937	5121	5136	TTGACAAGCAATTAAC	93	389
1157996	5054	5069	5253	5268	TTCCAGGATTAATGTA	63	390
1158028	5141	5156	5340	5355	CTGAGGCAAACGAAAC	106	391
1158062	5227	5242	5426	5441	GTTAAACTTATCTGTT	59	392
1158095	5295	5310	5494	5509	GATATTTAAGAACTCC	62	393
1158127	5392	5407	5591	5606	CACAGGAACAAGTCCT	84	394
1158160	5493	5508	5692	5707	CTTAGTTGGCATCAAG	69	395
1158194	5679	5694	5878	5893	TAAGGAGACAGCTTTC	84	396
1158227	5779	5794	5978	5993	TTAAAGAGTGTTCGCA	41	397
1158260	5903	5918	6102	6117	TTAGAGGGCCTCTATT	97	398
1158293	5998	6013	6197	6212	TTTATAGACCCCTGAC	78	399
1158327	6087	6102	6286	6301	ACATTGCCTACCACTC	84	400
1158361	6210	6225	6409	6424	GCACTCATATGCAATT	94	401
1158393	6329	6344	6528	6543	CAACAAGTAAGCCCCA	100	402
1158427	6440	6455	6639	6654	CTAATAGCAGCGGGAT	78	403
1158459	6541	6556	6740	6755	CAGCCTTTATCACTCA	51	404
1158492	6700	6715	6899	6914	CTGATTTTAAGGTTGC	20	405
1158523	6973	6988	7172	7187	AAAGAACTAGTGGTTC	104	406
1158556	7087	7102	7286	7301	ACTGATCTGACTTTGT	68	407
1158589	7163	7178	7362	7377	CCACGCCAACACAGTT	69	408
1158622	7314	7329	7513	7528	CTTCTCTTGACCTTAG	39	409
1158656	7421	7436	7620	7635	TTAAGAGAAGCCCAGG	76	410

1158689	7527	7542	7726	7741	TAGGGAAAAGTGGTTG	113	411
1158723	7658	7673	7857	7872	AGGATCCAAGCTACTG	113	412
1158757	7712	7727	7911	7926	CCAAAGACCTCGACAC	87	413
1158789	7785	7800	7984	7999	GCTGTGGTTTTAATAC	51	414
1158823	7877	7892	8076	8091	CCCAGCATTACAGTTC	90	415
1158856	7988	8003	8187	8202	TGTTATGTTCACCTGA	65	416
1158889	8044	8059	8243	8258	CCCTACTGAAGAGCAT	87	417
1158920	8218	8233	8417	8432	AGATTAGTAGTCAAAG	112	418
1158954	8332	8347	8531	8546	ACATCAAGGATGTATA	106	419
1158988	8449	8464	8648	8663	GCAGTAGGGCTTCTCA	108	420

Table 36

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	78	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	98	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	39	36
946407	3452	3467	3652	3667	CTCCAATGGACATCTC	71	421
1156454	17	32	N/A	N/A	AAGTCTCGGGCTGCAG	96	422
1156487	201	216	167	182	AGATAGCAGCACAACT	105	423
1156520	265	280	231	246	GCAGAGTTTGAGTGGT	109	424
1156554	358	373	324	339	CTGTGTTATGCCTGGT	103	425
1156588	488	503	454	469	AAGTAGACCAACTAAG	122	426
1156622	534	549	500	515	CTCACAAGGCAAATCG	112	427
1156656	616	631	582	597	GCCCCCCAGTTGCCGC	135	428
1156690	751	766	717	732	CACGGGCTGTCTGCTT	82	429
1156723	839	854	805	820	GGACTTTCTCCCCCAA	105	430
1156757	897	912	863	878	TTCCATTACGCAACTG	121	431
1156791	962	977	928	943	GGACAGTAGGTATAGT	89	432
1156825	N/A	N/A	1011	1026	ATTTTAAACGGGTCAT	93	433
1156859	N/A	N/A	1163	1178	CGGTTAAAAATAGGTT	94	434
1156893	1020	1035	1220	1235	TCACCGGAATTCGATC	363	435
1156927	1074	1089	1274	1289	ATGCCTACCGCACAGC	108	436
1156961	1200	1215	1400	1415	AACCTATTGACTATAT	81	437
1156995	1337	1352	1537	1552	ATCTCAACCTCCGTCA	66	438
1157028	1518	1533	1718	1733	TTAAAAGATCGCCTTC	57	439
1157061	1593	1608	1793	1808	TAGGCTTTAAATGACG	74	440
1157095	1866	1881	2066	2081	TCTTCTAAGTTTGTAC	37	441
1157129	2135	2150	2335	2350	TAAATTGGTTCTGGTC	51	442
1157163	2287	2302	2487	2502	TCAAACTAAGCTACTA	101	443

1157195	2347	2362	2547	2562	TTAAGTTGGTAATTAC	106	444
1157229	2453	2468	2653	2668	TAGATTCACTGAATCC	104	445
1157263	2571	2586	2771	2786	CGCACTGGCTCCTGGA	51	446
1157297	2683	2698	2883	2898	GCCTGCTACCTTCATC	64	447
1157330	2763	2778	2963	2978	TTGGCACACTGGCATG	76	448
1157364	2820	2835	3020	3035	AAACAACATATTGCCG	80	449
1157398	2898	2913	3098	3113	ATCCCTTTACACCTCA	64	450
1157431	2976	2991	3176	3191	TTCAGACAAGATTCAT	49	451
1157463	3137	3152	3337	3352	ATTACCCCAACTAAAC	91	452
1157497	3239	3254	3439	3454	CTCCCCCCCGCCTCAG	88	453
1157530	3341	3356	3541	3556	TTACACCTTGAGTCAT	79	454
1157596	3634	3649	3834	3849	TCAATAGTACTATAGC	75	455
1157629	3724	3739	3924	3939	GAATACTCTTCCAAGG	84	456
1157663	3881	3896	4081	4096	AATATTTGCCCCTCCC	85	457
1157696	3959	3974	4159	4174	CTGCAATCATAAACTA	90	458
1157730	4093	4108	4293	4308	TTAACTTCCCCCAGCT	100	459
1157763	4210	4225	4410	4425	CAGTTCAATACTTTCC	55	460
1157796	4288	4303	4488	4503	ACACACTACCATATCC	103	461
1157830	4453	4468	4653	4668	AAACTTGCTTACACAC	75	462
1157863	4619	4634	4818	4833	CCCACCCTCTAAGAGA	104	463
1157895	4755	4770	4954	4969	TACTTATCAATTCACC	46	464
1157929⁂	4821	4836	5020	5035	GTAGTAAGAATCTCAG	20	5
1157963	4923	4938	5122	5137	CTTGACAAGCAATTAA	70	465
1157997	5056	5071	5255	5270	TATTCCAGGATTAATG	71	466
1158029	5143	5158	5342	5357	GTCTGAGGCAAACGAA	71	467
1158063	5230	5245	5429	5444	CAAGTTAAACTTATCT	84	468
1158096	5298	5313	5497	5512	GTTGATATTTAAGAAC	115	469
1158128	5393	5408	5592	5607	CCACAGGAACAAGTCC	105	470
1158161⁂	5494	5509	5693	5708	CCTTAGTTGGCATCAA	18	6
1158195	5683	5698	5882	5897	TAAATAAGGAGACAGC	62	471
1158228	5780	5795	5979	5994	ATTAAAGAGTGTTCGC	31	472
1158261	5904	5919	6103	6118	TTTAGAGGGCCTCTAT	83	473
1158294	5999	6014	6198	6213	ATTTATAGACCCCTGA	108	474
1158328	6089	6104	6288	6303	AAACATTGCCTACCAC	109	475
1158362	6212	6227	6411	6426	AAGCACTCATATGCAA	102	476
1158394	6330	6345	6529	6544	ACAACAAGTAAGCCCC	107	477
1158428	6441	6456	6640	6655	TCTAATAGCAGCGGGA	84	478
1158460	6542	6557	6741	6756	TCAGCCTTTATCACTC	87	479
1158493	6701	6716	6900	6915	ACTGATTTTAAGGTTG	74	480
1158524	6975	6990	7174	7189	TGAAAGAACTAGTGGT	77	481
1158557	7088	7103	7287	7302	AACTGATCTGACTTTG	66	482
1158590	7165	7180	7364	7379	CCCCACGCCAACACAG	90	483
1158623	7317	7332	7516	7531	ACACTTCTCTTGACCT	40	484

1158657	7422	7437	7621	7636	GTTAAGAGAAGCCCAG	80	485
1158690	7528	7543	7727	7742	CTAGGGAAAAGTGGTT	122	486
1158724	7659	7674	7858	7873	AAGGATCCAAGCTACT	92	487
1158758	7713	7728	7912	7927	ACCAAAGACCTCGACA	86	488
1158790	7791	7806	7990	8005	TACTTAGCTGTGGTTT	77	489
1158824	7878	7893	8077	8092	ACCCAGCATTACAGTT	92	490
1158857	7989	8004	8188	8203	CTGTTATGTTCACCTG	44	491
1158890	8046	8061	8245	8260	GACCCTACTGAAGAGC	68	492
1158921	8220	8235	8419	8434	ACAGATTAGTAGTCAA	91	493
1158955	8333	8348	8532	8547	TACATCAAGGATGTAT	98	494
1158989	8450	8465	8649	8664	AGCAGTAGGGCTTCTC	97	495

Table 37

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	93	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	107	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	34	36
946421	7423	7438	7622	7637	TGTTAAGAGAAGCCCA	98	496
946426	8451	8466	8650	8665	CAGCAGTAGGGCTTCT	101	497
1156455	18	33	N/A	N/A	GAAGTCTCGGGCTGCA	94	498
1156488	202	217	168	183	AAGATAGCAGCACAAC	88	499
1156521	267	282	233	248	CTGCAGAGTTTGAGTG	119	500
1156555	359	374	325	340	TCTGTGTTATGCCTGG	83	501
1156589	490	505	456	471	TAAAGTAGACCAACTA	86	502
1156623	535	550	501	516	GCTCACAAGGCAAATC	104	503
1156657	618	633	584	599	CGGCCCCCCAGTTGCC	83	504
1156691	752	767	718	733	GCACGGGCTGTCTGCT	112	505
1156724	840	855	806	821	CGGACTTTCTCCCCCA	109	506
1156758	899	914	865	880	CTTTCCATTACGCAAC	100	507
1156792	964	979	930	945	AGGGACAGTAGGTATA	84	508
1156826	N/A	N/A	1012	1027	TATTTTAAACGGGTCA	97	509
1156860	N/A	N/A	1164	1179	TCGGTTAAAAATAGGT	84	510
1156894	1021	1036	1221	1236	ATCACCGGAATTCGAT	83	511
1156928	1076	1091	1276	1291	CAATGCCTACCGCACA	84	512
1156962	1201	1216	1401	1416	TAACCTATTGACTATA	78	513
1156996	1339	1354	1539	1554	TCATCTCAACCTCCGT	43	514
1157029	1519	1534	1719	1734	TTTAAAAGATCGCCTT	50	515
1157062	1597	1612	1797	1812	TAACTAGGCTTTAAAT	86	516
1157096	1923	1938	2123	2138	CTATCTGAAACTCTTG	43	517

1157130	2136	2151	2336	2351	CTAAATTGGTTCTGGT	34	518
1157164	2288	2303	2488	2503	TTCAAACTAAGCTACT	69	519
1157196	2349	2364	2549	2564	CATTAAGTTGGTAATT	88	520
1157230	2454	2469	2654	2669	CTAGATTCACTGAATC	93	521
1157264	2572	2587	2772	2787	TCGCACTGGCTCCTGG	58	522
1157298	2684	2699	2884	2899	CGCCTGCTACCTTCAT	70	523
1157331	2769	2784	2969	2984	GTGGCCTTGGCACACT	110	524
1157365	2838	2853	3038	3053	CATAAGTAAGTTCCAG	51	525
1157399	2899	2914	3099	3114	AATCCCTTTACACCTC	74	526
1157432	2977	2992	3177	3192	CTTCAGACAAGATTCA	76	527
1157464	3138	3153	3338	3353	CATTACCCCAACTAAA	85	528
1157498	3240	3255	3440	3455	ACTCCCCCCCGCCTCA	74	529
1157531	3342	3357	3542	3557	GTTACACCTTGAGTCA	47	530
1157564	3453	3468	3653	3668	TCTCCAATGGACATCT	92	531
1157597	3635	3650	3835	3850	GTCAATAGTACTATAG	42	532
1157630	3725	3740	3925	3940	GGAATACTCTTCCAAG	94	533
1157664	3882	3897	4082	4097	CAATATTTGCCCCTCC	70	534
1157697	3965	3980	4165	4180	GTTTATCTGCAATCAT	43	535
1157731	4094	4109	4294	4309	TTTAACTTCCCCCAGC	102	536
1157764	4211	4226	4411	4426	CCAGTTCAATACTTTC	87	537
1157797	4290	4305	4490	4505	CCACACACTACCATAT	83	538
1157831	4496	4511	4695	4710	TGCAGTTAAACAATGG	38	539
1157864	4620	4635	4819	4834	GCCCACCCTCTAAGAG	82	540
1157896	4761	4776	4960	4975	TGCCTTTACTTATCAA	74	541
1157930	4823	4838	5022	5037	CAGTAGTAAGAATCTC	46	542
1157964	4924	4939	5123	5138	GCTTGACAAGCAATTA	65	543
1157998	5057	5072	5256	5271	TTATTCCAGGATTAAT	105	544
1158030	5145	5160	5344	5359	CTGTCTGAGGCAAACG	63	545
1158064	5231	5246	5430	5445	GCAAGTTAAACTTATC	58	546
1158097	5304	5319	5503	5518	GCCATGGTTGATATTT	91	547
1158129	5394	5409	5593	5608	CCCACAGGAACAAGTC	86	548
1158162⁂	5495	5510	5694	5709	TCCTTAGTTGGCATCA	24	7
1158196	5706	5721	5905	5920	CTACAGACAAACACTA	94	549
1158229	5781	5796	5980	5995	CATTAAAGAGTGTTCG	66	550
1158262	5906	5921	6105	6120	TATTTAGAGGGCCTCT	66	551
1158295	6000	6015	6199	6214	AATTTATAGACCCCTG	96	552
1158329	6092	6107	6291	6306	GTAAAACATTGCCTAC	76	553
1158363	6214	6229	6413	6428	CCAAGCACTCATATGC	88	554
1158395	6331	6346	6530	6545	TACAACAAGTAAGCCC	80	555
1158429	6442	6457	6641	6656	TTCTAATAGCAGCGGG	41	556
1158461	6544	6559	6743	6758	ACTCAGCCTTTATCAC	105	557
1158494	6715	6730	6914	6929	GAATGTTTCTTGTCAC	57	558
1158525	6976	6991	7175	7190	CTGAAAGAACTAGTGG	80	559

1158558	7089	7104	7288	7303	TAACTGATCTGACTTT	74	560
1158591	7167	7182	7366	7381	ACCCCCACGCCAACAC	77	561
1158624	7319	7334	7518	7533	TGACACTTCTCTTGAC	70	562
1158691	7529	7544	7728	7743	GCTAGGGAAAAGTGGT	95	563
1158725	7660	7675	7859	7874	CAAGGATCCAAGCTAC	81	564
1158759	7714	7729	7913	7928	CACCAAAGACCTCGAC	82	565
1158791	7792	7807	7991	8006	CTACTTAGCTGTGGTT	67	566
1158825	7881	7896	8080	8095	CCCACCCAGCATTACA	82	567
1158858	7990	8005	8189	8204	TCTGTTATGTTCACCT	48	568
1158891	8047	8062	8246	8261	TGACCCTACTGAAGAG	79	569
1158922	8221	8236	8420	8435	GACAGATTAGTAGTCA	112	570
1158956	8334	8349	8533	8548	ATACATCAAGGATGTA	81	571

Table 38

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	110	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	115	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	60	36
1156456	19	34	N/A	N/A	AGAAGTCTCGGGCTGC	92	572
1156489	203	218	169	184	TAAGATAGCAGCACAA	103	573
1156522	274	289	240	255	GACCAAACTGCAGAGT	97	574
1156556	365	380	331	346	GCAGATTCTGTGTTAT	102	575
1156590	491	506	457	472	TTAAAGTAGACCAACT	73	576
1156624	539	554	505	520	AAGTGCTCACAAGGCA	116	577
1156658	619	634	585	600	GCGGCCCCCCAGTTGC	116	578
1156692	753	768	719	734	AGCACGGGCTGTCTGC	93	579
1156725	841	856	807	822	GCGGACTTTCTCCCCC	124	580
1156759	900	915	866	881	ACTTTCCATTACGCAA	91	581
1156793	965	980	931	946	GAGGGACAGTAGGTAT	81	582
1156827	N/A	N/A	1013	1028	ATATTTTAAACGGGTC	84	583
1156861	N/A	N/A	1165	1180	TTCGGTTAAAAATAGG	107	584
1156895	1022	1037	1222	1237	CATCACCGGAATTCGA	98	585
1156929	1077	1092	1277	1292	TCAATGCCTACCGCAC	97	586
1156963	1202	1217	1402	1417	GTAACCTATTGACTAT	67	587
1156997	1348	1363	1548	1563	GAAGAAGCTTCATCTC	85	588
1157030	1520	1535	1720	1735	TTTTAAAAGATCGCCT	67	589
1157063	1599	1614	1799	1814	GTTAACTAGGCTTTAA	77	590
1157097	1948	1963	2148	2163	CTTGTCTTAGCTTGTT	29	591
1157131	2137	2152	2337	2352	TCTAAATTGGTTCTGG	45	592

1157165	2305	2320	2505	2520	GAAAGTCCTTCACATT	78	593
1157197	2350	2365	2550	2565	ACATTAAGTTGGTAAT	96	594
1157231	2463	2478	2663	2678	GCTGTCTTCCTAGATT	64	595
1157265	2574	2589	2774	2789	AATCGCACTGGCTCCT	75	596
1157299	2686	2701	2886	2901	GCCGCCTGCTACCTTC	88	597
1157332	2778	2793	2978	2993	GCTTTCCCTGTGGCCT	90	598
1157366	2840	2855	3040	3055	ACCATAAGTAAGTTCC	42	599
1157400	2900	2915	3100	3115	AAATCCCTTTACACCT	77	600
1157433	3001	3016	3201	3216	GACTTGGCAGTCTGCC	90	601
1157465	3139	3154	3339	3354	TCATTACCCCAACTAA	83	602
1157499	3241	3256	3441	3456	AACTCCCCCCCGCCTC	94	603
1157532	3343	3358	3543	3558	TGTTACACCTTGAGTC	63	604
1157565	3457	3472	3657	3672	CATTTCTCCAATGGAC	88	605
1157598	3636	3651	3836	3851	TGTCAATAGTACTATA	82	606
1157631	3726	3741	3926	3941	GGGAATACTCTTCCAA	86	607
1157665	3883	3898	4083	4098	CCAATATTTGCCCCTC	60	608
1157698	3966	3981	4166	4181	AGTTTATCTGCAATCA	54	609
1157732	4095	4110	4295	4310	ATTTAACTTCCCCCAG	82	610
1157765	4212	4227	4412	4427	CCCAGTTCAATACTTT	75	611
1157798	4292	4307	4492	4507	AACCACACACTACCAT	107	612
1157832	4513	4528	4712	4727	ACCTTAACATCTTGTT	85	613
1157865	4622	4637	4821	4836	AAGCCCACCCTCTAAG	79	614
1157897	4762	4777	4961	4976	CTGCCTTTACTTATCA	56	615
1157931	4824	4839	5023	5038	TCAGTAGTAAGAATCT	44	616
1157965	4925	4940	5124	5139	AGCTTGACAAGCAATT	84	617
1157999	5068	5083	5267	5282	TTCGGCTTCTTTTATT	56	618
1158031	5150	5165	5349	5364	GATACCTGTCTGAGGC	67	619
1158065	5232	5247	5431	5446	TGCAAGTTAAACTTAT	75	620
1158098	5305	5320	5504	5519	TGCCATGGTTGATATT	63	621
1158130	5395	5410	5594	5609	GCCCACAGGAACAAGT	75	622
1158163	5496	5511	5695	5710	TTCCTTAGTTGGCATC	26	623
1158197	5718	5733	5917	5932	CCCAACACTGAACTAC	81	624
1158230	5782	5797	5981	5996	CCATTAAAGAGTGTTC	36	625
1158263	5907	5922	6106	6121	TTATTTAGAGGGCCTC	43	626
1158296	6001	6016	6200	6215	CAATTTATAGACCCCT	106	627
1158330	6093	6108	6292	6307	TGTAAAACATTGCCTA	107	628
1158364	6215	6230	6414	6429	GCCAAGCACTCATATG	76	629
1158396	6332	6347	6531	6546	CTACAACAAGTAAGCC	93	630
1158430	6443	6458	6642	6657	ATTCTAATAGCAGCGG	68	631
1158462	6548	6563	6747	6762	CAACACTCAGCCTTTA	101	632
1158495	6730	6745	6929	6944	ACTGTTGCTTGTTTGG	47	633
1158526	6985	7000	7184	7199	GAATACCATCTGAAAG	84	634
1158559	7090	7105	7289	7304	ATAACTGATCTGACTT	105	635

1158592	7170	7185	7369	7384	TCCACCCCCACGCCAA	109	636
1158625	7321	7336	7520	7535	GCTGACACTTCTCTTG	52	637
1158658	7424	7439	7623	7638	ATGTTAAGAGAAGCCC	117	638
1158692	7530	7545	7729	7744	AGCTAGGGAAAAGTGG	110	639
1158726	7661	7676	7860	7875	ACAAGGATCCAAGCTA	107	640
1158760	7715	7730	7914	7929	CCACCAAAGACCTCGA	73	641
1158792	7793	7808	7992	8007	GCTACTTAGCTGTGGT	72	642
1158826	7882	7897	8081	8096	TCCCACCCAGCATTAC	73	643
1158859	7992	8007	8191	8206	AGTCTGTTATGTTCAC	46	644
1158892	8048	8063	8247	8262	ATGACCCTACTGAAGA	85	645
1158923	8222	8237	8421	8436	AGACAGATTAGTAGTC	108	646
1158957	8336	8351	8535	8550	TTATACATCAAGGATG	96	647
1158990	8457	8472	8656	8671	AGTTTTCAGCAGTAGG	121	648

Table 39

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	82	18
556110	7198	7213	7397	7412	AAAAAAGGCTTAGCGC	100	649
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	131	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	39	36
1156457	20	35	N/A	N/A	CAGAAGTCTCGGGCTG	81	650
1156490	204	219	170	185	CTAAGATAGCAGCACA	89	651
1156523	277	292	243	258	CAAGACCAAACTGCAG	128	652
1156557	406	421	372	387	TTACACTGCTCTGGGT	98	653
1156591	492	507	458	473	TTTAAAGTAGACCAAC	149	654
1156625	541	556	507	522	GAAAGTGCTCACAAGG	94	655
1156659	620	635	586	601	TGCGGCCCCCCAGTTG	106	656
1156693	754	769	720	735	CAGCACGGGCTGTCTG	133	657
1156726	842	857	808	823	GGCGGACTTTCTCCCC	117	658
1156760	901	916	867	882	TACTTTCCATTACGCA	84	659
1156794	966	981	932	947	TGAGGGACAGTAGGTA	82	660
1156828	N/A	N/A	1014	1029	CATATTTTAAACGGGT	116	661
1156862	N/A	N/A	1166	1181	CTTCGGTTAAAAATAG	96	662
1156896	1025	1040	1225	1240	TCGCATCACCGGAATT	96	663
1156930	1079	1094	1279	1294	CCTCAATGCCTACCGC	83	664
1156964	1203	1218	1403	1418	AGTAACCTATTGACTA	116	665
1156998	1354	1369	1554	1569	CTCCATGAAGAAGCTT	51	666
1157031	1522	1537	1722	1737	CTTTTTAAAAGATCGC	69	667
1157064	1600	1615	1800	1815	CGTTAACTAGGCTTTA	48	668

1157098	1950	1965	2150	2165	TACTTGTCTTAGCTTG	49	669
1157132	2140	2155	2340	2355	TCTTCTAAATTGGTTC	51	670
1157166	2307	2322	2507	2522	ACGAAAGTCCTTCACA	89	671
1157198	2363	2378	2563	2578	GTCCAATGCAAAAACA	105	672
1157232	2477	2492	2677	2692	GAATCCTGTCTGCTGC	67	673
1157266	2575	2590	2775	2790	AAATCGCACTGGCTCC	94	674
1157300	2688	2703	2888	2903	AAGCCGCCTGCTACCT	116	675
1157333	2779	2794	2979	2994	CGCTTTCCCTGTGGCC	102	676
1157367	2841	2856	3041	3056	TACCATAAGTAAGTTC	96	677
1157401	2901	2916	3101	3116	TAAATCCCTTTACACC	88	678
1157434	3002	3017	3202	3217	GGACTTGGCAGTCTGC	73	679
1157466	3140	3155	3340	3355	TTCATTACCCCAACTA	58	680
1157500	3243	3258	3443	3458	AAAACTCCCCCCCGCC	104	681
1157533	3344	3359	3544	3559	CTGTTACACCTTGAGT	67	682
1157566	3466	3481	3666	3681	ACTACCAGCCATTTCT	51	683
1157599	3640	3655	3840	3855	AGTTTGTCAATAGTAC	58	684
1157632	3727	3742	3927	3942	TGGGAATACTCTTCCA	89	685
1157666	3885	3900	4085	4100	TGCCAATATTTGCCCC	80	686
1157699	3970	3985	4170	4185	CATGAGTTTATCTGCA	106	687
1157733	4097	4112	4297	4312	ATATTTAACTTCCCCC	70	688
1157766	4213	4228	4413	4428	CCCCAGTTCAATACTT	75	689
1157799	4294	4309	4494	4509	AGAACCACACACTACC	77	690
1157833	4514	4529	4713	4728	TACCTTAACATCTTGT	86	691
1157866	4623	4638	4822	4837	AAAGCCCACCCTCTAA	126	692
1157898	4781	4796	4980	4995	GTATGACATATAATCT	45	693
1157932	4825	4840	5024	5039	ATCAGTAGTAAGAATC	77	694
1157966	4926	4941	5125	5140	TAGCTTGACAAGCAAT	88	695
1158000	5070	5085	5269	5284	ATTTCGGCTTCTTTTA	43	696
1158032	5151	5166	5350	5365	AGATACCTGTCTGAGG	88	697
1158066	5236	5251	5435	5450	CAGATGCAAGTTAAAC	60	698
1158099	5310	5325	5509	5524	GAAAGTGCCATGGTTG	59	699
1158131	5408	5423	5607	5622	TCCCATCACTGAAGCC	56	700
1158164	5498	5513	5697	5712	ATTTCCTTAGTTGGCA	28	701
1158198	5720	5735	5919	5934	GCCCCAACACTGAACT	89	702
1158231	5783	5798	5982	5997	TCCATTAAAGAGTGTT	44	703
1158264	5908	5923	6107	6122	CTTATTTAGAGGGCCT	64	704
1158297	6002	6017	6201	6216	TCAATTTATAGACCCC	53	705
1158331	6094	6109	6293	6308	GTGTAAAACATTGCCT	100	706
1158365	6216	6231	6415	6430	AGCCAAGCACTCATAT	83	707
1158397	6333	6348	6532	6547	GCTACAACAAGTAAGC	91	708
1158431	6444	6459	6643	6658	CATTCTAATAGCAGCG	49	709
1158463	6575	6590	6774	6789	GACTGCTTAAAACTGC	64	710
1158496	6732	6747	6931	6946	AGACTGTTGCTTGTTT	99	711

1158527	6988	7003	7187	7202	GAAGAATACCATCTGA	95	712
1158560	7091	7106	7290	7305	CATAACTGATCTGACT	105	713
1158626	7322	7337	7521	7536	GGCTGACACTTCTCTT	48	714
1158659	7455	7470	7654	7669	TTAAGAGCTGCTATAA	94	715
1158693	7537	7552	7736	7751	CTGGAAAAGCTAGGGA	113	716
1158727	7662	7677	7861	7876	CACAAGGATCCAAGCT	82	717
1158761	7716	7731	7915	7930	CCCACCAAAGACCTCG	69	718
1158793	7794	7809	7993	8008	AGCTACTTAGCTGTGG	66	719
1158827	7889	7904	8088	8103	TACATGTTCCCACCCA	61	720
1158860	7997	8012	8196	8211	GGCCAAGTCTGTTATG	101	721
1158893	8049	8064	8248	8263	CATGACCCTACTGAAG	98	722
1158924	8227	8242	8426	8441	CCTGAAGACAGATTAG	76	723
1158958	8337	8352	8536	8551	ATTATACATCAAGGAT	83	724
1158991	8458	8473	8657	8672	AAGTTTTCAGCAGTAG	92	725

Table 40

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	81	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	132	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	49	36
946416	5909	5924	6108	6123	CCTTATTTAGAGGGCC	67	726
1156458	21	36	N/A	N/A	ACAGAAGTCTCGGGCT	81	727
1156491	205	220	171	186	GCTAAGATAGCAGCAC	71	728
1156524	280	295	246	261	CCCCAAGACCAAACTG	109	729
1156558	410	425	376	391	GTGTTTACACTGCTCT	94	730
1156592	495	510	461	476	CCTTTTAAAGTAGACC	122	731
1156626	545	560	511	526	TCCTGAAAGTGCTCAC	107	732
1156660	621	636	587	602	CTGCGGCCCCCCAGTT	75	733
1156694	756	771	722	737	AGCAGCACGGGCTGTC	90	734
1156727	843	858	809	824	TGGCGGACTTTCTCCC	91	735
1156761	902	917	868	883	TTACTTTCCATTACGC	84	736
1156795	967	982	933	948	TTGAGGGACAGTAGGT	79	737
1156829	N/A	N/A	1015	1030	TCATATTTTAAACGGG	77	738
1156863	N/A	N/A	1167	1182	TCTTCGGTTAAAAATA	81	739
1156897	1026	1041	1226	1241	CTCGCATCACCGGAAT	114	740
1156931	1080	1095	1280	1295	GCCTCAATGCCTACCG	111	741
1156965	1204	1219	1404	1419	TAGTAACCTATTGACT	136	742
1156999	1356	1371	1556	1571	TACTCCATGAAGAAGC	126	743
1157032	1533	1548	1733	1748	CGGTTTAATCTCTTTT	20	744

1157065	1640	1655	1840	1855	CCCAATTAATCTTTCC	53	745
1157099	1951	1966	2151	2166	ATACTTGTCTTAGCTT	40	746
1157133	2156	2171	2356	2371	TTCTAGCTTCAAGTAT	75	747
1157167	2308	2323	2508	2523	TACGAAAGTCCTTCAC	65	748
1157199	2364	2379	2564	2579	AGTCCAATGCAAAAAC	77	749
1157233	2479	2494	2679	2694	TGGAATCCTGTCTGCT	83	750
1157267	2577	2592	2777	2792	CCAAATCGCACTGGCT	84	751
1157301	2691	2706	2891	2906	GCCAAGCCGCCTGCTA	80	752
1157334	2781	2796	2981	2996	CTCGCTTTCCCTGTGG	83	753
1157368	2842	2857	3042	3057	TTACCATAAGTAAGTT	120	754
1157402	2908	2923	3108	3123	CCCCATATAAATCCCT	107	755
1157435	3003	3018	3203	3218	AGGACTTGGCAGTCTG	70	756
1157467	3141	3156	3341	3356	CTTCATTACCCCAACT	86	757
1157501	3244	3259	3444	3459	GAAAACTCCCCCCCGC	104	758
1157534	3345	3360	3545	3560	TCTGTTACACCTTGAG	52	759
1157567	3468	3483	3668	3683	TAACTACCAGCCATTT	76	760
1157600	3641	3656	3841	3856	CAGTTTGTCAATAGTA	48	761
1157633	3729	3744	3929	3944	ACTGGGAATACTCTTC	72	762
1157667	3894	3909	4094	4109	CCAACTAATTGCCAAT	60	763
1157700	3974	3989	4174	4189	CTGGCATGAGTTTATC	73	764
1157734	4098	4113	4298	4313	CATATTTAACTTCCCC	75	765
1157767	4216	4231	4416	4431	AACCCCCAGTTCAATA	80	766
1157800	4296	4311	4496	4511	AGAGAACCACACACTA	72	767
1157834	4515	4530	4714	4729	ATACCTTAACATCTTG	57	768
1157867	4630	4645	4829	4844	ATCAACAAAAGCCCAC	112	769
1157899	4783	4798	4982	4997	AGGTATGACATATAAT	65	770
1157933	4826	4841	5025	5040	CATCAGTAGTAAGAAT	86	771
1157967	4928	4943	5127	5142	TATAGCTTGACAAGCA	81	772
1158001	5071	5086	5270	5285	TATTTCGGCTTCTTTT	53	773
1158033	5152	5167	5351	5366	GAGATACCTGTCTGAG	60	774
1158067	5238	5253	5437	5452	TGCAGATGCAAGTTAA	51	775
1158100	5312	5327	5511	5526	GAGAAAGTGCCATGGT	74	776
1158132	5409	5424	5608	5623	ATCCCATCACTGAAGC	64	777
1158165	5499	5514	5698	5713	AATTTCCTTAGTTGGC	32	778
1158199	5722	5737	5921	5936	TTGCCCCAACACTGAA	93	779
1158232	5784	5799	5983	5998	GTCCATTAAAGAGTGT	53	780
1158298	6003	6018	6202	6217	GTCAATTTATAGACCC	82	781
1158332	6095	6110	6294	6309	AGTGTAAAACATTGCC	93	782
1158366	6217	6232	6416	6431	GAGCCAAGCACTCATA	94	783
1158398	6334	6349	6533	6548	AGCTACAACAAGTAAG	88	784
1158432	6447	6462	6646	6661	ATGCATTCTAATAGCA	101	785
1158464	6578	6593	6777	6792	TACGACTGCTTAAAAC	95	786
1158497	6734	6749	6933	6948	GAAGACTGTTGCTTGT	48	787

1158528	6989	7004	7188	7203	TGAAGAATACCATCTG	70	788
1158561	7092	7107	7291	7306	CCATAACTGATCTGAC	87	789
1158593	7215	7230	7414	7429	GTACCTGAAAAATCTT	97	790
1158627	7324	7339	7523	7538	GAGGCTGACACTTCTC	110	791
1158660	7456	7471	7655	7670	ATTAAGAGCTGCTATA	104	792
1158694	7538	7553	7737	7752	TCTGGAAAAGCTAGGG	121	793
1158728	7663	7678	7862	7877	CCACAAGGATCCAAGC	120	794
1158762	7717	7732	7916	7931	ACCCACCAAAGACCTC	91	795
1158794	7796	7811	7995	8010	AGAGCTACTTAGCTGT	84	796
1158828	7890	7905	8089	8104	TTACATGTTCCCACCC	81	797
1158861	8002	8017	8201	8216	AGCTTGGCCAAGTCTG	72	798
1158894	8052	8067	8251	8266	CTTCATGACCCTACTG	64	799
1158925	8239	8254	8438	8453	TACAGAAAGAGTCCTG	83	800
1158959	8346	8361	8545	8560	TCCTGACAAATTATAC	72	801
1158992	8459	8474	8658	8673	TAAGTTTTCAGCAGTA	114	802

Table 41

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	101	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	121	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	36	36
568504	7891	7906	8090	8105	GTTACATGTTCCCACC	63	803
946400	757	772	723	738	GAGCAGCACGGGCTGT	86	804
946405	2692	2707	2892	2907	AGCCAAGCCGCCTGCT	80	805
1156459	22	37	N/A	N/A	TACAGAAGTCTCGGGC	72	806
1156492	207	222	173	188	CAGCTAAGATAGCAGC	92	807
1156525	282	297	248	263	AACCCCAAGACCAAAC	89	808
1156559	411	426	377	392	AGTGTTTACACTGCTC	78	809
1156593	497	512	463	478	GGCCTTTTAAAGTAGA	72	810
1156627	566	581	532	547	CGTTTTTCAGCTTCCA	93	811
1156661	622	637	588	603	TCTGCGGCCCCCCAGT	75	812
1156728	844	859	810	825	ATGGCGGACTTTCTCC	71	813
1156762	903	918	869	884	TTTACTTTCCATTACG	84	814
1156796	969	984	935	950	TCTTGAGGGACAGTAG	107	815
1156830	N/A	N/A	1016	1031	ATCATATTTTAAACGG	68	816
1156864	N/A	N/A	1168	1183	TTCTTCGGTTAAAAAT	98	817
1156898	1027	1042	1227	1242	ACTCGCATCACCGGAA	85	818
1156932	1082	1097	1282	1297	CTGCCTCAATGCCTAC	56	819
1156966	1205	1220	1405	1420	TTAGTAACCTATTGAC	66	820

1157000	1399	1414	1599	1614	GCTCTGTAGTCCTTTC	58	821
1157033	1534	1549	1734	1749	TCGGTTTAATCTCTTT	37	822
1157066	1642	1657	1842	1857	CTCCCAATTAATCTTT	73	823
1157100	1952	1967	2152	2167	AATACTTGTCTTAGCT	59	824
1157134	2159	2174	2359	2374	CCCTTCTAGCTTCAAG	62	825
1157168	2309	2324	2509	2524	TTACGAAAGTCCTTCA	72	826
1157200	2369	2384	2569	2584	CTCAAAGTCCAATGCA	52	827
1157234	2490	2505	2690	2705	ACACTGGTTCCTGGAA	52	828
1157268	2578	2593	2778	2793	ACCAAATCGCACTGGC	97	829
1157335	2782	2797	2982	2997	ACTCGCTTTCCCTGTG	65	830
1157369	2843	2858	3043	3058	GTTACCATAAGTAAGT	98	831
1157403	2911	2926	3111	3126	CGTCCCCATATAAATC	99	832
1157436	3004	3019	3204	3219	CAGGACTTGGCAGTCT	86	833
1157468	3143	3158	3343	3358	TACTTCATTACCCCAA	66	834
1157502	3245	3260	3445	3460	TGAAAACTCCCCCCCG	79	835
1157535	3346	3361	3546	3561	TTCTGTTACACCTTGA	41	836
1157568	3469	3484	3669	3684	GTAACTACCAGCCATT	55	837
1157601	3643	3658	3843	3858	CCCAGTTTGTCAATAG	61	838
1157634	3730	3745	3930	3945	AACTGGGAATACTCTT	78	839
1157668	3895	3910	4095	4110	GCCAACTAATTGCCAA	67	840
1157701	3985	4000	4185	4200	CTTTAAGTTCTCTGGC	36	841
1157735	4102	4117	4302	4317	GGCTCATATTTAACTT	80	842
1157768	4218	4233	4418	4433	CCAACCCCCAGTTCAA	76	843
1157801	4302	4317	4502	4517	TCCAAAAGAGAACCAC	79	844
1157835	4516	4531	4715	4730	CATACCTTAACATCTT	68	845
1157868	4632	4647	4831	4846	TCATCAACAAAAGCCC	108	846
1157900	4784	4799	4983	4998	GAGGTATGACATATAA	46	847
1157934	4829	4844	5028	5043	TCTCATCAGTAGTAAG	45	848
1157968	4929	4944	5128	5143	TTATAGCTTGACAAGC	63	849
1158002	5074	5089	5273	5288	ATTTATTTCGGCTTCT	29	850
1158034	5153	5168	5352	5367	AGAGATACCTGTCTGA	78	851
1158068	5239	5254	5438	5453	CTGCAGATGCAAGTTA	51	852
1158101	5318	5333	5517	5532	GGTCAGGAGAAAGTGC	82	853
1158133	5413	5428	5612	5627	TACTATCCCATCACTG	58	854
1158166	5500	5515	5699	5714	AAATTTCCTTAGTTGG	46	855
1158200	5725	5740	5924	5939	AGATTGCCCCAACACT	62	856
1158233	5790	5805	5989	6004	GATCTGGTCCATTAAA	75	857
1158265	5910	5925	6109	6124	TCCTTATTTAGAGGGC	71	858
1158299	6004	6019	6203	6218	TGTCAATTTATAGACC	94	859
1158333	6096	6111	6295	6310	TAGTGTAAAACATTGC	65	860
1158367	6219	6234	6418	6433	AAGAGCCAAGCACTCA	88	861
1158399	6335	6350	6534	6549	AAGCTACAACAAGTAA	90	862
1158433	6448	6463	6647	6662	AATGCATTCTAATAGC	83	863

1158465	6579	6594	6778	6793	ATACGACTGCTTAAAA	80	864
1158498	6737	6752	6936	6951	CTTGAAGACTGTTGCT	58	865
1158529	6991	7006	7190	7205	TCTGAAGAATACCATC	85	866
1158562	7093	7108	7292	7307	CCCATAACTGATCTGA	58	867
1158594	7234	7249	7433	7448	TCGGTGCCTTTAGTGA	71	868
1158628	7327	7342	7526	7541	GGTGAGGCTGACACTT	73	869
1158661	7457	7472	7656	7671	TATTAAGAGCTGCTAT	75	870
1158695	7540	7555	7739	7754	CTTCTGGAAAAGCTAG	92	871
1158729	7664	7679	7863	7878	CCCACAAGGATCCAAG	91	872
1158763	7719	7734	7918	7933	CAACCCACCAAAGACC	98	873
1158795	7797	7812	7996	8011	TAGAGCTACTTAGCTG	82	874
1158862	8003	8018	8202	8217	TAGCTTGGCCAAGTCT	81	875
1158895	8055	8070	8254	8269	AACCTTCATGACCCTA	80	876
1158926	8266	8281	8465	8480	ACTAGCACCTGCAGAG	77	877
1158960	8347	8362	8546	8561	CTCCTGACAAATTATA	83	878
1158993	8461	8476	8660	8675	GTTAAGTTTTCAGCAG	83	879

Table 42

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	103	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	137	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	53	36
568486	6220	6235	6419	6434	GAAGAGCCAAGCACTC	109	880
1156460	23	38	N/A	N/A	TTACAGAAGTCTCGGG	89	881
1156493	208	223	174	189	ACAGCTAAGATAGCAG	98	882
1156526	316	331	282	297	CCGGAGCAGGAAGAAA	77	883
1156560	413	428	379	394	GAAGTGTTTACACTGC	89	884
1156594	499	514	465	480	GTGGCCTTTTAAAGTA	85	885
1156628	567	582	533	548	CCGTTTTTCAGCTTCC	94	886
1156662	623	638	589	604	ATCTGCGGCCCCCCAG	108	887
1156695	762	777	728	743	AATCGGAGCAGCACGG	74	888
1156729	845	860	811	826	AATGGCGGACTTTCTC	100	889
1156763	907	922	873	888	GGGCTTTACTTTCCAT	84	890
1156797	970	985	936	951	CTCTTGAGGGACAGTA	96	891
1156831	N/A	N/A	1046	1061	CTGCAAACTTTAGACA	93	892
1156865	N/A	N/A	1171	1186	TAGTTCTTCGGTTAAA	94	893
1156899	1028	1043	1228	1243	AACTCGCATCACCGGA	79	894
1156933	1090	1105	1290	1305	TGCGCTGGCTGCCTCA	75	895
1156967	1206	1221	1406	1421	CTTAGTAACCTATTGA	66	896

1157001	1416	1431	1616	1631	ATTGGTATTAATTCGG	30	897
1157034⁂	1535	1550	1735	1750	TTCGGTTTAATCTCTT	25	2
1157067	1644	1659	1844	1859	CACTCCCAATTAATCT	92	898
1157101	1954	1969	2154	2169	CCAATACTTGTCTTAG	36	899
1157135	2164	2179	2364	2379	ACTTCCCCTTCTAGCT	64	900
1157169	2310	2325	2510	2525	GTTACGAAAGTCCTTC	55	901
1157201	2370	2385	2570	2585	ACTCAAAGTCCAATGC	69	902
1157235	2495	2510	2695	2710	ATCAAACACTGGTTCC	52	903
1157269	2579	2594	2779	2794	CACCAAATCGCACTGG	107	904
1157302	2693	2708	2893	2908	AAGCCAAGCCGCCTGC	71	905
1157336	2784	2799	2984	2999	CCACTCGCTTTCCCTG	59	906
1157370	2844	2859	3044	3059	GGTTACCATAAGTAAG	63	907
1157404	2925	2940	3125	3140	CGGAAATCGGCCTACG	70	908
1157437	3006	3021	3206	3221	TCCAGGACTTGGCAGT	77	909
1157469	3144	3159	3344	3359	ATACTTCATTACCCCA	50	910
1157503	3246	3261	3446	3461	CTGAAAACTCCCCCCC	102	911
1157536	3371	3386	3571	3586	TATCCTGATATTGGAT	76	912
1157569	3470	3485	3670	3685	AGTAACTACCAGCCAT	55	913
1157602	3644	3659	3844	3859	ACCCAGTTTGTCAATA	90	914
1157635	3731	3746	3931	3946	CAACTGGGAATACTCT	80	915
1157669	3896	3911	4096	4111	TGCCAACTAATTGCCA	77	916
1157702	3991	4006	4191	4206	CTAAGACTTTAAGTTC	73	917
1157736	4109	4124	4309	4324	ACCCAGTGGCTCATAT	84	918
1157769	4219	4234	4419	4434	ACCAACCCCCAGTTCA	72	919
1157802	4351	4366	4551	4566	GCAGTTTCTATAGTAG	55	920
1157836	4517	4532	4716	4731	GCATACCTTAACATCT	46	921
1157869	4688	4703	4887	4902	ACTCAGAAGATGTTAT	70	922
1157901	4785	4800	4984	4999	GGAGGTATGACATATA	32	923
1157935	4838	4853	5037	5052	AGATAATGTTCTCATC	89	924
1157969	4930	4945	5129	5144	GTTATAGCTTGACAAG	43	925
1158003	5075	5090	5274	5289	CATTTATTTCGGCTTC	34	926
1158035	5154	5169	5353	5368	AAGAGATACCTGTCTG	78	927
1158069	5244	5259	5443	5458	CAATACTGCAGATGCA	48	928
1158102	5334	5349	5533	5548	AATCCCCTAGGGAAGG	95	929
1158134	5414	5429	5613	5628	GTACTATCCCATCACT	67	930
1158167	5517	5532	5716	5731	GAGATTCAATGCTAAA	42	931
1158201	5727	5742	5926	5941	CAAGATTGCCCCAACA	88	932
1158234	5793	5808	5992	6007	CCTGATCTGGTCCATT	56	933
1158266	5911	5926	6110	6125	TTCCTTATTTAGAGGG	86	934
1158300	6007	6022	6206	6221	CACTGTCAATTTATAG	81	935
1158334	6097	6112	6296	6311	ATAGTGTAAAACATTG	100	936
1158400	6378	6393	6577	6592	GTCAAGACAACTGCAT	97	937
1158434	6449	6464	6648	6663	CAATGCATTCTAATAG	82	938

1158466	6580	6595	6779	6794	AATACGACTGCTTAAA	70	939
1158499	6738	6753	6937	6952	TCTTGAAGACTGTTGC	56	940
1158530	6992	7007	7191	7206	GTCTGAAGAATACCAT	53	941
1158563	7094	7109	7293	7308	TCCCATAACTGATCTG	69	942
1158595	7236	7251	7435	7450	CTTCGGTGCCTTTAGT	77	943
1158629	7331	7346	7530	7545	ATCAGGTGAGGCTGAC	77	944
1158662	7458	7473	7657	7672	TTATTAAGAGCTGCTA	73	945
1158696‡	7548	7563	7747	7762	TTAACAGGCTTCTGGA	56	946
1158730	7665	7680	7864	7879	GCCCACAAGGATCCAA	85	947
1158764	7722	7737	7921	7936	GTTCAACCCACCAAAG	64	948
1158796	7798	7813	7997	8012	ATAGAGCTACTTAGCT	81	949
1158829	7892	7907	8091	8106	AGTTACATGTTCCCAC	67	950
1158863	8005	8020	8204	8219	GCTAGCTTGGCCAAGT	98	951
1158896	8080	8095	8279	8294	CGTGTTGTTTTCTCAG	77	952
1158927	8267	8282	8466	8481	AACTAGCACCTGCAGA	83	953
1158961	8348	8363	8547	8562	GCTCCTGACAAATTAT	83	954
1158994	8492	8507	8691	8706	TAGAGCTTCTCCATTT	115	955

Table 43

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	127	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	141	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	60	36
946424	8006	8021	8205	8220	TGCTAGCTTGGCCAAG	84	956
1156461	24	39	N/A	N/A	TTTACAGAAGTCTCGG	131	957
1156494	209	224	175	190	GACAGCTAAGATAGCA	88	958
1156527	317	332	283	298	ACCGGAGCAGGAAGAA	96	959
1156561	418	433	384	399	ACCCAGAAGTGTTTAC	84	960
1156595	503	518	469	484	TCAAGTGGCCTTTTAA	138	961
1156629	568	583	534	549	ACCGTTTTTCAGCTTC	130	962
1156663	625	640	591	606	TGATCTGCGGCCCCCC	150	963
1156696	763	778	729	744	AAATCGGAGCAGCACG	84	964
1156730	846	861	812	827	AAATGGCGGACTTTCT	83	965
1156764	908	923	874	889	AGGGCTTTACTTTCCA	105	966
1156798	971	986	937	952	TCTCTTGAGGGACAGT	107	967
1156832	N/A	N/A	1047	1062	GCTGCAAACTTTAGAC	109	968
1156866	N/A	N/A	1174	1189	AAGTAGTTCTTCGGTT	90	969
1156900	1029	1044	1229	1244	CAACTCGCATCACCGG	91	970
1156934	1091	1106	1291	1306	CTGCGCTGGCTGCCTC	70	971

1156968	1207	1222	1407	1422	TCTTAGTAACCTATTG	81	972
1157002	1417	1432	1617	1632	TATTGGTATTAATTCG	87	973
1157035	1536	1551	1736	1751	CTTCGGTTTAATCTCT	27	974
1157068	1647	1662	1847	1862	TACCACTCCCAATTAA	88	975
1157102	1955	1970	2155	2170	TCCAATACTTGTCTTA	32	976
1157136	2169	2184	2369	2384	AACCAACTTCCCCTTC	84	977
1157170	2311	2326	2511	2526	CGTTACGAAAGTCCTT	75	978
1157202	2375	2390	2575	2590	TCTTAACTCAAAGTCC	61	979
1157236	2496	2511	2696	2711	CATCAAACACTGGTTC	86	980
1157270	2580	2595	2780	2795	TCACCAAATCGCACTG	80	981
1157303	2695	2710	2895	2910	CCAAGCCAAGCCGCCT	95	982
1157337	2785	2800	2985	3000	ACCACTCGCTTTCCCT	65	983
1157371	2845	2860	3045	3060	AGGTTACCATAAGTAA	90	984
1157405	2926	2941	3126	3141	CCGGAAATCGGCCTAC	80	985
1157438	3014	3029	3214	3229	ACTATTTCTCCAGGAC	80	986
1157470	3145	3160	3345	3360	AATACTTCATTACCCC	55	987
1157504	3247	3262	3447	3462	ACTGAAAACTCCCCCC	103	988
1157537	3372	3387	3572	3587	TTATCCTGATATTGGA	112	989
1157570	3471	3486	3671	3686	GAGTAACTACCAGCCA	63	990
1157603	3647	3662	3847	3862	CTAACCCAGTTTGTCA	65	991
1157636	3732	3747	3932	3947	TCAACTGGGAATACTC	83	992
1157670	3897	3912	4097	4112	CTGCCAACTAATTGCC	132	993
1157703	3996	4011	4196	4211	CCATTCTAAGACTTTA	51	994
1157737	4112	4127	4312	4327	TACACCCAGTGGCTCA	70	995
1157770	4220	4235	4420	4435	GACCAACCCCCAGTTC	97	996
1157803	4352	4367	4552	4567	TGCAGTTTCTATAGTA	91	997
1157837	4518	4533	4717	4732	AGCATACCTTAACATC	81	998
1157870	4694	4709	4893	4908	GTTATGACTCAGAAGA	74	999
1157902	4786	4801	4985	5000	TGGAGGTATGACATAT	41	1000
1157936	4840	4855	5039	5054	GCAGATAATGTTCTCA	27	10
1157970	4931	4946	5130	5145	GGTTATAGCTTGACAA	22	9
1158004	5077	5092	5276	5291	CTCATTTATTTCGGCT	22	1001
1158036	5155	5170	5354	5369	GAAGAGATACCTGTCT	122	1002
1158070	5245	5260	5444	5459	GCAATACTGCAGATGC	119	1003
1158103	5335	5350	5534	5549	AAATCCCCTAGGGAAG	108	1004
1158135	5415	5430	5614	5629	TGTACTATCCCATCAC	49	1005
1158168	5525	5540	5724	5739	AGCCTTCAGAGATTCA	25	1006
1158202	5728	5743	5927	5942	CCAAGATTGCCCCAAC	86	1007
1158235	5794	5809	5993	6008	TCCTGATCTGGTCCAT	58	1008
1158267	5912	5927	6111	6126	ATTCCTTATTTAGAGG	111	1009
1158301	6012	6027	6211	6226	CTAATCACTGTCAATT	101	1010
1158335	6101	6116	6300	6315	GTCAATAGTGTAAAAC	67	1011
1158368	6240	6255	6439	6454	TACACTCACTAGAACA	97	1012

1158401	6382	6397	6581	6596	TGAAGTCAAGACAACT	99	1013
1158435	6456	6471	6655	6670	CGTTTCACAATGCATT	53	1014
1158467	6581	6596	6780	6795	AAATACGACTGCTTAA	78	1015
1158500	6755	6770	6954	6969	CACTTGCCAGTTTAAT	71	1016
1158531	6994	7009	7193	7208	TAGTCTGAAGAATACC	77	1017
1158564	7095	7110	7294	7309	GTCCCATAACTGATCT	65	1018
1158596	7237	7252	7436	7451	CCTTCGGTGCCTTTAG	88	1019
1158630	7332	7347	7531	7546	AATCAGGTGAGGCTGA	126	1020
1158663	7460	7475	7659	7674	TATTATTAAGAGCTGC	106	1021
1158697‡	7552	7567	7751	7766	GCTTTTAACAGGCTTC	67	1022
1158731	7667	7682	7866	7881	ATGCCCACAAGGATCC	67	1023
1158765	7724	7739	7923	7938	TAGTTCAACCCACCAA	114	1024
1158797	7800	7815	7999	8014	TAATAGAGCTACTTAG	116	1025
1158830	7893	7908	8092	8107	AAGTTACATGTTCCCA	61	1026
1158897	8094	8109	8293	8308	CTGAGAAAACAATACG	92	1027
1158928	8268	8283	8467	8482	GAACTAGCACCTGCAG	96	1028
1158962	8349	8364	8548	8563	AGCTCCTGACAAATTA	85	1029
1158995	8496	8511	N/A	N/A	AATTTAGAGCTTCTCC	79	1030

Table 44

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	101	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	135	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	55	36
946404	2312	2327	2512	2527	CCGTTACGAAAGTCCT	33	1031
946410	4113	4128	4313	4328	GTACACCCAGTGGCTC	94	1032
1156462	25	40	N/A	N/A	CTTTACAGAAGTCTCG	78	1033
1156495	210	225	176	191	GGACAGCTAAGATAGC	78	1034
1156528	318	333	284	299	AACCGGAGCAGGAAGA	116	1035
1156562	419	434	385	400	CACCCAGAAGTGTTTA	104	1036
1156596	505	520	471	486	GTTCAAGTGGCCTTTT	78	1037
1156630	569	584	535	550	TACCGTTTTTCAGCTT	131	1038
1156664	627	642	593	608	TCTGATCTGCGGCCCC	118	1039
1156697	764	779	730	745	GAAATCGGAGCAGCAC	99	1040
1156731	847	862	813	828	AAAATGGCGGACTTTC	70	1041
1156765	909	924	875	890	CAGGGCTTTACTTTCC	98	1042
1156799	978	993	944	959	CTTGTGTTCTCTTGAG	87	1043
1156833	N/A	N/A	1048	1063	AGCTGCAAACTTTAGA	74	1044
1156867	N/A	N/A	1175	1190	AAAGTAGTTCTTCGGT	83	1045

1156901	1030	1045	1230	1245	ACAACTCGCATCACCG	312	1046
1156935	1095	1110	1295	1310	GCCCCTGCGCTGGCTG	88	1047
1156969	1208	1223	1408	1423	ATCTTAGTAACCTATT	83	1048
1157003	1418	1433	1618	1633	CTATTGGTATTAATTC	93	1049
1157036	1537	1552	1737	1752	CCTTCGGTTTAATCTC	39	1050
1157069	1649	1664	1849	1864	CCTACCACTCCCAATT	79	1051
1157103	1956	1971	2156	2171	CTCCAATACTTGTCTT	46	1052
1157137	2170	2185	2370	2385	TAACCAACTTCCCCTT	84	1053
1157203	2376	2391	2576	2591	ATCTTAACTCAAAGTC	61	1054
1157237	2497	2512	2697	2712	TCATCAAACACTGGTT	64	1055
1157271	2581	2596	2781	2796	TTCACCAAATCGCACT	71	1056
1157304	2696	2711	2896	2911	GCCAAGCCAAGCCGCC	86	1057
1157338	2786	2801	2986	3001	AACCACTCGCTTTCCC	59	1058
1157372	2846	2861	3046	3061	AAGGTTACCATAAGTA	54	1059
1157406	2927	2942	3127	3142	CCCGGAAATCGGCCTA	100	1060
1157439	3016	3031	3216	3231	CTACTATTTCTCCAGG	59	1061
1157471	3146	3161	3346	3361	AAATACTTCATTACCC	76	1062
1157505	3248	3263	3448	3463	TACTGAAAACTCCCCC	78	1063
1157538	3373	3388	3573	3588	ATTATCCTGATATTGG	54	1064
1157571	3472	3487	3672	3687	AGAGTAACTACCAGCC	45	1065
1157604	3648	3663	3848	3863	TCTAACCCAGTTTGTC	69	1066
1157637	3733	3748	3933	3948	TTCAACTGGGAATACT	83	1067
1157671	3899	3914	4099	4114	CACTGCCAACTAATTG	61	1068
1157704	4025	4040	4225	4240	ACTTGGAAGTTGATAT	96	1069
1157771	4221	4236	4421	4436	AGACCAACCCCCAGTT	100	1070
1157804	4353	4368	4553	4568	CTGCAGTTTCTATAGT	78	1071
1157838	4520	4535	4719	4734	GAAGCATACCTTAACA	95	1072
1157871	4695	4710	4894	4909	GGTTATGACTCAGAAG	42	1073
1157903	4787	4802	4986	5001	ATGGAGGTATGACATA	80	1074
1157937	4846	4861	5045	5060	GCATATGCAGATAATG	64	1075
1157971	4932	4947	5131	5146	TGGTTATAGCTTGACA	18	1076
1158005	5078	5093	5277	5292	TCTCATTTATTTCGGC	21	1077
1158037	5156	5171	5355	5370	CGAAGAGATACCTGTC	77	1078
1158071	5246	5261	5445	5460	TGCAATACTGCAGATG	80	1079
1158104	5336	5351	5535	5550	GAAATCCCCTAGGGAA	94	1080
1158136	5416	5431	5615	5630	GTGTACTATCCCATCA	52	1081
1158169	5534	5549	5733	5748	CTTTCATAGAGCCTTC	57	1082
1158203	5729	5744	5928	5943	CCCAAGATTGCCCCAA	107	1083
1158236	5796	5811	5995	6010	AATCCTGATCTGGTCC	54	1084
1158268	5929	5944	6128	6143	TGTCTAAGAGGTTATT	90	1085
1158302	6013	6028	6212	6227	TCTAATCACTGTCAAT	68	1086
1158336	6102	6117	6301	6316	GGTCAATAGTGTAAAA	57	1087
1158369	6243	6258	6442	6457	TCATACACTCACTAGA	122	1088

1158402	6383	6398	6582	6597	CTGAAGTCAAGACAAC	117	1089
1158436	6470	6485	6669	6684	AATCATACTCCAGTCG	65	1090
1158468	6583	6598	6782	6797	ACAAATACGACTGCTT	84	1091
1158501	6756	6771	6955	6970	CCACTTGCCAGTTTAA	71	1092
1158532	6997	7012	7196	7211	CTATAGTCTGAAGAAT	78	1093
1158565	7100	7115	7299	7314	CTATTGTCCCATAACT	62	1094
1158597	7238	7253	7437	7452	GCCTTCGGTGCCTTTA	102	1095
1158631	7354	7369	7553	7568	GCAAGTCCTCATTACT	50	1096
1158664	7466	7481	7665	7680	GGGCTTTATTATTAAG	124	1097
1158698‡	7562	7577	7761	7776	GGGAGACCTTGCTTTT	79	1098
1158732	7674	7689	7873	7888	ATGGATCATGCCCACA	88	1099
1158766	7725	7740	7924	7939	ATAGTTCAACCCACCA	79	1100
1158798	7801	7816	8000	8015	ATAATAGAGCTACTTA	81	1101
1158831	7894	7909	8093	8108	CAAGTTACATGTTCCC	58	1102
1158864	8008	8023	8207	8222	GATGCTAGCTTGGCCA	102	1103
1158898	8164	8179	8363	8378	CAGGAGTGCCAACCAC	102	1104
1158929	8269	8284	8468	8483	AGAACTAGCACCTGCA	85	1105
1158963	8353	8368	8552	8567	GTCAAGCTCCTGACAA	67	1106
1158996	8497	8512	N/A	N/A	CAATTTAGAGCTTCTC	112	1107

Table 45

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	106	18
556074	5797	5812	5996	6011	AAATCCTGATCTGGTC	73	1108
556090	6471	6486	6670	6685	TAATCATACTCCAGTC	103	1109
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	128	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	51	36
568476	5338	5353	5537	5552	CTGAAATCCCCTAGGG	70	1110
1156463	28	43	N/A	N/A	GTCCTTTACAGAAGTC	65	1111
1156496	213	228	179	194	TAAGGACAGCTAAGAT	76	1112
1156529	319	334	285	300	GAACCGGAGCAGGAAG	72	1113
1156563	421	436	387	402	CACACCCAGAAGTGTT	87	1114
1156597	507	522	473	488	GAGTTCAAGTGGCCTT	83	1115
1156631	571	586	537	552	TCTACCGTTTTTCAGC	74	1116
1156665	628	643	594	609	CTCTGATCTGCGGCCC	106	1117
1156698	765	780	731	746	AGAAATCGGAGCAGCA	91	1118
1156732	848	863	814	829	CAAAATGGCGGACTTT	83	1119
1156766	916	931	882	897	GATAGTTCAGGGCTTT	90	1120
1156800	990	1005	956	971	CTTAAAGCACTTCTTG	134	1121

1156834	N/A	N/A	1054	1069	GATTTGAGCTGCAAAC	100	1122
1156868	N/A	N/A	1176	1191	AAAAGTAGTTCTTCGG	82	1123
1156902	1031	1046	1231	1246	AACAACTCGCATCACC	83	1124
1156936	1098	1113	1298	1313	GAAGCCCCTGCGCTGG	77	1125
1156970	1209	1224	1409	1424	TATCTTAGTAACCTAT	79	1126
1157004	1421	1436	1621	1636	CTTCTATTGGTATTAA	82	1127
1157037	1539	1554	1739	1754	CACCTTCGGTTTAATC	80	1128
1157070	1650	1665	1850	1865	TCCTACCACTCCCAAT	70	1129
1157104	1962	1977	2162	2177	ATACTTCTCCAATACT	115	1130
1157138	2171	2186	2371	2386	TTAACCAACTTCCCCT	57	1131
1157171	2313	2328	2513	2528	TCCGTTACGAAAGTCC	36	1132
1157204	2401	2416	2601	2616	GCTAGTCCTCAGGATT	53	1133
1157238	2501	2516	2701	2716	AGCTTCATCAAACACT	97	1134
1157272	2582	2597	2782	2797	CTTCACCAAATCGCAC	113	1135
1157305	2697	2712	2897	2912	TGCCAAGCCAAGCCGC	87	1136
1157339	2788	2803	2988	3003	CCAACCACTCGCTTTC	74	1137
1157373	2847	2862	3047	3062	AAAGGTTACCATAAGT	95	1138
1157407	2928	2943	3128	3143	ACCCGGAAATCGGCCT	106	1139
1157440	3021	3036	3221	3236	GCCATCTACTATTTCT	62	1140
1157472	3167	3182	3367	3382	GGTCATCTATTCACAA	71	1141
1157506	3249	3264	3449	3464	ATACTGAAAACTCCCC	86	1142
1157539	3374	3389	3574	3589	GATTATCCTGATATTG	96	1143
1157572	3473	3488	3673	3688	AAGAGTAACTACCAGC	94	1144
1157605	3649	3664	3849	3864	CTCTAACCCAGTTTGT	64	1145
1157638	3734	3749	3934	3949	CTTCAACTGGGAATAC	93	1146
1157672	3907	3922	4107	4122	TAACAGGCCACTGCCA	89	1147
1157705	4026	4041	4226	4241	AACTTGGAAGTTGATA	81	1148
1157738	4115	4130	4315	4330	TGGTACACCCAGTGGC	83	1149
1157772	4222	4237	4422	4437	CAGACCAACCCCCAGT	107	1150
1157805	4355	4370	4555	4570	CTCTGCAGTTTCTATA	69	1151
1157839	4521	4536	4720	4735	TGAAGCATACCTTAAC	69	1152
1157872	4696	4711	4895	4910	TGGTTATGACTCAGAA	52	1153
1157904	4788	4803	4987	5002	AATGGAGGTATGACAT	95	1154
1157938	4848	4863	5047	5062	TGGCATATGCAGATAA	31	1155
1157972	4933	4948	5132	5147	GTGGTTATAGCTTGAC	21	1156
1158006	5079	5094	5278	5293	CTCTCATTTATTTCGG	41	1157
1158038	5157	5172	5356	5371	ACGAAGAGATACCTGT	82	1158
1158072	5247	5262	5446	5461	ATGCAATACTGCAGAT	99	1159
1158137	5417	5432	5616	5631	AGTGTACTATCCCATC	22	1160
1158170	5535	5550	5734	5749	CCTTTCATAGAGCCTT	31	1161
1158204	5731	5746	5930	5945	CCCCCAAGATTGCCCC	89	1162
1158269	5930	5945	6129	6144	CTGTCTAAGAGGTTAT	93	1163
1158303	6014	6029	6213	6228	CTCTAATCACTGTCAA	89	1164

1158337	6103	6118	6302	6317	AGGTCAATAGTGTAAA	43	1165
1158370	6244	6259	6443	6458	CTCATACACTCACTAG	100	1166
1158403	6384	6399	6583	6598	CCTGAAGTCAAGACAA	100	1167
1158469	6584	6599	6783	6798	CACAAATACGACTGCT	76	1168
1158502	6776	6791	6975	6990	ACTGAACTGTTTAAAC	94	1169
1158533	6998	7013	7197	7212	TCTATAGTCTGAAGAA	74	1170
1158566	7102	7117	7301	7316	TACTATTGTCCCATAA	78	1171
1158598	7239	7254	7438	7453	AGCCTTCGGTGCCTTT	95	1172
1158632	7356	7371	7555	7570	AGGCAAGTCCTCATTA	84	1173
1158665	7471	7486	7670	7685	GATTTGGGCTTTATTA	77	1174
1158699‡	7577	7592	7776	7791	GAGAAGTTGCTTGTGG	45	1175
1158733	7675	7690	7874	7889	TATGGATCATGCCCAC	73	1176
1158767	7726	7741	7925	7940	CATAGTTCAACCCACC	65	1177
1158799	7802	7817	8001	8016	TATAATAGAGCTACTT	85	1178
1158832	7895	7910	8094	8109	ACAAGTTACATGTTCC	79	1179
1158865	8010	8025	8209	8224	AAGATGCTAGCTTGGC	76	1180
1158899	8165	8180	8364	8379	CCAGGAGTGCCAACCA	95	1181
1158930	8270	8285	8469	8484	AAGAACTAGCACCTGC	87	1182
1158964	8354	8369	8553	8568	AGTCAAGCTCCTGACA	87	1183
1158997	8500	8515	N/A	N/A	CAACAATTTAGAGCTT	88	1184

Table 46

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	104	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	104	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	60	36
567936	5248	5263	5447	5462	CATGCAATACTGCAGA	85	1185
946414	5339	5354	5538	5553	CCTGAAATCCCCTAGG	104	1186
1156464	30	45	N/A	N/A	CAGTCCTTTACAGAAG	88	1187
1156497	214	229	180	195	ATAAGGACAGCTAAGA	92	1188
1156530	320	335	286	301	TGAACCGGAGCAGGAA	95	1189
1156564	429	444	395	410	GTCAGGGACACACCCA	111	1190
1156598	508	523	474	489	CGAGTTCAAGTGGCCT	82	1191
1156632	572	587	538	553	TTCTACCGTTTTTCAG	90	1192
1156666	629	644	595	610	ACTCTGATCTGCGGCC	87	1193
1156699	766	781	732	747	GAGAAATCGGAGCAGC	85	1194
1156733	849	864	815	830	GCAAAATGGCGGACTT	104	1195
1156767	917	932	883	898	TGATAGTTCAGGGCTT	91	1196
1156801	N/A	N/A	960	975	ACCTCTTAAAGCACTT	82	1197

1156835	N/A	N/A	1055	1070	AGATTTGAGCTGCAAA	89	1198
1156869	N/A	N/A	1177	1192	AAAAAGTAGTTCTTCG	84	1199
1156903	1032	1047	1232	1247	GAACAACTCGCATCAC	85	1200
1156937	1100	1115	1300	1315	CAGAAGCCCCTGCGCT	97	1201
1156971	1210	1225	1410	1425	ATATCTTAGTAACCTA	85	1202
1157005	1422	1437	1622	1637	CCTTCTATTGGTATTA	72	1203
1157038	1540	1555	1740	1755	TCACCTTCGGTTTAAT	72	1204
1157071	1651	1666	1851	1866	ATCCTACCACTCCCAA	66	1205
1157105	1963	1978	2163	2178	TATACTTCTCCAATAC	82	1206
1157139	2181	2196	2381	2396	GATGTGATTTTTAACC	48	1207
1157172	2314	2329	2514	2529	TTCCGTTACGAAAGTC	67	1208
1157205	2402	2417	2602	2617	TGCTAGTCCTCAGGAT	81	1209
1157239	2504	2519	2704	2719	CCTAGCTTCATCAAAC	102	1210
1157273	2584	2599	2784	2799	TCCTTCACCAAATCGC	64	1211
1157306	2704	2719	2904	2919	GTGTGGTTGCCAAGCC	57	1212
1157340	2790	2805	2990	3005	TACCAACCACTCGCTT	99	1213
1157374	2870	2885	3070	3085	CCCATTATATTAGAAA	90	1214
1157408	2929	2944	3129	3144	CACCCGGAAATCGGCC	101	1215
1157441	3022	3037	3222	3237	TGCCATCTACTATTTC	81	1216
1157473	3168	3183	3368	3383	AGGTCATCTATTCACA	61	1217
1157507	3278	3293	3478	3493	ATATTTTGCCCCCACC	98	1218
1157540	3376	3391	3576	3591	CTGATTATCCTGATAT	67	1219
1157573	3474	3489	3674	3689	AAAGAGTAACTACCAG	78	1220
1157606	3650	3665	3850	3865	TCTCTAACCCAGTTTG	84	1221
1157639	3736	3751	3936	3951	AGCTTCAACTGGGAAT	87	1222
1157673	3908	3923	4108	4123	GTAACAGGCCACTGCC	86	1223
1157706	4027	4042	4227	4242	CAACTTGGAAGTTGAT	90	1224
1157739	4116	4131	4316	4331	CTGGTACACCCAGTGG	96	1225
1157773	4225	4240	4425	4440	GGCCAGACCAACCCCC	97	1226
1157806	4375	4390	4575	4590	TCATTAAGCCACTTCC	81	1227
1157840	4522	4537	4721	4736	TTGAAGCATACCTTAA	72	1228
1157873	4697	4712	4896	4911	CTGGTTATGACTCAGA	99	1229
1157905	4790	4805	4989	5004	CCAATGGAGGTATGAC	54	1230
1157939	4850	4865	5049	5064	TTTGGCATATGCAGAT	76	1231
1157973	4935	4950	5134	5149	TTGTGGTTATAGCTTG	32	1232
1158007	5093	5108	5292	5307	TGATCCCAACTCATCT	86	1233
1158039	5158	5173	5357	5372	AACGAAGAGATACCTG	88	1234
1158138	5418	5433	5617	5632	AAGTGTACTATCCCAT	49	1235
1158171	5536	5551	5735	5750	TCCTTTCATAGAGCCT	44	1236
1158205	5732	5747	5931	5946	CCCCCCAAGATTGCCC	86	1237
1158237	5798	5813	5997	6012	CAAATCCTGATCTGGT	76	1238
1158270‡	5931	5946	6130	6145	CCTGTCTAAGAGGTTA	79	1239
1158304	6015	6030	6214	6229	ACTCTAATCACTGTCA	65	1240

1158338	6105	6120	6304	6319	TAAGGTCAATAGTGTA	59	1241
1158371	6245	6260	6444	6459	TCTCATACACTCACTA	89	1242
1158404	6386	6401	6585	6600	GACCTGAAGTCAAGAC	101	1243
1158437	6472	6487	6671	6686	TTAATCATACTCCAGT	81	1244
1158470	6585	6600	6784	6799	TCACAAATACGACTGC	77	1245
1158503	6788	6803	6987	7002	GCACTAAAGATCACTG	77	1246
1158534	6999	7014	7198	7213	TTCTATAGTCTGAAGA	86	1247
1158567	7103	7118	7302	7317	ATACTATTGTCCCATA	69	1248
1158599	7241	7256	7440	7455	TAAGCCTTCGGTGCCT	96	1249
1158633	7357	7372	7556	7571	GAGGCAAGTCCTCATT	89	1250
1158666	7473	7488	7672	7687	GAGATTTGGGCTTTAT	66	1251
1158700ǂ	7578	7593	7777	7792	AGAGAAGTTGCTTGTG	67	1252
1158734	7676	7691	7875	7890	TTATGGATCATGCCCA	72	1253
1158768	7727	7742	7926	7941	ACATAGTTCAACCCAC	82	1254
1158800	7803	7818	8002	8017	TTATAATAGAGCTACT	96	1255
1158833	7896	7911	8095	8110	TACAAGTTACATGTTC	80	1256
1158866	8011	8026	8210	8225	TAAGATGCTAGCTTGG	75	1257
1158900	8166	8181	8365	8380	ACCAGGAGTGCCAACC	92	1258
1158931	8271	8286	8470	8485	CAAGAACTAGCACCTG	93	1259
1158965	8355	8370	8554	8569	AAGTCAAGCTCCTGAC	96	1260
1158998	8501	8516	N/A	N/A	ACAACAATTTAGAGCT	89	1261

Table 47

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	105	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	137	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	54	36
568469	4523	4538	4722	4737	TTTGAAGCATACCTTA	101	1262
1156465	33	48	N/A	N/A	CCCCAGTCCTTTACAG	91	1263
1156498	215	230	181	196	TATAAGGACAGCTAAG	79	1264
1156531	321	336	287	302	CTGAACCGGAGCAGGA	113	1265
1156565	430	445	396	411	AGTCAGGGACACACCC	116	1266
1156599	509	524	475	490	GCGAGTTCAAGTGGCC	105	1267
1156633	577	592	543	558	AATTTTTCTACCGTTT	89	1268
1156667	630	645	596	611	CACTCTGATCTGCGGC	128	1269
1156700	767	782	733	748	CGAGAAATCGGAGCAG	78	1270
1156734	850	865	816	831	GGCAAAATGGCGGACT	114	1271
1156768	919	934	885	900	TGTGATAGTTCAGGGC	112	1272
1156802	N/A	N/A	961	976	TACCTCTTAAAGCACT	117	1273

1156836	N/A	N/A	1056	1071	AAGATTTGAGCTGCAA	101	1274
1156870	N/A	N/A	1178	1193	CAAAAAGTAGTTCTTC	118	1275
1156904	1033	1048	1233	1248	AGAACAACTCGCATCA	88	1276
1156938	1102	1117	1302	1317	AGCAGAAGCCCCTGCG	101	1277
1156972	1211	1226	1411	1426	AATATCTTAGTAACCT	81	1278
1157006	1423	1438	1623	1638	CCCTTCTATTGGTATT	93	1279
1157039	1541	1556	1741	1756	ATCACCTTCGGTTTAA	60	1280
1157072	1653	1668	1853	1868	TCATCCTACCACTCCC	66	1281
1157106	1964	1979	2164	2179	CTATACTTCTCCAATA	113	1282
1157140	2193	2208	2393	2408	TAGTAGCTTTTTGATG	69	1283
1157173	2316	2331	2516	2531	ACTTCCGTTACGAAAG	99	1284
1157206	2403	2418	2603	2618	ATGCTAGTCCTCAGGA	120	1285
1157240	2505	2520	2705	2720	TCCTAGCTTCATCAAA	93	1286
1157274	2589	2604	2789	2804	TAGCTTCCTTCACCAA	101	1287
1157307	2705	2720	2905	2920	CGTGTGGTTGCCAAGC	55	1288
1157341	2791	2806	2991	3006	TTACCAACCACTCGCT	98	1289
1157375	2871	2886	3071	3086	CCCCATTATATTAGAA	106	1290
1157409	2930	2945	3130	3145	ACACCCGGAAATCGGC	92	1291
1157442	3026	3041	3226	3241	AACTTGCCATCTACTA	118	1292
1157474	3169	3184	3369	3384	CAGGTCATCTATTCAC	49	1293
1157508	3279	3294	3479	3494	CATATTTTGCCCCCAC	85	1294
1157541	3377	3392	3577	3592	TCTGATTATCCTGATA	89	1295
1157574	3503	3518	3703	3718	TAAAGTCTGATTAAGG	96	1296
1157607	3652	3667	3852	3867	CTTCTCTAACCCAGTT	85	1297
1157640	3757	3772	3957	3972	CTGCACTGTGCTGTAC	105	1298
1157674	3909	3924	4109	4124	CGTAACAGGCCACTGC	98	1299
1157707	4028	4043	4228	4243	CCAACTTGGAAGTTGA	69	1300
1157740	4117	4132	4317	4332	ACTGGTACACCCAGTG	108	1301
1157774	4229	4244	4429	4444	AGTAGGCCAGACCAAC	96	1302
1157807	4376	4391	4576	4591	ATCATTAAGCCACTTC	47	1303
1157874	4698	4713	4897	4912	GCTGGTTATGACTCAG	91	1304
1157906	4791	4806	4990	5005	CCCAATGGAGGTATGA	77	1305
1157940	4876	4891	5075	5090	TGGTAGCTTTCATTTG	26	1306
1157974	4938	4953	5137	5152	TTTTTGTGGTTATAGC	25	1307
1158008	5094	5109	5293	5308	TTGATCCCAACTCATC	67	1308
1158040	5159	5174	5358	5373	TAACGAAGAGATACCT	78	1309
1158073	5249	5264	5448	5463	ACATGCAATACTGCAG	97	1310
1158105	5340	5355	5539	5554	TCCTGAAATCCCCTAG	112	1311
1158139	5419	5434	5618	5633	GAAGTGTACTATCCCA	28	1312
1158172	5537	5552	5736	5751	TTCCTTTCATAGAGCC	30	1313
1158206	5733	5748	5932	5947	CCCCCCCAAGATTGCC	116	1314
1158238	5799	5814	5998	6013	TCAAATCCTGATCTGG	82	1315
1158271‡	5932	5947	6131	6146	ACCTGTCTAAGAGGTT	109	1316

1158305	6016	6031	6215	6230	TACTCTAATCACTGTC	85	1317
1158339	6106	6121	6305	6320	ATAAGGTCAATAGTGT	62	1318
1158372	6246	6261	6445	6460	GTCTCATACACTCACT	104	1319
1158405	6388	6403	6587	6602	CAGACCTGAAGTCAAG	86	1320
1158438	6473	6488	6672	6687	TTTAATCATACTCCAG	76	1321
1158471	6586	6601	6785	6800	ATCACAAATACGACTG	66	1322
1158504	6789	6804	6988	7003	TGCACTAAAGATCACT	63	1323
1158535	7000	7015	7199	7214	CTTCTATAGTCTGAAG	82	1324
1158568	7105	7120	7304	7319	CAATACTATTGTCCCA	53	1325
1158600	7243	7258	7442	7457	TTTAAGCCTTCGGTGC	87	1326
1158634	7358	7373	7557	7572	TGAGGCAAGTCCTCAT	95	1327
1158667	7476	7491	7675	7690	CTTGAGATTTGGGCTT	88	1328
1158701‡	7580	7595	7779	7794	GCAGAGAAGTTGCTTG	98	1329
1158735	7677	7692	7876	7891	ATTATGGATCATGCCC	83	1330
1158769	7728	7743	7927	7942	AACATAGTTCAACCCA	88	1331
1158801	7806	7821	8005	8020	GTATTATAATAGAGCT	96	1332
1158834	7897	7912	8096	8111	CTACAAGTTACATGTT	109	1333
1158867	8012	8027	8211	8226	CTAAGATGCTAGCTTG	126	1334
1158901	8167	8182	8366	8381	AACCAGGAGTGCCAAC	123	1335
1158932	8272	8287	8471	8486	CCAAGAACTAGCACCT	122	1336
1158966	8357	8372	8556	8571	TCAAGTCAAGCTCCTG	97	1337
1158999	8502	8517	N/A	N/A	CACAACAATTTAGAGC	117	1338

Table 48

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	85	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	112	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	60	36
1156466	34	49	N/A	N/A	GCCCCAGTCCTTTACA	97	1339
1156499	216	231	182	197	CTATAAGGACAGCTAA	96	1340
1156532	322	337	288	303	TCTGAACCGGAGCAGG	81	1341
1156566	434	449	400	415	AGCCAGTCAGGGACAC	103	1342
1156600	510	525	476	491	AGCGAGTTCAAGTGGC	73	1343
1156634	578	593	544	559	AAATTTTTCTACCGTT	103	1344
1156668	633	648	599	614	GCCCACTCTGATCTGC	104	1345
1156701	769	784	735	750	TTCGAGAAATCGGAGC	111	1346
1156735	851	866	817	832	TGGCAAAATGGCGGAC	81	1347
1156769	920	935	886	901	GTGTGATAGTTCAGGG	92	1348
1156803	N/A	N/A	976	991	CCGGAACTTTTAAAAT	87	1349

1156837	N/A	N/A	1057	1072	AAAGATTTGAGCTGCA	104	1350
1156871	N/A	N/A	1180	1195	GGCAAAAAGTAGTTCT	69	1351
1156905	1034	1049	1234	1249	GAGAACAACTCGCATC	80	1352
1156939	1110	1125	1310	1325	GCCCCCTCAGCAGAAG	75	1353
1156973	1212	1227	1412	1427	CAATATCTTAGTAACC	71	1354
1157007	1424	1439	1624	1639	GCCCTTCTATTGGTAT	103	1355
1157040	1542	1557	1742	1757	AATCACCTTCGGTTTA	101	1356
1157073	1655	1670	1855	1870	TTTCATCCTACCACTC	73	1357
1157107	1971	1986	2171	2186	CTATCTTCTATACTTC	76	1358
1157141	2194	2209	2394	2409	TTAGTAGCTTTTTGAT	61	1359
1157174	2318	2333	2518	2533	TTACTTCCGTTACGAA	108	1360
1157207	2404	2419	2604	2619	AATGCTAGTCCTCAGG	43	1361
1157241	2506	2521	2706	2721	GTCCTAGCTTCATCAA	82	1362
1157275	2591	2606	2791	2806	CCTAGCTTCCTTCACC	83	1363
1157308	2708	2723	2908	2923	CTCCGTGTGGTTGCCA	76	1364
1157342	2792	2807	2992	3007	TTTACCAACCACTCGC	82	1365
1157376	2872	2887	3072	3087	CCCCCATTATATTAGA	72	1366
1157410	2931	2946	3131	3146	AACACCCGGAAATCGG	74	1367
1157443	3027	3042	3227	3242	AAACTTGCCATCTACT	104	1368
1157475	3171	3186	3371	3386	AACAGGTCATCTATTC	67	1369
1157509	3280	3295	3480	3495	ACATATTTTGCCCCCA	81	1370
1157542	3378	3393	3578	3593	GTCTGATTATCCTGAT	67	1371
1157575	3510	3525	3710	3725	GCACTTTTAAAGTCTG	26	1372
1157608	3659	3674	3859	3874	TACACTCCTTCTCTAA	118	1373
1157641	3764	3779	3964	3979	ACCAAAGCTGCACTGT	85	1374
1157675	3910	3925	4110	4125	CCGTAACAGGCCACTG	70	1375
1157708	4029	4044	4229	4244	GCCAACTTGGAAGTTG	119	1376
1157741	4118	4133	4318	4333	CACTGGTACACCCAGT	85	1377
1157775	4230	4245	4430	4445	CAGTAGGCCAGACCAA	86	1378
1157808	4377	4392	4577	4592	GATCATTAAGCCACTT	90	1379
1157841	4526	4541	4725	4740	ATTTTTGAAGCATACC	59	1380
1157875	4699	4714	4898	4913	GGCTGGTTATGACTCA	60	1381
1157907	4792	4807	4991	5006	CCCCAATGGAGGTATG	63	1382
1157941	4878	4893	5077	5092	ATTGGTAGCTTTCATT	30	1383
1157975	4970	4985	5169	5184	GCCTCTTCATTGTATT	90	1384
1158009	5095	5110	5294	5309	CTTGATCCCAACTCAT	89	1385
1158041	5160	5175	5359	5374	ATAACGAAGAGATACC	94	1386
1158074	5251	5266	5450	5465	TAACATGCAATACTGC	82	1387
1158106	5341	5356	5540	5555	ATCCTGAAATCCCCTA	92	1388
1158140	5420	5435	5619	5634	TGAAGTGTACTATCCC	28	1389
1158173	5539	5554	5738	5753	TATTCCTTTCATAGAG	89	1390
1158207	5734	5749	5933	5948	TCCCCCCCAAGATTGC	103	1391
1158239	5800	5815	5999	6014	CTCAAATCCTGATCTG	63	1392

1158272‡	5936	5951	6135	6150	TCCCACCTGTCTAAGA	96	1393
1158306	6017	6032	6216	6231	TTACTCTAATCACTGT	67	1394
1158340	6107	6122	6306	6321	TATAAGGTCAATAGTG	62	1395
1158373	6251	6266	6450	6465	GCAAGGTCTCATACAC	52	1396
1158406	6407	6422	6606	6621	TACTTGCCAACAGAAC	81	1397
1158439	6475	6490	6674	6689	CTTTTAATCATACTCC	84	1398
1158472	6587	6602	6786	6801	AATCACAAATACGACT	77	1399
1158505	6790	6805	6989	7004	ATGCACTAAAGATCAC	66	1400
1158536	7002	7017	7201	7216	TCCTTCTATAGTCTGA	86	1401
1158569	7106	7121	7305	7320	TCAATACTATTGTCCC	34	1402
1158601	7244	7259	7443	7458	CTTTAAGCCTTCGGTG	103	1403
1158635	7359	7374	7558	7573	TTGAGGCAAGTCCTCA	97	1404
1158668	7478	7493	7677	7692	CGCTTGAGATTTGGGC	67	1405
1158702‡	7583	7598	7782	7797	GTGGCAGAGAAGTTGC	83	1406
1158736	7678	7693	7877	7892	GATTATGGATCATGCC	53	1407
1158770	7729	7744	7928	7943	TAACATAGTTCAACCC	83	1408
1158802	7807	7822	8006	8021	AGTATTATAATAGAGC	80	1409
1158835	7898	7913	8097	8112	TCTACAAGTTACATGT	77	1410
1158868	8013	8028	8212	8227	GCTAAGATGCTAGCTT	90	1411
1158902	8169	8184	8368	8383	GAAACCAGGAGTGCCA	96	1412
1158933	8273	8288	8472	8487	TCCAAGAACTAGCACC	105	1413
1158967	8358	8373	8557	8572	ATCAAGTCAAGCTCCT	89	1414
1159000	8503	8518	N/A	N/A	CCACAACAATTTAGAG	127	1415

Table 49

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	110	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	134	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	60	36
568454	3028	3043	3228	3243	CAAACTTGCCATCTAC	89	1416
568459	3516	3531	3716	3731	GGTTAAGCACTTTTAA	62	1417
1156467	52	67	18	33	GGAGAGGCCAGTTGCG	110	1418
1156500	217	232	183	198	CCTATAAGGACAGCTA	85	1419
1156533	323	338	289	304	TTCTGAACCGGAGCAG	77	1420
1156567	443	458	409	424	ACCTTGGGCAGCCAGT	104	1421
1156601	511	526	477	492	AAGCGAGTTCAAGTGG	85	1422
1156635	580	595	546	561	GGAAATTTTTCTACCG	92	1423
1156669	640	655	606	621	GCCAGTGGCCCACTCT	108	1424
1156702	770	785	736	751	GTTCGAGAAATCGGAG	85	1425

1156736	852	867	818	833	GTGGCAAAATGGCGGA	79	1426
1156770	921	936	887	902	AGTGTGATAGTTCAGG	93	1427
1156804	N/A	N/A	977	992	CCCGGAACTTTTAAAA	107	1428
1156838	N/A	N/A	1058	1073	GAAAGATTTGAGCTGC	110	1429
1156872	N/A	N/A	1183	1198	GGAGGCAAAAAGTAGT	91	1430
1156906	1035	1050	1235	1250	GGAGAACAACTCGCAT	83	1431
1156940	1126	1141	1326	1341	TCCTCAAGCTCCGCCT	77	1432
1156974	1213	1228	1413	1428	GCAATATCTTAGTAAC	77	1433
1157008	1426	1441	1626	1641	TTGCCCTTCTATTGGT	89	1434
1157041	1544	1559	1744	1759	TTAATCACCTTCGGTT	73	1435
1157074	1659	1674	1859	1874	ATTGTTTCATCCTACC	78	1436
1157108	2008	2023	2208	2223	CAGTGCTATTTTATCC	22	1437
1157142	2200	2215	2400	2415	GTCCTTTTAGTAGCTT	50	1438
1157175	2319	2334	2519	2534	ATTACTTCCGTTACGA	57	1439
1157208	2405	2420	2605	2620	TAATGCTAGTCCTCAG	62	1440
1157242	2507	2522	2707	2722	AGTCCTAGCTTCATCA	73	1441
1157276	2631	2646	2831	2846	CCTAGCTTCACCACCA	67	1442
1157309	2710	2725	2910	2925	TCCTCCGTGTGGTTGC	82	1443
1157343	2793	2808	2993	3008	TTTTACCAACCACTCG	69	1444
1157377	2873	2888	3073	3088	TCCCCCATTATATTAG	86	1445
1157411	2932	2947	3132	3147	CAACACCCGGAAATCG	82	1446
1157476	3176	3191	3376	3391	GTAAAAACAGGTCATC	79	1447
1157510	3281	3296	3481	3496	AACATATTTTGCCCCC	78	1448
1157543	3386	3401	3586	3601	CTGTGGTGGTCTGATT	67	1449
1157609	3660	3675	3860	3875	GTACACTCCTTCTCTA	83	1450
1157642	3767	3782	3967	3982	TGAACCAAAGCTGCAC	98	1451
1157676	3911	3926	4111	4126	ACCGTAACAGGCCACT	80	1452
1157709	4030	4045	4230	4245	TGCCAACTTGGAAGTT	68	1453
1157742	4119	4134	4319	4334	GCACTGGTACACCCAG	109	1454
1157776	4231	4246	4431	4446	CCAGTAGGCCAGACCA	87	1455
1157809	4378	4393	4578	4593	GGATCATTAAGCCACT	85	1456
1157842	4580	4595	4779	4794	TCTTAATCAGTTACAA	91	1457
1157876	4701	4716	4900	4915	CAGGCTGGTTATGACT	74	1458
1157908	4793	4808	4992	5007	TCCCCAATGGAGGTAT	91	1459
1157942	4879	4894	5078	5093	AATTGGTAGCTTTCAT	36	1460
1157976	4974	4989	5173	5188	CATTGCCTCTTCATTG	64	1461
1158010	5097	5112	5296	5311	CACTTGATCCCAACTC	56	1462
1158042	5161	5176	5360	5375	GATAACGAAGAGATAC	81	1463
1158075	5252	5267	5451	5466	CTAACATGCAATACTG	99	1464
1158107	5343	5358	5542	5557	CAATCCTGAAATCCCC	84	1465
1158141	5422	5437	5621	5636	AGTGAAGTGTACTATC	56	1466
1158174	5540	5555	5739	5754	CTATTCCTTTCATAGA	111	1467
1158208	5735	5750	5934	5949	ATCCCCCCCAAGATTG	95	1468

1158240	5802	5817	6001	6016	CGCTCAAATCCTGATC	77	1469
1158273	5938	5953	6137	6152	TCTCCCACCTGTCTAA	77	1470
1158307	6018	6033	6217	6232	ATTACTCTAATCACTG	72	1471
1158341	6108	6123	6307	6322	ATATAAGGTCAATAGT	84	1472
1158374	6252	6267	6451	6466	TGCAAGGTCTCATACA	68	1473
1158407	6409	6424	6608	6623	TTTACTTGCCAACAGA	73	1474
1158440	6476	6491	6675	6690	ACTTTTAATCATACTC	79	1475
1158473	6588	6603	6787	6802	CAATCACAAATACGAC	82	1476
1158506	6792	6807	6991	7006	CAATGCACTAAAGATC	90	1477
1158537	7009	7024	7208	7223	TGGAAGCTCCTTCTAT	119	1478
1158570	7107	7122	7306	7321	TTCAATACTATTGTCC	42	1479
1158602	7245	7260	7444	7459	ACTTTAAGCCTTCGGT	87	1480
1158636	7360	7375	7559	7574	GTTGAGGCAAGTCCTC	97	1481
1158669	7479	7494	7678	7693	CCGCTTGAGATTTGGG	72	1482
1158703#	7590	7605	7789	7804	TGGCGATGTGGCAGAG	65	1483
1158737	7679	7694	7878	7893	CGATTATGGATCATGC	56	1484
1158771	7730	7745	7929	7944	CTAACATAGTTCAACC	84	1485
1158803	7814	7829	8013	8028	CTGGATAAGTATTATA	72	1486
1158836	7899	7914	8098	8113	GTCTACAAGTTACATG	87	1487
1158869	8014	8029	8213	8228	CGCTAAGATGCTAGCT	106	1488
1158903	8171	8186	8370	8385	TGGAAACCAGGAGTGC	86	1489
1158934	8275	8290	8474	8489	ACTCCAAGAACTAGCA	89	1490
1158968	8359	8374	8558	8573	AATCAAGTCAAGCTCC	86	1491
1159001	8504	8519	N/A	N/A	ACCACAACAATTTAGA	110	1492

Table 50

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	87	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	119	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	36	36
1156468	64	79	30	45	CTTAAGAGGGCAGGAG	104	1493
1156501	218	233	184	199	GCCTATAAGGACAGCT	89	1494
1156534	324	339	290	305	CTTCTGAACCGGAGCA	127	1495
1156568	456	471	422	437	CGAAGACACAGAGACC	90	1496
1156602	512	527	478	493	AAAGCGAGTTCAAGTG	112	1497
1156636	581	596	547	562	CGGAAATTTTTCTACC	92	1498
1156670	649	664	615	630	CCGTTGGCTGCCAGTG	94	1499
1156703	771	786	737	752	TGTTCGAGAAATCGGA	83	1500
1156737	860	875	826	841	GTTGAGAAGTGGCAAA	80	1501

1156771	924	939	890	905	TAAAGTGTGATAGTTC	86	1502
1156805	N/A	N/A	978	993	CCCCGGAACTTTTAAA	77	1503
1156839	N/A	N/A	1061	1076	GTGGAAAGATTTGAGC	83	1504
1156873	N/A	N/A	1190	1205	TTGTGAGGGAGGCAAA	80	1505
1156907	1036	1051	1236	1251	CGGAGAACAACTCGCA	104	1506
1156941	1128	1143	1328	1343	TTTCCTCAAGCTCCGC	46	1507
1156975	1216	1231	1416	1431	TAAGCAATATCTTAGT	84	1508
1157009	1429	1444	1629	1644	GCATTGCCCTTCTATT	30	1509
1157042	1545	1560	1745	1760	TTTAATCACCTTCGGT	34	1510
1157075	1663	1678	1863	1878	CCAAATTGTTTCATCC	37	1511
1157109	2009	2024	2209	2224	TCAGTGCTATTTTATC	26	1512
1157143	2202	2217	2402	2417	CAGTCCTTTTAGTAGC	43	1513
1157176	2320	2335	2520	2535	AATTACTTCCGTTACG	57	1514
1157209	2406	2421	2606	2621	TTAATGCTAGTCCTCA	61	1515
1157243	2508	2523	2708	2723	CAGTCCTAGCTTCATC	91	1516
1157277	2632	2647	2832	2847	TCCTAGCTTCACCACC	56	1517
1157310	2712	2727	2912	2927	CCTCCTCCGTGTGGTT	68	1518
1157344	2794	2809	2994	3009	TTTTTACCAACCACTC	74	1519
1157378	2874	2889	3074	3089	CTCCCCCATTATATTA	69	1520
1157412	2934	2949	3134	3149	TACAACACCCGGAAAT	84	1521
1157444	3029	3044	3229	3244	ACAAACTTGCCATCTA	61	1522
1157477	3189	3204	3389	3404	TCAGGGTGAGGAAGTA	50	1523
1157511	3308	3323	3508	3523	GACAGACCTAAGGGAA	66	1524
1157544	3387	3402	3587	3602	CCTGTGGTGGTCTGAT	46	1525
1157576	3517	3532	3717	3732	GGGTTAAGCACTTTTA	43	1526
1157610	3662	3677	3862	3877	CGGTACACTCCTTCTC	60	1527
1157643	3769	3784	3969	3984	TATGAACCAAAGCTGC	93	1528
1157677	3912	3927	4112	4127	AACCGTAACAGGCCAC	50	1529
1157710	4034	4049	4234	4249	TACTTGCCAACTTGGA	49	1530
1157743	4121	4136	4321	4336	ATGCACTGGTACACCC	76	1531
1157777	4233	4248	4433	4448	GCCCAGTAGGCCAGAC	75	1532
1157810	4380	4395	4580	4595	CAGGATCATTAAGCCA	58	1533
1157843	4586	4601	4785	4800	CACAATTCTTAATCAG	59	1534
1157877	4702	4717	4901	4916	CCAGGCTGGTTATGAC	56	1535
1157909	4795	4810	4994	5009	ATTCCCCAATGGAGGT	64	1536
1157943	4881	4896	5080	5095	TAAATTGGTAGCTTTC	26	1537
1157977	4977	4992	5176	5191	GGACATTGCCTCTTCA	46	1538
1158011	5098	5113	5297	5312	CCACTTGATCCCAACT	53	1539
1158043	5162	5177	5361	5376	TGATAACGAAGAGATA	85	1540
1158076	5253	5268	5452	5467	CCTAACATGCAATACT	88	1541
1158108	5360	5375	5559	5574	TCGATGGAAAAATTTC	70	1542
1158142	5423	5438	5622	5637	GAGTGAAGTGTACTAT	38	1543
1158175	5541	5556	5740	5755	GCTATTCCTTTCATAG	34	1544

1158209	5736	5751	5935	5950	AATCCCCCCCAAGATT	105	1545
1158241	5804	5819	6003	6018	TCCGCTCAAATCCTGA	74	1546
1158274	5939	5954	6138	6153	ATCTCCCACCTGTCTA	55	1547
1158308	6020	6035	6219	6234	GTATTACTCTAATCAC	66	1548
1158342	6109	6124	6308	6323	TATATAAGGTCAATAG	95	1549
1158375	6253	6268	6452	6467	CTGCAAGGTCTCATAC	76	1550
1158408	6410	6425	6609	6624	ATTTACTTGCCAACAG	53	1551
1158441	6485	6500	6684	6699	GGGAACACAACTTTTA	67	1552
1158474	6589	6604	6788	6803	TCAATCACAAATACGA	70	1553
1158507	6798	6813	6997	7012	CATAAACAATGCACTA	86	1554
1158538	7010	7025	7209	7224	CTGGAAGCTCCTTCTA	75	1555
1158571	7108	7123	7307	7322	ATTCAATACTATTGTC	76	1556
1158603	7246	7261	7445	7460	TACTTTAAGCCTTCGG	71	1557
1158637	7362	7377	7561	7576	GAGTTGAGGCAAGTCC	48	1558
1158670	7480	7495	7679	7694	ACCGCTTGAGATTTGG	68	1559
1158704‡	7591	7606	7790	7805	GTGGCGATGTGGCAGA	59	1560
1158738	7680	7695	7879	7894	CCGATTATGGATCATG	37	1561
1158772	7731	7746	7930	7945	TCTAACATAGTTCAAC	71	1562
1158804	7815	7830	8014	8029	ACTGGATAAGTATTAT	54	1563
1158837	7900	7915	8099	8114	AGTCTACAAGTTACAT	97	1564
1158870	8015	8030	8214	8229	CCGCTAAGATGCTAGC	80	1565
1158904	8176	8191	8375	8390	CGTCCTGGAAACCAGG	79	1566
1158935	8276	8291	8475	8490	AACTCCAAGAACTAGC	70	1567
1158969	8360	8375	8559	8574	CAATCAAGTCAAGCTC	97	1568
1159002	8505	8520	N/A	N/A	AACCACAACAATTTAG	84	1569

Table 51

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	132	18
556131	8177	8192	8376	8391	CCGTCCTGGAAACCAG	84	1570
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	119	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	49	36
568477	5424	5439	5623	5638	TGAGTGAAGTGTACTA	58	1571
568491	6831	6846	7030	7045	TTAAGACCAAGGGAGG	71	1572
1156469	65	80	31	46	GCTTAAGAGGGCAGGA	107	1573
1156502	219	234	185	200	AGCCTATAAGGACAGC	77	1574
1156535	325	340	291	306	CCTTCTGAACCGGAGC	104	1575
1156569	457	472	423	438	CCGAAGACACAGAGAC	98	1576
1156603	513	528	479	494	GAAAGCGAGTTCAAGT	101	1577

1156637	582	597	548	563	ACGGAAATTTTTCTAC	96	1578
1156671	650	665	616	631	GCCGTTGGCTGCCAGT	108	1579
1156704	772	787	738	753	TTGTTCGAGAAATCGG	95	1580
1156738	862	877	828	843	CGGTTGAGAAGTGGCA	111	1581
1156772	925	940	891	906	TTAAAGTGTGATAGTT	94	1582
1156806	N/A	N/A	979	994	CCCCCGGAACTTTTAA	112	1583
1156840	N/A	N/A	1064	1079	CGTGTGGAAAGATTTG	100	1584
1156874	N/A	N/A	1193	1208	CCTTTGTGAGGGAGGC	105	1585
1156908	1037	1052	1237	1252	ACGGAGAACAACTCGC	99	1586
1156942	1129	1144	1329	1344	GTTTCCTCAAGCTCCG	41	1587
1156976	1217	1232	1417	1432	CTAAGCAATATCTTAG	85	1588
1157010	1431	1446	1631	1646	AAGCATTGCCCTTCTA	54	1589
1157043	1546	1561	1746	1761	TTTTAATCACCTTCGG	56	1590
1157076	1707	1722	1907	1922	CGTACTTCTGTCTTCC	36	1591
1157110	2033	2048	2233	2248	GTTACCAATAATTTCC	29	1592
1157144	2204	2219	2404	2419	ACCAGTCCTTTTAGTA	102	1593
1157177	2321	2336	2521	2536	GAATTACTTCCGTTAC	64	1594
1157210	2407	2422	2607	2622	ATTAATGCTAGTCCTC	64	1595
1157244	2510	2525	2710	2725	CTCAGTCCTAGCTTCA	58	1596
1157278	2633	2648	2833	2848	TTCCTAGCTTCACCAC	64	1597
1157311	2713	2728	2913	2928	GCCTCCTCCGTGTGGT	101	1598
1157345	2796	2811	2996	3011	GATTTTTACCAACCAC	58	1599
1157379	2875	2890	3075	3090	ACTCCCCCATTATATT	98	1600
1157413	2935	2950	3135	3150	CTACAACACCCGGAAA	67	1601
1157445	3032	3047	3232	3247	CCCACAAACTTGCCAT	99	1602
1157478	3194	3209	3394	3409	CGAATTCAGGGTGAGG	32	1603
1157512	3309	3324	3509	3524	AGACAGACCTAAGGGA	79	1604
1157545	3391	3406	3591	3606	TAAACCTGTGGTGGTC	70	1605
1157577	3531	3546	3731	3746	ATAACAAGTTTAAGGG	59	1606
1157611	3663	3678	3863	3878	GCGGTACACTCCTTCT	72	1607
1157644	3776	3791	3976	3991	GACTGAATATGAACCA	49	1608
1157678	3913	3928	4113	4128	CAACCGTAACAGGCCA	77	1609
1157711	4035	4050	4235	4250	TTACTTGCCAACTTGG	30	1610
1157744	4123	4138	4323	4338	TAATGCACTGGTACAC	122	1611
1157778	4241	4256	4441	4456	TAATGTCAGCCCAGTA	93	1612
1157811	4381	4396	4581	4596	TCAGGATCATTAAGCC	63	1613
1157844	4591	4606	4790	4805	ACTATCACAATTCTTA	87	1614
1157878	4705	4720	4904	4919	CTGCCAGGCTGGTTAT	99	1615
1157910	4796	4811	4995	5010	TATTCCCCAATGGAGG	83	1616
1157944	4884	4899	5083	5098	CTTTAAATTGGTAGCT	55	1617
1157978	4978	4993	5177	5192	TGGACATTGCCTCTTC	71	1618
1158012	5099	5114	5298	5313	TCCACTTGATCCCAAC	53	1619
1158044	5163	5178	5362	5377	CTGATAACGAAGAGAT	103	1620

1158077	5254	5269	5453	5468	CCCTAACATGCAATAC	86	1621
1158109	5361	5376	5560	5575	CTCGATGGAAAAATTT	92	1622
1158176	5550	5565	5749	5764	GCACATCATGCTATTC	55	1623
1158210	5737	5752	5936	5951	GAATCCCCCCCAAGAT	115	1624
1158242	5805	5820	6004	6019	TTCCGCTCAAATCCTG	65	1625
1158275	5941	5956	6140	6155	TAATCTCCCACCTGTC	93	1626
1158309	6021	6036	6220	6235	AGTATTACTCTAATCA	77	1627
1158343	6110	6125	6309	6324	CTATATAAGGTCAATA	84	1628
1158376	6254	6269	6453	6468	ACTGCAAGGTCTCATA	101	1629
1158409	6412	6427	6611	6626	GCATTTACTTGCCAAC	89	1630
1158442	6499	6514	6698	6713	TACTCCAAGCATTGGG	100	1631
1158475	6590	6605	6789	6804	TTCAATCACAAATACG	81	1632
1158539	7012	7027	7211	7226	AACTGGAAGCTCCTTC	83	1633
1158572	7115	7130	7314	7329	GAAATCTATTCAATAC	76	1634
1158604	7247	7262	7446	7461	CTACTTTAAGCCTTCG	69	1635
1158638	7363	7378	7562	7577	GGAGTTGAGGCAAGTC	59	1636
1158671	7481	7496	7680	7695	CACCGCTTGAGATTTG	53	1637
1158705‡	7607	7622	7806	7821	GATCAAAAGGCACGGG	70	1638
1158739	7681	7696	7880	7895	ACCGATTATGGATCAT	64	1639
1158773	7736	7751	7935	7950	CCTTTTCTAACATAGT	77	1640
1158805	7816	7831	8015	8030	CACTGGATAAGTATTA	60	1641
1158838	7901	7916	8100	8115	CAGTCTACAAGTTACA	73	1642
1158871	8016	8031	8215	8230	TCCGCTAAGATGCTAG	85	1643
1158936‡	8299	8314	8498	8513	GCTGTTACCTCCCACC	74	1644
1158970	8361	8376	8560	8575	ACAATCAAGTCAAGCT	85	1645
1159003	8506	8521	N/A	N/A	GAACCACAACAATTTA	81	1646

Table 52

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	116	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	116	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	36	36
946398	66	81	32	47	CGCTTAAGAGGGCAGG	88	1647
946402	1435	1450	1635	1650	CTAAAAGCATTGCCCT	65	1648
946413	5100	5115	5299	5314	ATCCACTTGATCCCAA	84	1649
1156503	220	235	186	201	CAGCCTATAAGGACAG	78	1650
1156536	326	341	292	307	ACCTTCTGAACCGGAG	78	1651
1156570	459	474	425	440	CTCCGAAGACACAGAG	103	1652
1156604	514	529	480	495	GGAAAGCGAGTTCAAG	76	1653

1156638	583	598	549	564	CACGGAAATTTTTCTA	92	1654
1156672	651	666	617	632	GGCCGTTGGCTGCCAG	79	1655
1156705	775	790	741	756	TTTTTGTTCGAGAAAT	107	1656
1156739	863	878	829	844	ACGGTTGAGAAGTGGC	78	1657
1156773	926	941	892	907	ATTAAAGTGTGATAGT	83	1658
1156807	N/A	N/A	980	995	ACCCCCGGAACTTTTA	91	1659
1156841	N/A	N/A	1078	1093	ACTTAAATTACTAGCG	110	1660
1156875	N/A	N/A	1194	1209	GCCTTTGTGAGGGAGG	123	1661
1156909	1039	1054	1239	1254	AGACGGAGAACAACTC	114	1662
1156943	1130	1145	1330	1345	GGTTTCCTCAAGCTCC	66	1663
1156977	1218	1233	1418	1433	GCTAAGCAATATCTTA	68	1664
1157044	1547	1562	1747	1762	CTTTTAATCACCTTCG	26	1665
1157077	1708	1723	1908	1923	CCGTACTTCTGTCTTC	36	1666
1157111⁂	2034	2049	2234	2249	GGTTACCAATAATTTC	11	3
1157145	2208	2223	2408	2423	TTACACCAGTCCTTTT	63	1667
1157178	2322	2337	2522	2537	TGAATTACTTCCGTTA	64	1668
1157211	2408	2423	2608	2623	AATTAATGCTAGTCCT	84	1669
1157245	2515	2530	2715	2730	TGCTCCTCAGTCCTAG	74	1670
1157279	2635	2650	2835	2850	TTTTCCTAGCTTCACC	33	1671
1157312	2715	2730	2915	2930	TCGCCTCCTCCGTGTG	67	1672
1157346	2797	2812	2997	3012	GGATTTTTACCAACCA	86	1673
1157380	2876	2891	3076	3091	AACTCCCCCATTATAT	101	1674
1157414	2936	2951	3136	3151	CCTACAACACCCGGAA	100	1675
1157446	3033	3048	3233	3248	ACCCACAAACTTGCCA	102	1676
1157479	3197	3212	3397	3412	AAACGAATTCAGGGTG	77	1677
1157513	3311	3326	3511	3526	CTAGACAGACCTAAGG	98	1678
1157546	3392	3407	3592	3607	GTAAACCTGTGGTGGT	44	1679
1157578	3559	3574	3759	3774	GACCATCCCAAAATGC	92	1680
1157612	3664	3679	3864	3879	AGCGGTACACTCCTTC	50	1681
1157645	3777	3792	3977	3992	TGACTGAATATGAACC	59	1682
1157679	3914	3929	4114	4129	CCAACCGTAACAGGCC	73	1683
1157712	4036	4051	4236	4251	GTTACTTGCCAACTTG	37	1684
1157745	4124	4139	4324	4339	TTAATGCACTGGTACA	78	1685
1157779	4242	4257	4442	4457	TTAATGTCAGCCCAGT	63	1686
1157812	4382	4397	4582	4597	TTCAGGATCATTAAGC	82	1687
1157845	4593	4608	4792	4807	GAACTATCACAATTCT	97	1688
1157879	4710	4725	4909	4924	TCATACTGCCAGGCTG	71	1689
1157911	4797	4812	4996	5011	TTATTCCCCAATGGAG	82	1690
1157945	4885	4900	5084	5099	ACTTTAAATTGGTAGC	72	1691
1157979	4979	4994	5178	5193	ATGGACATTGCCTCTT	63	1692
1158045	5164	5179	5363	5378	TCTGATAACGAAGAGA	79	1693
1158078	5255	5270	5454	5469	TCCCTAACATGCAATA	70	1694
1158110	5362	5377	5561	5576	GCTCGATGGAAAAATT	90	1695

1158143	5425	5440	5624	5639	CTGAGTGAAGTGTACT	52	1696
1158177	5551	5566	5750	5765	AGCACATCATGCTATT	74	1697
1158211	5739	5754	5938	5953	AAGAATCCCCCCCAAG	72	1698
1158243	5807	5822	6006	6021	TCTTCCGCTCAAATCC	59	1699
1158276	5942	5957	6141	6156	ATAATCTCCCACCTGT	83	1700
1158310	6022	6037	6221	6236	AAGTATTACTCTAATC	91	1701
1158344	6112	6127	6311	6326	CCCTATATAAGGTCAA	87	1702
1158377	6255	6270	6454	6469	CACTGCAAGGTCTCAT	59	1703
1158410	6414	6429	6613	6628	CTGCATTTACTTGCCA	83	1704
1158443	6500	6515	6699	6714	CTACTCCAAGCATTGG	73	1705
1158476	6593	6608	6792	6807	AGCTTCAATCACAAAT	77	1706
1158508	6834	6849	7033	7048	GAATTAAGACCAAGGG	64	1707
1158540	7013	7028	7212	7227	CAACTGGAAGCTCCTT	77	1708
1158573	7118	7133	7317	7332	GCTGAAATCTATTCAA	259	1709
1158605	7248	7263	7447	7462	CCTACTTTAAGCCTTC	65	1710
1158639	7364	7379	7563	7578	GGGAGTTGAGGCAAGT	94	1711
1158672	7483	7498	7682	7697	AGCACCGCTTGAGATT	58	1712
1158706‡	7608	7623	7807	7822	AGATCAAAAGGCACGG	80	1713
1158740	7682	7697	7881	7896	AACCGATTATGGATCA	51	1714
1158774	7737	7752	7936	7951	GCCTTTTCTAACATAG	101	1715
1158806	7818	7833	8017	8032	GTCACTGGATAAGTAT	52	1716
1158839	7902	7917	8101	8116	CCAGTCTACAAGTTAC	50	1717
1158872	8017	8032	8216	8231	TTCCGCTAAGATGCTA	91	1718
1158905	8179	8194	8378	8393	CCCCGTCCTGGAAACC	79	1719
1158937	8300	8315	8499	8514	TGCTGTTACCTCCCAC	86	1720
1158971	8362	8377	8561	8576	TACAATCAAGTCAAGC	102	1721
1159004	8535	8550	N/A	N/A	CCCCAATCAAGATTTT	121	1722

Table 53

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	105	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	117	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	45	36
946406	2937	2952	3137	3152	ACCTACAACACCCGGA	75	1723
1156470	67	82	33	48	GCGCTTAAGAGGGCAG	94	1724
1156504	221	236	187	202	CCAGCCTATAAGGACA	101	1725
1156537	329	344	295	310	CAGACCTTCTGAACCG	90	1726
1156571	460	475	426	441	TCTCCGAAGACACAGA	100	1727
1156605	515	530	481	496	TGGAAAGCGAGTTCAA	104	1728

1156639	584	599	550	565	GCACGGAAATTTTTCT	103	1729
1156673	667	682	633	648	CCGCCTGAGCCCCGGG	109	1730
1156706	798	813	764	779	CCAAGACAGCCACACG	90	1731
1156740	864	879	830	845	GACGGTTGAGAAGTGG	75	1732
1156774	927	942	893	908	GATTAAAGTGTGATAG	84	1733
1156808	N/A	N/A	981	996	AACCCCCGGAACTTTT	99	1734
1156842	N/A	N/A	1079	1094	TACTTAAATTACTAGC	72	1735
1156876	N/A	N/A	1195	1210	CGCCTTTGTGAGGGAG	103	1736
1156910	1040	1055	1240	1255	TAGACGGAGAACAACT	71	1737
1156944	1132	1147	1332	1347	GCGGTTTCCTCAAGCT	80	1738
1156978	1219	1234	1419	1434	CGCTAAGCAATATCTT	42	1739
1157011	1436	1451	1636	1651	TCTAAAAGCATTGCCC	71	1740
1157045	1554	1569	1754	1769	TCAAGGTCTTTTAATC	59	1741
1157078	1710	1725	1910	1925	TCCCGTACTTCTGTCT	59	1742
1157112	2036	2051	2236	2251	TTGGTTACCAATAATT	76	1743
1157146	2209	2224	2409	2424	ATTACACCAGTCCTTT	60	1744
1157179	2323	2338	2523	2538	TTGAATTACTTCCGTT	46	1745
1157212	2409	2424	2609	2624	CAATTAATGCTAGTCC	72	1746
1157246	2519	2534	2719	2734	CGCTTGCTCCTCAGTC	38	1747
1157280	2654	2669	2854	2869	CGCTCCTTCCTGGAAT	119	1748
1157313	2716	2731	2916	2931	CTCGCCTCCTCCGTGT	90	1749
1157347	2798	2813	2998	3013	CGGATTTTTACCAACC	62	1750
1157381	2878	2893	3078	3093	GAAACTCCCCCATTAT	94	1751
1157447	3081	3096	3281	3296	GGCTATCAAATTCATT	58	1752
1157480	3198	3213	3398	3413	AAAACGAATTCAGGGT	75	1753
1157514	3312	3327	3512	3527	TCTAGACAGACCTAAG	106	1754
1157547	3393	3408	3593	3608	TGTAAACCTGTGGTGG	52	1755
1157579	3562	3577	3762	3777	TAAGACCATCCCAAAA	84	1756
1157613	3665	3680	3865	3880	CAGCGGTACACTCCTT	64	1757
1157646	3786	3801	3986	4001	CTCCTGAGATGACTGA	61	1758
1157680	3915	3930	4115	4130	CCCAACCGTAACAGGC	78	1759
1157713	4037	4052	4237	4252	AGTTACTTGCCAACTT	93	1760
1157746	4125	4140	4325	4340	ATTAATGCACTGGTAC	84	1761
1157780	4243	4258	4443	4458	GTTAATGTCAGCCCAG	45	1762
1157813	4383	4398	4583	4598	CTTCAGGATCATTAAG	97	1763
1157846	4594	4609	4793	4808	TGAACTATCACAATTC	76	1764
1157880	4712	4727	4911	4926	CATCATACTGCCAGGC	41	1765
1157912	4799	4814	4998	5013	GCTTATTCCCCAATGG	27	1766
1157946	4888	4903	5087	5102	GTAACTTTAAATTGGT	45	1767
1157980	4980	4995	5179	5194	GATGGACATTGCCTCT	63	1768
1158013	5102	5117	5301	5316	CAATCCACTTGATCCC	44	1769
1158046	5165	5180	5364	5379	TTCTGATAACGAAGAG	92	1770
1158079	5256	5271	5455	5470	ATCCCTAACATGCAAT	77	1771

1158111	5363	5378	5562	5577	GGCTCGATGGAAAAAT	67	1772
1158144	5426	5441	5625	5640	TCTGAGTGAAGTGTAC	66	1773
1158178	5552	5567	5751	5766	CAGCACATCATGCTAT	85	1774
1158212	5740	5755	5939	5954	GAAGAATCCCCCCCAA	89	1775
1158244	5825	5840	6024	6039	CCTTAAAGTTACATTC	67	1776
1158277	5944	5959	6143	6158	TCATAATCTCCCACCT	90	1777
1158311	6051	6066	6250	6265	GTTAACATGCAAACTT	87	1778
1158345	6113	6128	6312	6327	TCCCTATATAAGGTCA	95	1779
1158378	6256	6271	6455	6470	TCACTGCAAGGTCTCA	52	1780
1158411	6415	6430	6614	6629	ACTGCATTTACTTGCC	92	1781
1158444	6501	6516	6700	6715	ACTACTCCAAGCATTG	64	1782
1158477	6594	6609	6793	6808	CAGCTTCAATCACAAA	67	1783
1158509	6838	6853	7037	7052	GTAAGAATTAAGACCA	63	1784
1158541	7015	7030	7214	7229	TTCAACTGGAAGCTCC	42	1785
1158574	7125	7140	7324	7339	GCATAAAGCTGAAATC	96	1786
1158606	7252	7267	7451	7466	TTGTCCTACTTTAAGC	70	1787
1158640	7366	7381	7565	7580	GAGGGAGTTGAGGCAA	76	1788
1158673	7484	7499	7683	7698	AAGCACCGCTTGAGAT	92	1789
1158707‡	7611	7626	7810	7825	GCTAGATCAAAAGGCA	87	1790
1158741	7683	7698	7882	7897	AAACCGATTATGGATC	97	1791
1158775	7738	7753	7937	7952	GGCCTTTTCTAACATA	98	1792
1158807	7819	7834	8018	8033	AGTCACTGGATAAGTA	59	1793
1158840	7903	7918	8102	8117	TCCAGTCTACAAGTTA	69	1794
1158873	8021	8036	8220	8235	CAGCTTCCGCTAAGAT	111	1795
1158906	8182	8197	8381	8396	GAACCCCGTCCTGGAA	118	1796
1158938	8306	8321	8505	8520	ATATTGTGCTGTTACC	109	1797
1158972	8392	8407	8591	8606	TTATATTAGGTTCTCG	106	1798
1159005	8536	8551	N/A	N/A	TCCCCAATCAAGATTT	82	1799

Table 54

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	94	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	114	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	41	36
567919	6839	6854	7038	7053	TGTAAGAATTAAGACC	82	1800
567964	7016	7031	7215	7230	ATTCAACTGGAAGCTC	83	1801
946411	4244	4259	4444	4459	AGTTAATGTCAGCCCA	66	1802
946418	6502	6517	6701	6716	CACTACTCCAAGCATT	77	1803
946423	7749	7764	7948	7963	GGCAAATTAATGGCCT	75	1804

1156471	68	83	34	49	TGCGCTTAAGAGGGCA	93	1805
1156505	223	238	189	204	GGCCAGCCTATAAGGA	94	1806
1156538	330	345	296	311	TCAGACCTTCTGAACC	106	1807
1156572	461	476	427	442	GTCTCCGAAGACACAG	105	1808
1156606	516	531	482	497	ATGGAAAGCGAGTTCA	86	1809
1156640	585	600	551	566	CGCACGGAAATTTTTC	117	1810
1156674	668	683	634	649	CCCGCCTGAGCCCCGG	102	1811
1156707	807	822	773	788	GACTTGCTCCCAAGAC	93	1812
1156741	865	880	831	846	GGACGGTTGAGAAGTG	104	1813
1156775	928	943	894	909	AGATTAAAGTGTGATA	73	1814
1156809	N/A	N/A	982	997	AAACCCCCGGAACTTT	95	1815
1156843	N/A	N/A	1098	1113	CAAACTACACATGCAG	94	1816
1156877	N/A	N/A	1196	1211	CCGCCTTTGTGAGGGA	86	1817
1156911	1041	1056	1241	1256	ATAGACGGAGAACAAC	79	1818
1156945	1133	1148	1333	1348	TGCGGTTTCCTCAAGC	74	1819
1156979	1220	1235	1420	1435	ACGCTAAGCAATATCT	63	1820
1157012	1437	1452	1637	1652	ATCTAAAAGCATTGCC	82	1821
1157046	1562	1577	1762	1777	CATGGATTTCAAGGTC	89	1822
1157079	1712	1727	1912	1927	CTTCCCGTACTTCTGT	57	1823
1157113	2037	2052	2237	2252	ATTGGTTACCAATAAT	96	1824
1157147	2210	2225	2410	2425	AATTACACCAGTCCTT	58	1825
1157180	2324	2339	2524	2539	CTTGAATTACTTCCGT	44	1826
1157213	2410	2425	2610	2625	TCAATTAATGCTAGTC	65	1827
1157247	2521	2536	2721	2736	CTCGCTTGCTCCTCAG	46	1828
1157281	2657	2672	2857	2872	ACTCGCTCCTTCCTGG	52	1829
1157314	2717	2732	2917	2932	GCTCGCCTCCTCCGTG	73	1830
1157348	2799	2814	2999	3014	ACGGATTTTTACCAAC	66	1831
1157382	2879	2894	3079	3094	CGAAACTCCCCCATTA	85	1832
1157415	2938	2953	3138	3153	AACCTACAACACCCGG	66	1833
1157448	3089	3104	3289	3304	CTCAATTTGGCTATCA	40	1834
1157481	3199	3214	3399	3414	CAAAACGAATTCAGGG	74	1835
1157515	3313	3328	3513	3528	TTCTAGACAGACCTAA	71	1836
1157548	3394	3409	3594	3609	CTGTAAACCTGTGGTG	85	1837
1157580	3563	3578	3763	3778	TTAAGACCATCCCAAA	95	1838
1157614	3666	3681	3866	3881	ACAGCGGTACACTCCT	58	1839
1157647	3794	3809	3994	4009	CTGAAGTTCTCCTGAG	62	1840
1157681	3916	3931	4116	4131	TCCCAACCGTAACAGG	98	1841
1157714	4039	4054	4239	4254	GGAGTTACTTGCCAAC	76	1842
1157747	4126	4141	4326	4341	AATTAATGCACTGGTA	81	1843
1157814	4386	4401	4586	4601	TCCCTTCAGGATCATT	90	1844
1157847	4595	4610	4794	4809	CTGAACTATCACAATT	72	1845
1157881	4713	4728	4912	4927	CCATCATACTGCCAGG	83	1846
1157913	4800	4815	4999	5014	TGCTTATTCCCCAATG	48	1847

1157947	4889	4904	5088	5103	CGTAACTTTAAATTGG	21	1848
1157981	4981	4996	5180	5195	AGATGGACATTGCCTC	52	1849
1158014	5103	5118	5302	5317	TCAATCCACTTGATCC	86	1850
1158047	5166	5181	5365	5380	CTTCTGATAACGAAGA	105	1851
1158080	5258	5273	5457	5472	TTATCCCTAACATGCA	92	1852
1158112	5364	5379	5563	5578	AGGCTCGATGGAAAAA	72	1853
1158145	5469	5484	5668	5683	CACTTTAGAGGCTTTT	58	1854
1158179	5555	5570	5754	5769	TAACAGCACATCATGC	79	1855
1158213	5741	5756	5940	5955	AGAAGAATCCCCCCCA	113	1856
1158245	5826	5841	6025	6040	GCCTTAAAGTTACATT	90	1857
1158278	5945	5960	6144	6159	ATCATAATCTCCCACC	80	1858
1158312	6068	6083	6267	6282	GATTGTAAGCATTTAA	46	1859
1158346	6114	6129	6313	6328	TTCCCTATATAAGGTC	94	1860
1158379	6261	6276	6460	6475	TAAACTCACTGCAAGG	86	1861
1158412	6416	6431	6615	6630	TACTGCATTTACTTGC	80	1862
1158478	6601	6616	6800	6815	ATGTACTCAGCTTCAA	56	1863
1158575	7129	7144	7328	7343	TCCAGCATAAAGCTGA	109	1864
1158607	7258	7273	7457	7472	CCATGGTTGTCCTACT	90	1865
1158641	7367	7382	7566	7581	AGAGGGAGTTGAGGCA	60	1866
1158674	7486	7501	7685	7700	TCAAGCACCGCTTGAG	112	1867
1158708‡	7612	7627	7811	7826	TGCTAGATCAAAAGGC	92	1868
1158742	7684	7699	7883	7898	GAAACCGATTATGGAT	66	1869
1158808	7823	7838	8022	8037	TTTTAGTCACTGGATA	55	1870
1158841	7912	7927	8111	8126	CCTATCTTCTCCAGTC	113	1871
1158874	8023	8038	8222	8237	ATCAGCTTCCGCTAAG	96	1872
1158907	8183	8198	8382	8397	TGAACCCCGTCCTGGA	97	1873
1158939	8307	8322	8506	8521	GATATTGTGCTGTTAC	117	1874
1158973	8393	8408	8592	8607	GTTATATTAGGTTCTC	93	1875
1159006	8538	8553	N/A	N/A	TTTCCCCAATCAAGAT	104	1876

Table 55

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	78	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	112	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	36	36
946412	4715	4730	4914	4929	GGCCATCATACTGCCA	119	1877
946425	8184	8199	8383	8398	TTGAACCCCGTCCTGG	88	1878
1156472	69	84	35	50	CTGCGCTTAAGAGGGC	66	1879
1156506	228	243	194	209	GGAATGGCCAGCCTAT	83	1880

1156539	331	346	297	312	TTCAGACCTTCTGAAC	108	1881
1156573	469	484	435	450	ATGGCTTTGTCTCCGA	85	1882
1156607	517	532	483	498	CATGGAAAGCGAGTTC	80	1883
1156641	586	601	552	567	CCGCACGGAAATTTTT	85	1884
1156675	671	686	637	652	CTCCCCGCCTGAGCCC	123	1885
1156708	808	823	774	789	CGACTTGCTCCCAAGA	78	1886
1156742	866	881	832	847	GGGACGGTTGAGAAGT	93	1887
1156776	931	946	897	912	GGAAGATTAAAGTGTG	79	1888
1156810	N/A	N/A	983	998	AAAACCCCCGGAACTT	91	1889
1156844	N/A	N/A	1106	1121	CTTGAATGCAAACTAC	106	1890
1156878	N/A	N/A	1197	1212	GCCGCCTTTGTGAGGG	75	1891
1156912	1042	1057	1242	1257	TATAGACGGAGAACAA	70	1892
1156946	1134	1149	1334	1349	CTGCGGTTTCCTCAAG	71	1893
1156980	1232	1247	1432	1447	GTTAAAAACTTAACGC	96	1894
1157013	1438	1453	1638	1653	AATCTAAAAGCATTGC	70	1895
1157047	1563	1578	1763	1778	TCATGGATTTCAAGGT	49	1896
1157080	1714	1729	1914	1929	GCCTTCCCGTACTTCT	40	1897
1157114	2040	2055	2240	2255	TAAATTGGTTACCAAT	75	1898
1157148	2211	2226	2411	2426	AAATTACACCAGTCCT	55	1899
1157181	2325	2340	2525	2540	TCTTGAATTACTTCCG	24	1900
1157214	2411	2426	2611	2626	GTCAATTAATGCTAGT	59	1901
1157248	2522	2537	2722	2737	GCTCGCTTGCTCCTCA	61	1902
1157282	2659	2674	2859	2874	GCACTCGCTCCTTCCT	34	1903
1157315	2718	2733	2918	2933	TGCTCGCCTCCTCCGT	66	1904
1157349	2800	2815	3000	3015	CACGGATTTTTACCAA	81	1905
1157383	2880	2895	3080	3095	ACGAAACTCCCCCATT	64	1906
1157416	2940	2955	3140	3155	GAAACCTACAACACCC	80	1907
1157449	3090	3105	3290	3305	TCTCAATTTGGCTATC	71	1908
1157482	3200	3215	3400	3415	ACAAAACGAATTCAGG	69	1909
1157516	3314	3329	3514	3529	ATTCTAGACAGACCTA	67	1910
1157549	3395	3410	3595	3610	ACTGTAAACCTGTGGT	106	1911
1157581	3564	3579	3764	3779	GTTAAGACCATCCCAA	81	1912
1157615	3667	3682	3867	3882	CACAGCGGTACACTCC	60	1913
1157648	3810	3825	4010	4025	GCCTACTCAAGCTCTT	80	1914
1157682	3917	3932	4117	4132	ATCCCAACCGTAACAG	87	1915
1157715	4040	4055	4240	4255	GGGAGTTACTTGCCAA	90	1916
1157748	4128	4143	4328	4343	CAAATTAATGCACTGG	85	1917
1157781	4245	4260	4445	4460	TAGTTAATGTCAGCCC	59	1918
1157815	4387	4402	4587	4602	ATCCCTTCAGGATCAT	81	1919
1157848	4596	4611	4795	4810	GCTGAACTATCACAAT	73	1920
1157914	4801	4816	5000	5015	ATGCTTATTCCCCAAT	48	1921
1157948	4890	4905	5089	5104	CCGTAACTTTAAATTG	45	1922
1157982	4982	4997	5181	5196	GAGATGGACATTGCCT	42	1923

1158015	5104	5119	5303	5318	CTCAATCCACTTGATC	68	1924
1158048	5168	5183	5367	5382	CTCTTCTGATAACGAA	77	1925
1158081	5259	5274	5458	5473	CTTATCCCTAACATGC	59	1926
1158113	5365	5380	5564	5579	AAGGCTCGATGGAAAA	93	1927
1158146	5471	5486	5670	5685	ATCACTTTAGAGGCTT	47	1928
1158180	5556	5571	5755	5770	CTAACAGCACATCATG	68	1929
1158214	5742	5757	5941	5956	GAGAAGAATCCCCCCC	83	1930
1158246	5827	5842	6026	6041	TGCCTTAAAGTTACAT	81	1931
1158279	5946	5961	6145	6160	GATCATAATCTCCCAC	59	1932
1158313	6069	6084	6268	6283	AGATTGTAAGCATTTA	58	1933
1158347	6115	6130	6314	6329	CTTCCCTATATAAGGT	90	1934
1158380	6265	6280	6464	6479	CTGATAAACTCACTGC	52	1935
1158413	6419	6434	6618	6633	CAGTACTGCATTTACT	80	1936
1158445	6503	6518	6702	6717	TCACTACTCCAAGCAT	79	1937
1158479	6602	6617	6801	6816	AATGTACTCAGCTTCA	52	1938
1158510	6842	6857	7041	7056	GCATGTAAGAATTAAG	72	1939
1158542	7018	7033	7217	7232	GAATTCAACTGGAAGC	93	1940
1158576	7130	7145	7329	7344	CTCCAGCATAAAGCTG	88	1941
1158608	7259	7274	7458	7473	TCCATGGTTGTCCTAC	65	1942
1158642	7387	7402	7586	7601	TCGGATGCTTCACTCC	63	1943
1158675	7487	7502	7686	7701	TTCAAGCACCGCTTGA	88	1944
1158709ǂ	7613	7628	7812	7827	GTGCTAGATCAAAAGG	75	1945
1158743	7685	7700	7884	7899	TGAAACCGATTATGGA	97	1946
1158776	7750	7765	7949	7964	AGGCAAATTAATGGCC	92	1947
1158809	7824	7839	8023	8038	GTTTTAGTCACTGGAT	42	1948
1158842	7913	7928	8112	8127	GCCTATCTTCTCCAGT	73	1949
1158875	8027	8042	8226	8241	GGAGATCAGCTTCCGC	107	1950
1158940	8308	8323	8507	8522	AGATATTGTGCTGTTA	83	1951
1158974	8394	8409	8593	8608	AGTTATATTAGGTTCT	78	1952
1159007	995	1010	N/A	N/A	CGCCTCTTAAAGCACT	112	1953

Table 56

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	82	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	126	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	49	36
946399	230	245	196	211	CTGGAATGGCCAGCCT	85	1954
946408	3668	3683	3868	3883	GCACAGCGGTACACTC	91	1955
946415	5743	5758	5942	5957	AGAGAAGAATCCCCCC	72	1956

1156473	71	86	37	52	CGCTGCGCTTAAGAGG	90	1957
1156540	338	353	304	319	TATGAGCTTCAGACCT	109	1958
1156574	473	488	439	454	GCGAATGGCTTTGTCT	93	1959
1156608	519	534	485	500	GCCATGGAAAGCGAGT	91	1960
1156642	587	602	553	568	CCCGCACGGAAATTTT	83	1961
1156676	672	687	638	653	GCTCCCCGCCTGAGCC	92	1962
1156709	810	825	776	791	TGCGACTTGCTCCCAA	113	1963
1156743	867	882	833	848	AGGGACGGTTGAGAAG	86	1964
1156777	945	960	911	926	TACCACCTTTTGAAGG	87	1965
1156811	N/A	N/A	984	999	CAAAACCCCCGGAACT	100	1966
1156845	N/A	N/A	1107	1122	ACTTGAATGCAAACTA	89	1967
1156879	N/A	N/A	1199	1214	CCGCCGCCTTTGTGAG	75	1968
1156913	1043	1058	1243	1258	TTATAGACGGAGAACA	92	1969
1156947	1135	1150	1335	1350	TCTGCGGTTTCCTCAA	51	1970
1156981	1233	1248	1433	1448	CGTTAAAAACTTAACG	87	1971
1157014	1458	1473	1658	1673	GTTTAAGTCACCTTCA	37	1972
1157048	1564	1579	1764	1779	GTCATGGATTTCAAGG	48	1973
1157081	1715	1730	1915	1930	CGCCTTCCCGTACTTC	43	1974
1157115	2061	2076	2261	2276	TAAATTGATGGGCTTT	63	1975
1157149	2212	2227	2412	2427	TAAATTACACCAGTCC	56	1976
1157182	2327	2342	2527	2542	GATCTTGAATTACTTC	51	1977
1157215	2412	2427	2612	2627	TGTCAATTAATGCTAG	58	1978
1157249	2524	2539	2724	2739	TTGCTCGCTTGCTCCT	60	1979
1157283	2660	2675	2860	2875	TGCACTCGCTCCTTCC	67	1980
1157316	2719	2734	2919	2934	CTGCTCGCCTCCTCCG	84	1981
1157350	2801	2816	3001	3016	TCACGGATTTTTACCA	72	1982
1157384	2881	2896	3081	3096	TACGAAACTCCCCCAT	94	1983
1157417	2941	2956	3141	3156	AGAAACCTACAACACC	106	1984
1157450	3094	3109	3294	3309	ATTGTCTCAATTTGGC	37	1985
1157483	3201	3216	3401	3416	TACAAAACGAATTCAG	80	1986
1157517	3316	3331	3516	3531	GGATTCTAGACAGACC	56	1987
1157550	3396	3411	3596	3611	AACTGTAAACCTGTGG	108	1988
1157582	3565	3580	3765	3780	TGTTAAGACCATCCCA	91	1989
1157649	3811	3826	4011	4026	GGCCTACTCAAGCTCT	86	1990
1157683	3919	3934	4119	4134	CAATCCCAACCGTAAC	91	1991
1157716	4041	4056	4241	4256	TGGGAGTTACTTGCCA	81	1992
1157749	4129	4144	4329	4344	CCAAATTAATGCACTG	87	1993
1157782	4246	4261	4446	4461	GTAGTTAATGTCAGCC	41	1994
1157816	4388	4403	4588	4603	AATCCCTTCAGGATCA	92	1995
1157849	4597	4612	4796	4811	AGCTGAACTATCACAA	95	1996
1157882	4717	4732	4916	4931	TAGGCCATCATACTGC	94	1997
1157915	4803	4818	5002	5017	TTATGCTTATTCCCCA	25	1998
1157949	4891	4906	5090	5105	TCCGTAACTTTAAATT	64	1999

1157983	4983	4998	5182	5197	TGAGATGGACATTGCC	26	2000
1158016	5105	5120	5304	5319	CCTCAATCCACTTGAT	102	2001
1158049	5171	5186	5370	5385	CAACTCTTCTGATAAC	84	2002
1158082	5260	5275	5459	5474	ACTTATCCCTAACATG	87	2003
1158114	5367	5382	5566	5581	AAAAGGCTCGATGGAA	89	2004
1158147	5472	5487	5671	5686	GATCACTTTAGAGGCT	108	2005
1158181	5557	5572	5756	5771	TCTAACAGCACATCAT	78	2006
1158247	5829	5844	6028	6043	CCTGCCTTAAAGTTAC	80	2007
1158280	5947	5962	6146	6161	TGATCATAATCTCCCA	57	2008
1158314	6071	6086	6270	6285	TAAGATTGTAAGCATT	77	2009
1158348	6116	6131	6315	6330	CCTTCCCTATATAAGG	141	2010
1158381	6266	6281	6465	6480	GCTGATAAACTCACTG	45	2011
1158414	6421	6436	6620	6635	AACAGTACTGCATTTA	64	2012
1158446	6504	6519	6703	6718	ATCACTACTCCAAGCA	80	2013
1158480	6606	6621	6805	6820	GCAAAATGTACTCAGC	77	2014
1158511	6846	6861	7045	7060	TCCTGCATGTAAGAAT	85	2015
1158543	7019	7034	7218	7233	TGAATTCAACTGGAAG	64	2016
1158577	7134	7149	7333	7348	GTTACTCCAGCATAAA	100	2017
1158609	7260	7275	7459	7474	CTCCATGGTTGTCCTA	61	2018
1158643	7388	7403	7587	7602	TTCGGATGCTTCACTC	52	2019
1158676	7488	7503	7687	7702	CTTCAAGCACCGCTTG	79	2020
1158710ǂ	7615	7630	7814	7829	CTGTGCTAGATCAAAA	72	2021
1158744	7686	7701	7885	7900	TTGAAACCGATTATGG	58	2022
1158777	7751	7766	7950	7965	CAGGCAAATTAATGGC	77	2023
1158810	7825	7840	8024	8039	GGTTTTAGTCACTGGA	15	2024
1158843	7920	7935	8119	8134	CTCAAATGCCTATCTT	81	2025
1158876	8028	8043	8227	8242	TGGAGATCAGCTTCCG	82	2026
1158908	8185	8200	8384	8399	TTTGAACCCCGTCCTG	94	2027
1158941	8309	8324	8508	8523	AAGATATTGTGCTGTT	87	2028
1158975	8395	8410	8594	8609	CAGTTATATTAGGTTC	92	2029
1159008	996	1011	N/A	N/A	CCGCCTCTTAAAGCAC	109	2030

Table 57

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	105	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	123	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	51	36
1156475	113	128	79	94	GCTGAGGCTTCCCGGC	85	2031
1156508	235	250	201	216	ACCACCTGGAATGGCC	85	2032

1156542	341	356	307	322	AGGTATGAGCTTCAGA	99	2033
1156576	475	490	441	456	AAGCGAATGGCTTTGT	94	2034
1156610	521	536	487	502	TCGCCATGGAAAGCGA	85	2035
1156644	590	605	556	571	CGGCCCGCACGGAAAT	76	2036
1156678	680	695	646	661	ACAGAGCTGCTCCCCG	82	2037
1156711	812	827	778	793	CCTGCGACTTGCTCCC	80	2038
1156745	870	885	836	851	TGCAGGGACGGTTGAG	122	2039
1156779	949	964	915	930	AGTTTACCACCTTTTG	77	2040
1156813	N/A	N/A	986	1001	CACAAAACCCCCGGAA	81	2041
1156847	N/A	N/A	1112	1127	ATGGAACTTGAATGCA	99	2042
1156881	N/A	N/A	1205	1220	CACCTTCCGCCGCCTT	125	2043
1156915	1045	1060	1245	1260	ATTTATAGACGGAGAA	91	2044
1156949	1138	1153	1338	1353	TTATCTGCGGTTTCCT	55	2045
1156983	1286	1301	1486	1501	CTACTCTTCTAAGTCT	51	2046
1157016	1460	1475	1660	1675	CTGTTTAAGTCACCTT	24	2047
1157050	1579	1594	1779	1794	CGCAATTCTCCCTGCG	77	2048
1157083	1718	1733	1918	1933	CTTCGCCTTCCCGTAC	65	2049
1157117	2063	2078	2263	2278	ATTAAATTGATGGGCT	80	2050
1157151	2239	2254	2439	2454	CCAAAAGCCTTCTGCC	66	2051
1157184	2334	2349	2534	2549	TACTCTTGATCTTGAA	54	2052
1157217	2415	2430	2615	2630	AGCTGTCAATTAATGC	90	2053
1157251	2536	2551	2736	2751	ACGAACTGCTGCTTGC	34	2054
1157285	2663	2678	2863	2878	AATTGCACTCGCTCCT	71	2055
1157318	2735	2750	2935	2950	CCTCTACGCACAACGC	41	2056
1157352	2803	2818	3003	3018	CCTCACGGATTTTTAC	101	2057
1157386	2883	2898	3083	3098	AGTACGAAACTCCCCC	72	2058
1157419	2960	2975	3160	3175	GAGTATAAGCCTGAAA	84	2059
1157452	3112	3127	3312	3327	GCTTACAGATTTGCTG	92	2060
1157485	3208	3223	3408	3423	CTACATTTACAAAACG	71	2061
1157519	3318	3333	3518	3533	TAGGATTCTAGACAGA	44	2062
1157552	3417	3432	3617	3632	AGAACTGCTCTAGTTT	106	2063
1157584	3567	3582	3767	3782	CCTGTTAAGACCATCC	60	2064
1157617	3672	3687	3872	3887	AACAGCACAGCGGTAC	98	2065
1157651	3813	3828	4013	4028	TTGGCCTACTCAAGCT	108	2066
1157685	3922	3937	4122	4137	CACCAATCCCAACCGT	95	2067
1157718	4043	4058	4243	4258	ATTGGGAGTTACTTGC	37	2068
1157751	4132	4147	4332	4347	TGCCCAAATTAATGCA	71	2069
1157784	4249	4264	4449	4464	ATTGTAGTTAATGTCA	50	2070
1157818	4398	4413	4598	4613	CATCAGAAGAAATCCC	83	2071
1157851	4602	4617	4801	4816	ATTCAAGCTGAACTAT	90	2072
1157884	4720	4735	4919	4934	ATCTAGGCCATCATAC	68	2073
1157917	4806	4821	5005	5020	GGGTTATGCTTATTCC	72	2074
1157951	4895	4910	5094	5109	AGATTCCGTAACTTTA	22	2075

1157985	5016	5031	5215	5230	CGCTTTTATTCTGCTT	94	2076
1158018	5109	5124	5308	5323	GCCTCCTCAATCCACT	84	2077
1158051	5213	5228	5412	5427	TTAACAGCTGCCTGCT	44	2078
1158084	5262	5277	5461	5476	GCACTTATCCCTAACA	42	2079
1158116	5369	5384	5568	5583	TAAAAAGGCTCGATGG	61	2080
1158149	5476	5491	5675	5690	CACTGATCACTTTAGA	59	2081
1158183	5562	5577	5761	5776	CTGATTCTAACAGCAC	45	2082
1158216	5745	5760	5944	5959	TTAGAGAAGAATCCCC	69	2083
1158249	5870	5885	6069	6084	ATTATATGCTCATCAC	49	2084
1158282	5950	5965	6149	6164	CTCTGATCATAATCTC	65	2085
1158316	6073	6088	6272	6287	TCTAAGATTGTAAGCA	47	2086
1158350	6168	6183	6367	6382	ATGAAATGCCTCTGCA	87	2087
1158383	6270	6285	6469	6484	GTATGCTGATAAACTC	48	2088
1158416	6426	6441	6625	6640	ATCAGAACAGTACTGC	65	2089
1158448	6507	6522	6706	6721	ACAATCACTACTCCAA	69	2090
1158482	6669	6684	6868	6883	AAGGCTTCAGTCCCCT	86	2091
1158513	6853	6868	7052	7067	TGAGTGTTCCTGCATG	64	2092
1158545	7021	7036	7220	7235	GGTGAATTCAACTGGA	51	2093
1158579	7136	7151	7335	7350	CAGTTACTCCAGCATA	76	2094
1158611	7267	7282	7466	7481	AGGAAGGCTCCATGGT	89	2095
1158645	7390	7405	7589	7604	CCTTCGGATGCTTCAC	42	2096
1158678	7491	7506	7690	7705	CCCCTTCAAGCACCGC	86	2097
1158712‡	7622	7637	7821	7836	GAAGGGTCTGTGCTAG	60	2098
1158746	7688	7703	7887	7902	CCTTGAAACCGATTAT	64	2099
1158779	7753	7768	7952	7967	TGCAGGCAAATTAATG	89	2100
1158812	7835	7850	8034	8049	GGTTTAAGTTGGTTTT	10	2101
1158845	7925	7940	8124	8139	AGCCACTCAAATGCCT	72	2102
1158878	8032	8047	8231	8246	GCATTGGAGATCAGCT	89	2103
1158910	8187	8202	8386	8401	GATTTGAACCCCGTCC	102	2104
1158943	8311	8326	8510	8525	CAAAGATATTGTGCTG	110	2105
1158977	8397	8412	8596	8611	GGCAGTTATATTAGGT	84	2106
1159010	998	1013	N/A	N/A	CGCCGCCTCTTAAAGC	87	2107

Table 58

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	113	18
556033	3320	3335	3520	3535	TTTAGGATTCTAGACA	75	2108
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	124	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	31	36

568503	7762	7777	7961	7976	TTAACAATTTGCAGGC	34	2109
946409	3936	3951	4136	4151	ACCTAAACCCACCCCA	101	2110
1156477	119	134	85	100	AGGCGAGCTGAGGCTT	81	2111
1156510	238	253	204	219	ACCACCACCTGGAATG	78	2112
1156544	343	358	309	324	TTAGGTATGAGCTTCA	82	2113
1156578	477	492	443	458	CTAAGCGAATGGCTTT	78	2114
1156612	524	539	490	505	AAATCGCCATGGAAAG	99	2115
1156646	592	607	558	573	CACGGCCCGCACGGAA	101	2116
1156680	698	713	664	679	ACGCCTCAATCCCACA	73	2117
1156713	815	830	781	796	AGTCCTGCGACTTGCT	74	2118
1156747	874	889	840	855	GCCTTGCAGGGACGGT	110	2119
1156781	951	966	917	932	ATAGTTTACCACCTTT	61	2120
1156815	N/A	N/A	988	1003	CTCACAAAACCCCCGG	82	2121
1156849	N/A	N/A	1114	1129	TTATGGAACTTGAATG	93	2122
1156883	1008	1023	1208	1223	GATCACCTTCCGCCGC	94	2123
1156917	1048	1063	1248	1263	CGTATTTATAGACGGA	109	2124
1156951	1140	1155	1340	1355	ACTTATCTGCGGTTTC	29	2125
1156985	1289	1304	1489	1504	ATGCTACTCTTCTAAG	60	2126
1157018	1467	1482	1667	1682	CTTTAAGCTGTTTAAG	104	2127
1157052	1582	1597	1782	1797	TGACGCAATTCTCCCT	67	2128
1157085	1726	1741	1926	1941	ATTCTTTTCTTCGCCT	52	2129
1157119	2077	2092	2277	2292	CTGCACCACCAGAAAT	80	2130
1157153	2271	2286	2471	2486	TATTTAAGGCCTTCCA	38	2131
1157186	2336	2351	2536	2551	ATTACTCTTGATCTTG	29	2132
1157219	2423	2438	2623	2638	CCTGGGTCAGCTGTCA	49	2133
1157253	2538	2553	2738	2753	CCACGAACTGCTGCTT	46	2134
1157287	2665	2680	2865	2880	CAAATTGCACTCGCTC	66	2135
1157320	2737	2752	2937	2952	ATCCTCTACGCACAAC	58	2136
1157354	2807	2822	3007	3022	CCGACCTCACGGATTT	61	2137
1157388	2885	2900	3085	3100	TCAGTACGAAACTCCC	59	2138
1157421	2962	2977	3162	3177	ATGAGTATAAGCCTGA	45	2139
1157454	3115	3130	3315	3330	ACTGCTTACAGATTTG	39	2140
1157487	3223	3238	3423	3438	TTACACATCCAAACTC	99	2141
1157554	3419	3434	3619	3634	TGAGAACTGCTCTAGT	65	2142
1157586	3569	3584	3769	3784	TCCCTGTTAAGACCAT	73	2143
1157619	3675	3690	3875	3890	GCCAACAGCACAGCGG	92	2144
1157653	3817	3832	4017	4032	ACATTTGGCCTACTCA	54	2145
1157720	4045	4060	4245	4260	TCATTGGGAGTTACTT	43	2146
1157753	4143	4158	4343	4358	GACACTTTCCTTGCCC	52	2147
1157786	4254	4269	4454	4469	CCATAATTGTAGTTAA	93	2148
1157820	4404	4419	4604	4619	AGCTACCATCAGAAGA	66	2149
1157853	4604	4619	4803	4818	ACATTCAAGCTGAACT	105	2150
1157886	4724	4739	4923	4938	CTGCATCTAGGCCATC	35	2151

1157919	4808	4823	5007	5022	CAGGGTTATGCTTATT	25	2152
1157953	4897	4912	5096	5111	GTAGATTCCGTAACTT	27	2153
1157987	5018	5033	5217	5232	TTCGCTTTTATTCTGC	31	2154
1158020	5128	5143	5327	5342	AACATTGGCACACAGC	46	2155
1158053	5215	5230	5414	5429	TGTTAACAGCTGCCTG	61	2156
1158086	5264	5279	5463	5478	AAGCACTTATCCCTAA	75	2157
1158118	5371	5386	5570	5585	TTTAAAAAGGCTCGAT	72	2158
1158151	5481	5496	5680	5695	CAAGGCACTGATCACT	52	2159
1158185	5567	5582	5766	5781	AACATCTGATTCTAAC	73	2160
1158218	5767	5782	5966	5981	CGCAGACAAAGTTTCT	43	2161
1158251	5880	5895	6079	6094	GCCTGGAATTATTATA	69	2162
1158284	5952	5967	6151	6166	TACTCTGATCATAATC	83	2163
1158318	6075	6090	6274	6289	ACTCTAAGATTGTAAG	75	2164
1158352	6171	6186	6370	6385	AGGATGAAATGCCTCT	78	2165
1158385	6273	6288	6472	6487	TGAGTATGCTGATAAA	59	2166
1158418	6431	6446	6630	6645	GCGGGATCAGAACAGT	60	2167
1158450	6509	6524	6708	6723	CAACAATCACTACTCC	84	2168
1158484	6673	6688	6872	6887	ACTAAAGGCTTCAGTC	74	2169
1158515	6878	6893	7077	7092	TGGCCCTTCGCATACG	72	2170
1158547	7026	7041	7225	7240	CCACTGGTGAATTCAA	45	2171
1158581	7142	7157	7341	7356	ACATGCCAGTTACTCC	61	2172
1158613	7273	7288	7472	7487	TGCCACAGGAAGGCTC	110	2173
1158647	7392	7407	7591	7606	TTCCTTCGGATGCTTC	50	2174
1158680	7493	7508	7692	7707	CTCCCCTTCAAGCACC	96	2175
1158714	7642	7657	7841	7856	GCTGCATCGAGGTGAG	76	2176
1158748	7690	7705	7889	7904	TACCTTGAAACCGATT	64	2177
1158814	7839	7854	8038	8053	TACTGGTTTAAGTTGG	33	2178
1158847	7938	7953	8137	8152	CAAAAGCCCTCTCAGC	114	2179
1158880	8034	8049	8233	8248	GAGCATTGGAGATCAG	71	2180
1158912	8189	8204	8388	8403	GGGATTTGAACCCCGT	101	2181
1158945	8322	8337	8521	8536	TGTATATAGTTCAAAG	91	2182
1158979	8402	8417	8601	8616	GACAAGGCAGTTATAT	99	2183
1159012	1001	1016	N/A	N/A	TTCCGCCGCCTCTTAA	78	2184

Table 59

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	92	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	112	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	37	36

1156476	114	129	80	95	AGCTGAGGCTTCCCGG	88	2185
1156509	236	251	202	217	CACCACCTGGAATGGC	92	2186
1156543	342	357	308	323	TAGGTATGAGCTTCAG	96	2187
1156577	476	491	442	457	TAAGCGAATGGCTTTG	93	2188
1156611	523	538	489	504	AATCGCCATGGAAAGC	104	2189
1156645	591	606	557	572	ACGGCCCGCACGGAAA	84	2190
1156679	696	711	662	677	GCCTCAATCCCACACC	98	2191
1156712	813	828	779	794	TCCTGCGACTTGCTCC	85	2192
1156746	871	886	837	852	TTGCAGGGACGGTTGA	110	2193
1156780	950	965	916	931	TAGTTTACCACCTTTT	85	2194
1156814	N/A	N/A	987	1002	TCACAAAACCCCCGGA	84	2195
1156848	N/A	N/A	1113	1128	TATGGAACTTGAATGC	76	2196
1156882	1007	1022	1207	1222	ATCACCTTCCGCCGCC	85	2197
1156916	1047	1062	1247	1262	GTATTTATAGACGGAG	100	2198
1156950	1139	1154	1339	1354	CTTATCTGCGGTTTCC	38	2199
1156984	1288	1303	1488	1503	TGCTACTCTTCTAAGT	81	2200
1157017	1462	1477	1662	1677	AGCTGTTTAAGTCACC	38	2201
1157051	1581	1596	1781	1796	GACGCAATTCTCCCTG	73	2202
1157084	1720	1735	1920	1935	TTCTTCGCCTTCCCGT	34	2203
1157118	2064	2079	2264	2279	AATTAAATTGATGGGC	83	2204
1157152	2270	2285	2470	2485	ATTTAAGGCCTTCCAA	70	2205
1157185	2335	2350	2535	2550	TTACTCTTGATCTTGA	34	2206
1157218	2422	2437	2622	2637	CTGGGTCAGCTGTCAA	67	2207
1157252	2537	2552	2737	2752	CACGAACTGCTGCTTG	45	2208
1157286	2664	2679	2864	2879	AAATTGCACTCGCTCC	72	2209
1157319	2736	2751	2936	2951	TCCTCTACGCACAACG	89	2210
1157353	2806	2821	3006	3021	CGACCTCACGGATTTT	84	2211
1157387	2884	2899	3084	3099	CAGTACGAAACTCCCC	70	2212
1157420	2961	2976	3161	3176	TGAGTATAAGCCTGAA	75	2213
1157453	3114	3129	3314	3329	CTGCTTACAGATTTGC	51	2214
1157486	3218	3233	3418	3433	CATCCAAACTCTACAT	77	2215
1157520	3319	3334	3519	3534	TTAGGATTCTAGACAG	57	2216
1157553	3418	3433	3618	3633	GAGAACTGCTCTAGTT	66	2217
1157585	3568	3583	3768	3783	CCCTGTTAAGACCATC	79	2218
1157618	3673	3688	3873	3888	CAACAGCACAGCGGTA	105	2219
1157652	3816	3831	4016	4031	CATTTGGCCTACTCAA	66	2220
1157686	3923	3938	4123	4138	CCACCAATCCCAACCG	74	2221
1157719	4044	4059	4244	4259	CATTGGGAGTTACTTG	68	2222
1157752	4141	4156	4341	4356	CACTTTCCTTGCCCAA	31	2223
1157785	4250	4265	4450	4465	AATTGTAGTTAATGTC	64	2224
1157819	4403	4418	4603	4618	GCTACCATCAGAAGAA	78	2225
1157852	4603	4618	4802	4817	CATTCAAGCTGAACTA	61	2226
1157885	4722	4737	4921	4936	GCATCTAGGCCATCAT	43	2227

1157918	4807	4822	5006	5021	AGGGTTATGCTTATTC	37	2228
1157952	4896	4911	5095	5110	TAGATTCCGTAACTTT	42	2229
1157986	5017	5032	5216	5231	TCGCTTTTATTCTGCT	78	2230
1158019	5126	5141	5325	5340	CATTGGCACACAGCAC	79	2231
1158052	5214	5229	5413	5428	GTTAACAGCTGCCTGC	93	2232
1158085	5263	5278	5462	5477	AGCACTTATCCCTAAC	60	2233
1158117	5370	5385	5569	5584	TTAAAAAGGCTCGATG	79	2234
1158150	5477	5492	5676	5691	GCACTGATCACTTTAG	37	2235
1158184	5564	5579	5763	5778	ATCTGATTCTAACAGC	60	2236
1158217	5747	5762	5946	5961	GATTAGAGAAGAATCC	86	2237
1158250	5876	5891	6075	6090	GGAATTATTATATGCT	46	2238
1158283	5951	5966	6150	6165	ACTCTGATCATAATCT	65	2239
1158317	6074	6089	6273	6288	CTCTAAGATTGTAAGC	84	2240
1158351	6170	6185	6369	6384	GGATGAAATGCCTCTG	76	2241
1158384	6272	6287	6471	6486	GAGTATGCTGATAAAC	63	2242
1158417	6430	6445	6629	6644	CGGGATCAGAACAGTA	76	2243
1158449	6508	6523	6707	6722	AACAATCACTACTCCA	74	2244
1158483	6672	6687	6871	6886	CTAAAGGCTTCAGTCC	77	2245
1158514	6855	6870	7054	7069	GCTGAGTGTTCCTGCA	78	2246
1158546	7022	7037	7221	7236	TGGTGAATTCAACTGG	67	2247
1158580	7141	7156	7340	7355	CATGCCAGTTACTCCA	67	2248
1158612	7269	7284	7468	7483	ACAGGAAGGCTCCATG	75	2249
1158646	7391	7406	7590	7605	TCCTTCGGATGCTTCA	44	2250
1158679	7492	7507	7691	7706	TCCCCTTCAAGCACCG	81	2251
1158713	7640	7655	7839	7854	TGCATCGAGGTGAGGG	79	2252
1158747	7689	7704	7888	7903	ACCTTGAAACCGATTA	55	2253
1158780	7761	7776	7960	7975	TAACAATTTGCAGGCA	40	2254
1158813	7837	7852	8036	8051	CTGGTTTAAGTTGGTT	39	2255
1158846	7935	7950	8134	8149	AAGCCCTCTCAGCCAC	62	2256
1158879	8033	8048	8232	8247	AGCATTGGAGATCAGC	64	2257
1158911	8188	8203	8387	8402	GGATTTGAACCCCGTC	70	2258
1158944	8314	8329	8513	8528	GTTCAAAGATATTGTG	100	2259
1158978	8398	8413	8597	8612	AGGCAGTTATATTAGG	74	2260
1159011	1000	1015	N/A	N/A	TCCGCCGCCTCTTAAA	74	2261

Table 60

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	83	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	99	32

559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	27	36
1156474	99	114	65	80	GCGCCGGGCTTCTGCG	71	2262
1156507	232	247	198	213	ACCTGGAATGGCCAGC	79	2263
1156541	339	354	305	320	GTATGAGCTTCAGACC	106	2264
1156575	474	489	440	455	AGCGAATGGCTTTGTC	95	2265
1156609	520	535	486	501	CGCCATGGAAAGCGAG	80	2266
1156643	588	603	554	569	GCCCGCACGGAAATTT	77	2267
1156677	673	688	639	654	TGCTCCCCGCCTGAGC	76	2268
1156710	811	826	777	792	CTGCGACTTGCTCCCA	90	2269
1156744	869	884	835	850	GCAGGGACGGTTGAGA	92	2270
1156778	948	963	914	929	GTTTACCACCTTTTGA	97	2271
1156812	N/A	N/A	985	1000	ACAAAACCCCCGGAAC	253	2272
1156846	N/A	N/A	1111	1126	TGGAACTTGAATGCAA	90	2273
1156880	N/A	N/A	1203	1218	CCTTCCGCCGCCTTTG	79	2274
1156914	1044	1059	1244	1259	TTTATAGACGGAGAAC	106	2275
1156948	1136	1151	1336	1351	ATCTGCGGTTTCCTCA	42	2276
1156982	1247	1262	1447	1462	AGCTATTAAAATTACG	78	2277
1157015	1459	1474	1659	1674	TGTTTAAGTCACCTTC	26	2278
1157049	1565	1580	1765	1780	CGTCATGGATTTCAAG	60	2279
1157082	1717	1732	1917	1932	TTCGCCTTCCCGTACT	37	2280
1157116	2062	2077	2262	2277	TTAAATTGATGGGCTT	78	2281
1157150	2213	2228	2413	2428	TTAAATTACACCAGTC	50	2282
1157183	2333	2348	2533	2548	ACTCTTGATCTTGAAT	57	2283
1157216	2414	2429	2614	2629	GCTGTCAATTAATGCT	76	2284
1157250	2535	2550	2735	2750	CGAACTGCTGCTTGCT	60	2285
1157284	2661	2676	2861	2876	TTGCACTCGCTCCTTC	67	2286
1157317	2721	2736	2921	2936	GCCTGCTCGCCTCCTC	59	2287
1157351	2802	2817	3002	3017	CTCACGGATTTTTACC	93	2288
1157385	2882	2897	3082	3097	GTACGAAACTCCCCCA	62	2289
1157418	2942	2957	3142	3157	GAGAAACCTACAACAC	89	2290
1157451	3100	3115	3300	3315	GCTGAAATTGTCTCAA	55	2291
1157484	3202	3217	3402	3417	TTACAAAACGAATTCA	90	2292
1157518	3317	3332	3517	3532	AGGATTCTAGACAGAC	28	2293
1157551	3411	3426	3611	3626	GCTCTAGTTTCTATAA	73	2294
1157583	3566	3581	3766	3781	CTGTTAAGACCATCCC	54	2295
1157616	3670	3685	3870	3885	CAGCACAGCGGTACAC	93	2296
1157650	3812	3827	4012	4027	TGGCCTACTCAAGCTC	108	2297
1157684	3921	3936	4121	4136	ACCAATCCCAACCGTA	82	2298
1157717	4042	4057	4242	4257	TTGGGAGTTACTTGCC	30	2299
1157750	4130	4145	4330	4345	CCCAAATTAATGCACT	49	2300
1157783	4247	4262	4447	4462	TGTAGTTAATGTCAGC	33	2301
1157817	4390	4405	4590	4605	GAAATCCCTTCAGGAT	86	2302
1157850	4599	4614	4798	4813	CAAGCTGAACTATCAC	73	2303

1157883	4719	4734	4918	4933	TCTAGGCCATCATACT	60	2304
1157916	4805	4820	5004	5019	GGTTATGCTTATTCCC	63	2305
1157950	4894	4909	5093	5108	GATTCCGTAACTTTAA	31	2306
1157984	4984	4999	5183	5198	TTGAGATGGACATTGC	13	2307
1158017	5106	5121	5305	5320	TCCTCAATCCACTTGA	56	2308
1158050	5173	5188	5372	5387	AGCAACTCTTCTGATA	70	2309
1158083	5261	5276	5460	5475	CACTTATCCCTAACAT	90	2310
1158115	5368	5383	5567	5582	AAAAAGGCTCGATGGA	48	2311
1158148	5475	5490	5674	5689	ACTGATCACTTTAGAG	64	2312
1158182	5560	5575	5759	5774	GATTCTAACAGCACAT	69	2313
1158215	5744	5759	5943	5958	TAGAGAAGAATCCCCC	66	2314
1158248	5863	5878	6062	6077	GCTCATCACTTTATGA	90	2315
1158281	5949	5964	6148	6163	TCTGATCATAATCTCC	61	2316
1158315	6072	6087	6271	6286	CTAAGATTGTAAGCAT	72	2317
1158349	6117	6132	6316	6331	CCCTTCCCTATATAAG	95	2318
1158382	6267	6282	6466	6481	TGCTGATAAACTCACT	54	2319
1158415	6422	6437	6621	6636	GAACAGTACTGCATTT	72	2320
1158447	6505	6520	6704	6719	AATCACTACTCCAAGC	71	2321
1158481	6609	6624	6808	6823	CCAGCAAAATGTACTC	54	2322
1158512	6851	6866	7050	7065	AGTGTTCCTGCATGTA	69	2323
1158544	7020	7035	7219	7234	GTGAATTCAACTGGAA	50	2324
1158578	7135	7150	7334	7349	AGTTACTCCAGCATAA	69	2325
1158610	7264	7279	7463	7478	AAGGCTCCATGGTTGT	68	2326
1158644	7389	7404	7588	7603	CTTCGGATGCTTCACT	67	2327
1158677	7490	7505	7689	7704	CCCTTCAAGCACCGCT	72	2328
1158711‡	7616	7631	7815	7830	TCTGTGCTAGATCAAA	39	2329
1158745	7687	7702	7886	7901	CTTGAAACCGATTATG	62	2330
1158778	7752	7767	7951	7966	GCAGGCAAATTAATGG	55	2331
1158811	7831	7846	8030	8045	TAAGTTGGTTTTAGTC	22	2332
1158844	7924	7939	8123	8138	GCCACTCAAATGCCTA	82	2333
1158877	8030	8045	8229	8244	ATTGGAGATCAGCTTC	48	2334
1158909	8186	8201	8385	8400	ATTTGAACCCCGTCCT	69	2335
1158942	8310	8325	8509	8524	AAAGATATTGTGCTGT	89	2336
1158976	8396	8411	8595	8610	GCAGTTATATTAGGTT	85	2337
1159009	997	1012	N/A	N/A	GCCGCCTCTTAAAGCA	111	2338

Table 61

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	82	18

556094	6674	6689	6873	6888	GACTAAAGGCTTCAGT	85	2339
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	108	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	39	36
568456	3118	3133	3318	3333	CAAACTGCTTACAGAT	69	2340
1156478	120	135	86	101	CAGGCGAGCTGAGGCT	93	2341
1156511	243	258	209	224	TAAATACCACCACCTG	98	2342
1156545	344	359	310	325	GTTAGGTATGAGCTTC	85	2343
1156579	478	493	444	459	ACTAAGCGAATGGCTT	109	2344
1156613	525	540	491	506	CAAATCGCCATGGAAA	86	2345
1156647	593	608	559	574	CCACGGCCCGCACGGA	94	2346
1156681	711	726	677	692	CCACTCTTGGAAAACG	77	2347
1156714	818	833	784	799	TGCAGTCCTGCGACTT	85	2348
1156748	875	890	841	856	AGCCTTGCAGGGACGG	121	2349
1156782	952	967	918	933	TATAGTTTACCACCTT	86	2350
1156816	N/A	N/A	989	1004	CCTCACAAAACCCCCG	113	2351
1156850	N/A	N/A	1115	1130	CTTATGGAACTTGAAT	105	2352
1156884	1011	1026	1211	1226	TTCGATCACCTTCCGC	88	2353
1156918	1062	1077	1262	1277	CAGCTCGGGCGAGGCG	87	2354
1156952	1141	1156	1341	1356	AACTTATCTGCGGTTT	94	2355
1156986	1293	1308	1493	1508	CCTCATGCTACTCTTC	46	2356
1157019	1492	1507	1692	1707	AATCACCTACAACTTT	74	2357
1157053	1583	1598	1783	1798	ATGACGCAATTCTCCC	85	2358
1157086	1727	1742	1927	1942	TATTCTTTCTTCGCC	51	2359
1157120	2080	2095	2280	2295	CTTCTGCACCACCAGA	87	2360
1157154	2273	2288	2473	2488	TATATTTAAGGCCTTC	55	2361
1157187	2337	2352	2537	2552	AATTACTCTTGATCTT	49	2362
1157220	2424	2439	2624	2639	ACCTGGGTCAGCTGTC	86	2363
1157254	2539	2554	2739	2754	ACCACGAACTGCTGCT	48	2364
1157288	2666	2681	2866	2881	CCAAATTGCACTCGCT	64	2365
1157321	2739	2754	2939	2954	GGATCCTCTACGCACA	81	2366
1157355	2808	2823	3008	3023	GCCGACCTCACGGATT	55	2367
1157389	2886	2901	3086	3101	CTCAGTACGAAACTCC	70	2368
1157422	2963	2978	3163	3178	CATGAGTATAAGCCTG	50	2369
1157488	3226	3241	3426	3441	CAGTTACACATCCAAA	55	2370
1157521	3321	3336	3521	3536	CTTTAGGATTCTAGAC	93	2371
1157555	3420	3435	3620	3635	GTGAGAACTGCTCTAG	64	2372
1157587	3624	3639	3824	3839	TATAGCATCTGTGGAA	80	2373
1157620	3676	3691	3876	3891	TGCCAACAGCACAGCG	99	2374
1157654	3818	3833	4018	4033	AACATTTGGCCTACTC	58	2375
1157687	3937	3952	4137	4152	TACCTAAACCCACCCC	94	2376
1157721	4046	4061	4246	4261	ATCATTGGGAGTTACT	46	2377
1157754	4144	4159	4344	4359	TGACACTTTCCTTGCC	34	2378
1157787	4255	4270	4455	4470	CCCATAATTGTAGTTA	55	2379

1157821	4410	4425	4610	4625	TACAAAAGCTACCATC	88	2380
1157854	4605	4620	4804	4819	GACATTCAAGCTGAAC	47	2381
1157887	4726	4741	4925	4940	CTCTGCATCTAGGCCA	60	2382
1157920	4809	4824	5008	5023	TCAGGGTTATGCTTAT	36	2383
1157954	4898	4913	5097	5112	GGTAGATTCCGTAACT	40	2384
1157988	5045	5060	5244	5259	TAATGTAGTGTAACAT	71	2385
1158021	5132	5147	5331	5346	ACGAAACATTGGCACA	38	2386
1158054	5216	5231	5415	5430	CTGTTAACAGCTGCCT	48	2387
1158087	5266	5281	5465	5480	ATAAGCACTTATCCCT	50	2388
1158119	5372	5387	5571	5586	TTTTAAAAAGGCTCGA	88	2389
1158152	5482	5497	5681	5696	TCAAGGCACTGATCAC	51	2390
1158186	5571	5586	5770	5785	CAGTAACATCTGATTC	43	2391
1158219	5768	5783	5967	5982	TCGCAGACAAAGTTTC	69	2392
1158252	5882	5897	6081	6096	GTGCCTGGAATTATTA	61	2393
1158285	5957	5972	6156	6171	CCTTTTACTCTGATCA	44	2394
1158319	6076	6091	6275	6290	CACTCTAAGATTGTAA	67	2395
1158353	6173	6188	6372	6387	GAAGGATGAAATGCCT	93	2396
1158386	6274	6289	6473	6488	TTGAGTATGCTGATAA	39	2397
1158419	6432	6447	6631	6646	AGCGGGATCAGAACAG	57	2398
1158451	6510	6525	6709	6724	TCAACAATCACTACTC	84	2399
1158516	6898	6913	7097	7112	CTTACTGGGTCTGGCT	59	2400
1158548	7033	7048	7232	7247	ATTTTGTCCACTGGTG	50	2401
1158582	7145	7160	7344	7359	CTCACATGCCAGTTAC	49	2402
1158614	7289	7304	7488	7503	GCTTTGTTGTCTCTCC	7	2403
1158648	7394	7409	7593	7608	CATTCCTTCGGATGCT	62	2404
1158681	7512	7527	7711	7726	GCCCGCTTTCCCCCTT	129	2405
1158715	7648	7663	7847	7862	CTACTGGCTGCATCGA	46	2406
1158749	7691	7706	7890	7905	TTACCTTGAAACCGAT	69	2407
1158781	7763	7778	7962	7977	GTTAACAATTTGCAGG	60	2408
1158815	7840	7855	8039	8054	TTACTGGTTTAAGTTG	76	2409
1158848	7940	7955	8139	8154	CCCAAAAGCCCTCTCA	88	2410
1158881	8035	8050	8234	8249	AGAGCATTGGAGATCA	80	2411
1158913	8190	8205	8389	8404	AGGGATTTGAACCCCG	103	2412
1158946	8324	8339	8523	8538	GATGTATATAGTTCAA	93	2413
1158980	8419	8434	8618	8633	GGCTATTACCTGAAAA	94	2414
1159013	1002	1017	N/A	N/A	CTTCCGCCGCCTCTTA	91	2415

Table 62

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	87	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	123	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	45	36
946419	6899	6914	7098	7113	TCTTACTGGGTCTGGC	55	2416
1156479	121	136	87	102	TCAGGCGAGCTGAGGC	93	2417
1156512	244	259	210	225	CTAAATACCACCACCT	88	2418
1156546	345	360	311	326	GGTTAGGTATGAGCTT	92	2419
1156580	480	495	446	461	CAACTAAGCGAATGGC	76	2420
1156614	526	541	492	507	GCAAATCGCCATGGAA	79	2421
1156648	594	609	560	575	CCCACGGCCCGCACGG	86	2422
1156682	717	732	683	698	GAAAACCCACTCTTGG	90	2423
1156715	825	840	791	806	AACTGCTTGCAGTCCT	95	2424
1156749	889	904	855	870	CGCAACTGAGCCCCAG	82	2425
1156783	953	968	919	934	GTATAGTTTACCACCT	91	2426
1156817	N/A	N/A	999	1014	TCATCAAACACCTCAC	108	2427
1156851	N/A	N/A	1116	1131	GCTTATGGAACTTGAA	90	2428
1156885	1012	1027	1212	1227	ATTCGATCACCTTCCG	81	2429
1156919	1064	1079	1264	1279	CACAGCTCGGGCGAGG	75	2430
1156953	1142	1157	1342	1357	AAACTTATCTGCGGTT	81	2431
1156987	1327	1342	1527	1542	CCGTCATGTTTTAGAA	42	2432
1157020	1510	1525	1710	1725	TCGCCTTCAAATTATT	65	2433
1157054	1584	1599	1784	1799	AATGACGCAATTCTCC	79	2434
1157087	1728	1743	1928	1943	CTATTCTTTTCTTCGC	63	2435
1157121	2084	2099	2284	2299	CTAACTTCTGCACCAC	62	2436
1157155	2274	2289	2474	2489	CTATATTTAAGGCCTT	74	2437
1157188	2338	2353	2538	2553	TAATTACTCTTGATCT	52	2438
1157221	2425	2440	2625	2640	CACCTGGGTCAGCTGT	75	2439
1157255	2540	2555	2740	2755	CACCACGAACTGCTGC	81	2440
1157289	2667	2682	2867	2882	ACCAAATTGCACTCGC	60	2441
1157322	2741	2756	2941	2956	TAGGATCCTCTACGCA	77	2442
1157356	2809	2824	3009	3024	TGCCGACCTCACGGAT	76	2443
1157390	2887	2902	3087	3102	CCTCAGTACGAAACTC	84	2444
1157423	2966	2981	3166	3181	ATTCATGAGTATAAGC	71	2445
1157455	3119	3134	3319	3334	ACAAACTGCTTACAGA	83	2446
1157489	3228	3243	3428	3443	CTCAGTTACACATCCA	30	2447
1157522	3323	3338	3523	3538	GCCTTTAGGATTCTAG	70	2448
1157556	3421	3436	3621	3636	CGTGAGAACTGCTCTA	63	2449

1157588	3625	3640	3825	3840	CTATAGCATCTGTGGA	71	2450
1157621	3692	3707	3892	3907	TCCCTGAAGGTGTTCG	82	2451
1157655	3819	3834	4019	4034	CAACATTTGGCCTACT	83	2452
1157688	3938	3953	4138	4153	TTACCTAAACCCACCC	62	2453
1157722	4047	4062	4247	4262	AATCATTGGGAGTTAC	76	2454
1157755	4146	4161	4346	4361	TATGACACTTTCCTTG	75	2455
1157788	4256	4271	4456	4471	TCCCATAATTGTAGTT	73	2456
1157822	4422	4437	4622	4637	CTTACTTGATAATACA	65	2457
1157855	4610	4625	4809	4824	TAAGAGACATTCAAGC	83	2458
1157888	4744	4759	4943	4958	TCACCAAGGAGCTGTT	88	2459
1157921	4810	4825	5009	5024	CTCAGGGTTATGCTTA	60	2460
1157955	4900	4915	5099	5114	ATGGTAGATTCCGTAA	86	2461
1157989	5046	5061	5245	5260	TTAATGTAGTGTAACA	70	2462
1158022	5133	5148	5332	5347	AACGAAACATTGGCAC	52	2463
1158055	5217	5232	5416	5431	TCTGTTAACAGCTGCC	49	2464
1158088	5267	5282	5466	5481	AATAAGCACTTATCCC	69	2465
1158120	5373	5388	5572	5587	ATTTTAAAAAGGCTCG	73	2466
1158153	5483	5498	5682	5697	ATCAAGGCACTGATCA	77	2467
1158187	5572	5587	5771	5786	GCAGTAACATCTGATT	43	2468
1158220	5769	5784	5968	5983	TTCGCAGACAAAGTTT	78	2469
1158253	5885	5900	6084	6099	CATGTGCCTGGAATTA	74	2470
1158286	5958	5973	6157	6172	ACCTTTTACTCTGATC	66	2471
1158320	6077	6092	6276	6291	CCACTCTAAGATTGTA	60	2472
1158354	6174	6189	6373	6388	TGAAGGATGAAATGCC	71	2473
1158387	6275	6290	6474	6489	TTTGAGTATGCTGATA	53	2474
1158420	6433	6448	6632	6647	CAGCGGGATCAGAACA	77	2475
1158452	6512	6527	6711	6726	CTTCAACAATCACTAC	98	2476
1158485	6675	6690	6874	6889	AGACTAAAGGCTTCAG	88	2477
1158549	7055	7070	7254	7269	AGCTTGTTCACCTGTT	63	2478
1158583	7146	7161	7345	7360	GCTCACATGCCAGTTA	68	2479
1158615	7290	7305	7489	7504	CGCTTTGTTGTCTCTC	13	2480
1158649	7396	7411	7595	7610	AGCATTCCTTCGGATG	86	2481
1158682	7514	7529	7713	7728	TTGCCCGCTTTCCCCC	81	2482
1158716	7649	7664	7848	7863	GCTACTGGCTGCATCG	57	2483
1158750	7692	7707	7891	7906	GTTACCTTGAAACCGA	53	2484
1158782	7764	7779	7963	7978	TGTTAACAATTTGCAG	80	2485
1158816	7842	7857	8041	8056	ACTTACTGGTTTAAGT	103	2486
1158849	7941	7956	8140	8155	ACCCAAAAGCCCTCTC	87	2487
1158882	8036	8051	8235	8250	AAGAGCATTGGAGATC	67	2488
1158914	8193	8208	8392	8407	CGCAGGGATTTGAACC	85	2489
1158947	8325	8340	8524	8539	GGATGTATATAGTTCA	70	2490
1158981	8420	8435	8619	8634	AGGCTATTACCTGAAA	105	2491
1159014	1003	1018	N/A	N/A	CCTTCCGCCGCCTCTT	97	2492

Table 63

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	80	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	112	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	40	36
568447	2339	2354	2539	2554	GTAATTACTCTTGATC	53	2493
1156480	123	138	89	104	CTTCAGGCGAGCTGAG	104	2494
1156513	248	263	214	229	TTATCTAAATACCACC	98	2495
1156547	346	361	312	327	TGGTTAGGTATGAGCT	96	2496
1156581	481	496	447	462	CCAACTAAGCGAATGG	82	2497
1156615	527	542	493	508	GGCAAATCGCCATGGA	78	2498
1156649	595	610	561	576	CCCCACGGCCCGCACG	109	2499
1156683	718	733	684	699	TGAAAACCCACTCTTG	100	2500
1156716	827	842	793	808	CCAACTGCTTGCAGTC	75	2501
1156750	890	905	856	871	ACGCAACTGAGCCCCA	144	2502
1156784	955	970	921	936	AGGTATAGTTTACCAC	107	2503
1156818	N/A	N/A	1004	1019	ACGGGTCATCAAACAC	86	2504
1156852	N/A	N/A	1117	1132	AGCTTATGGAACTTGA	84	2505
1156886	1013	1028	1213	1228	AATTCGATCACCTTCC	84	2506
1156920	1065	1080	1265	1280	GCACAGCTCGGGCGAG	120	2507
1156954	1143	1158	1343	1358	AAAACTTATCTGCGGT	46	2508
1156988	1328	1343	1528	1543	TCCGTCATGTTTTAGA	50	2509
1157021	1511	1526	1711	1726	ATCGCCTTCAAATTAT	40	2510
1157055	1586	1601	1786	1801	TAAATGACGCAATTCT	92	2511
1157088	1805	1820	2005	2020	GCTTCCTACTTTTCAG	56	2512
1157122	2086	2101	2286	2301	TTCTAACTTCTGCACC	67	2513
1157156	2275	2290	2475	2490	ACTATATTTAAGGCCT	60	2514
1157222	2427	2442	2627	2642	AGCACCTGGGTCAGCT	105	2515
1157256	2543	2558	2743	2758	CTTCACCACGAACTGC	57	2516
1157290	2668	2683	2868	2883	CACCAAATTGCACTCG	46	2517
1157323	2742	2757	2942	2957	CTAGGATCCTCTACGC	89	2518
1157357	2810	2825	3010	3025	TTGCCGACCTCACGGA	N.D.	2519
1157391	2891	2906	3091	3106	TACACCTCAGTACGAA	72	2520
1157424	2967	2982	3167	3182	GATTCATGAGTATAAG	50	2521
1157456	3120	3135	3320	3335	TACAAACTGCTTACAG	61	2522
1157490	3229	3244	3429	3444	CCTCAGTTACACATCC	51	2523
1157523	3324	3339	3524	3539	TGCCTTTAGGATTCTA	55	2524
1157557	3436	3451	3636	3651	TTCCACAGACCTCAAC	104	2525
1157589	3626	3641	3826	3841	ACTATAGCATCTGTGG	91	2526

1157622	3693	3708	3893	3908	GTCCCTGAAGGTGTTC	77	2527
1157656	3820	3835	4020	4035	TCAACATTTGGCCTAC	79	2528
1157689	3939	3954	4139	4154	ATTACCTAAACCCACC	110	2529
1157723	4048	4063	4248	4263	AAATCATTGGGAGTTA	76	2530
1157756	4156	4171	4356	4371	AGTATCAAATTATGAC	N.D.	2531
1157789	4257	4272	4457	4472	TTCCCATAATTGTAGT	82	2532
1157823	4423	4438	4623	4638	TCTTACTTGATAATAC	90	2533
1157856	4611	4626	4810	4825	CTAAGAGACATTCAAG	73	2534
1157889	4745	4760	4944	4959	TTCACCAAGGAGCTGT	63	2535
1157922	4811	4826	5010	5025	TCTCAGGGTTATGCTT	41	2536
1157956	4901	4916	5100	5115	AATGGTAGATTCCGTA	53	2537
1157990	5048	5063	5247	5262	GATTAATGTAGTGTAA	77	2538
1158023	5134	5149	5333	5348	AAACGAAACATTGGCA	54	2539
1158056	5218	5233	5417	5432	ATCTGTTAACAGCTGC	29	2540
1158089	5268	5283	5467	5482	AAATAAGCACTTATCC	82	2541
1158121	5385	5400	5584	5599	ACAAGTCCTACAATTT	69	2542
1158154	5484	5499	5683	5698	CATCAAGGCACTGATC	87	2543
1158188	5573	5588	5772	5787	AGCAGTAACATCTGAT	59	2544
1158221	5770	5785	5969	5984	GTTCGCAGACAAAGTT	64	2545
1158254	5893	5908	6092	6107	TCTATTGCCATGTGCC	59	2546
1158287	5959	5974	6158	6173	TACCTTTTACTCTGAT	58	2547
1158321	6078	6093	6277	6292	ACCACTCTAAGATTGT	111	2548
1158355	6190	6205	6389	6404	ATCCTGAATGGCTTCA	100	2549
1158388	6278	6293	6477	6492	AATTTTGAGTATGCTG	46	2550
1158421	6434	6449	6633	6648	GCAGCGGGATCAGAAC	66	2551
1158453	6534	6549	6733	6748	TATCACTCAGCTGGAT	66	2552
1158486	6676	6691	6875	6890	AAGACTAAAGGCTTCA	79	2553
1158517	6920	6935	7119	7134	TAAAGTAAATAGGCTA	79	2554
1158550	7058	7073	7257	7272	AAAAGCTTGTTCACCT	79	2555
1158584	7148	7163	7347	7362	TTGCTCACATGCCAGT	60	2556
1158616	7304	7319	7503	7518	CCTTAGGATAATAGCG	40	2557
1158650	7397	7412	7596	7611	AAGCATTCCTTCGGAT	108	2558
1158683	7520	7535	7719	7734	AAGTGGTTGCCCGCTT	78	2559
1158717	7650	7665	7849	7864	AGCTACTGGCTGCATC	N.D.	2560
1158751	7693	7708	7892	7907	CGTTACCTTGAAACCG	64	2561
1158783	7773	7788	7972	7987	ATACCCTTCTGTTAAC	98	2562
1158817	7844	7859	8043	8058	CCACTTACTGGTTTAA	67	2563
1158850	7942	7957	8141	8156	CACCCAAAAGCCCTCT	83	2564
1158883	8037	8052	8236	8251	GAAGAGCATTGGAGAT	51	2565
1158915	8194	8209	8393	8408	CCGCAGGGATTTGAAC	98	2566
1158948	8326	8341	8525	8540	AGGATGTATATAGTTC	98	2567
1158982	8421	8436	8620	8635	CAGGCTATTACCTGAA	114	2568
1159015	1004	1019	N/A	N/A	ACCTTCCGCCGCCTCT	67	2569

Table 64

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395254	4843	4862	5042	5061	GGCATATGCAGATAATGTTC	97	18
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	141	32
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	52	36
567926	4746	4761	4945	4960	ATTCACCAAGGAGCTG	61	2570
568506	8195	8210	8394	8409	GCCGCAGGGATTTGAA	69	2571
1156481	130	145	96	111	GACCTGCCTTCAGGCG	N.D.	2572
1156514	251	266	217	232	GTTTTATCTAAATACC	71	2573
1156548	347	362	313	328	CTGGTTAGGTATGAGC	97	2574
1156582	482	497	448	463	ACCAACTAAGCGAATG	112	2575
1156616	528	543	494	509	AGGCAAATCGCCATGG	95	2576
1156650	597	612	563	578	CCCCCCACGGCCCGCA	74	2577
1156684	719	734	685	700	GTGAAAACCCACTCTT	90	2578
1156717	828	843	794	809	CCCAACTGCTTGCAGT	91	2579
1156751	891	906	857	872	TACGCAACTGAGCCCC	100	2580
1156785	956	971	922	937	TAGGTATAGTTTACCA	98	2581
1156819	N/A	N/A	1005	1020	AACGGGTCATCAAACA	125	2582
1156853	N/A	N/A	1118	1133	CAGCTTATGGAACTTG	133	2583
1156887	1014	1029	1214	1229	GAATTCGATCACCTTC	101	2584
1156921	1067	1082	1267	1282	CCGCACAGCTCGGGCG	86	2585
1156955	1144	1159	1344	1359	AAAAACTTATCTGCGG	51	2586
1156989	1329	1344	1529	1544	CTCCGTCATGTTTTAG	33	2587
1157022	1512	1527	1712	1727	GATCGCCTTCAAATTA	61	2588
1157056	1587	1602	1787	1802	TTAAATGACGCAATTC	96	2589
1157089	1831	1846	2031	2046	GTTTCCTAGCTTGTCT	43	2590
1157123	2089	2104	2289	2304	ACCTTCTAACTTCTGC	36	2591
1157157	2276	2291	2476	2491	TACTATATTTAAGGCC	99	2592
1157189	2340	2355	2540	2555	GGTAATTACTCTTGAT	50	2593
1157223	2431	2446	2631	2646	GTGTAGCACCTGGGTC	36	2594
1157257	2545	2560	2745	2760	ATCTTCACCACGAACT	78	2595
1157291	2669	2684	2869	2884	TCACCAAATTGCACTC	79	2596
1157324	2743	2758	2943	2958	TCTAGGATCCTCTACG	124	2597
1157358	2813	2828	3013	3028	ATATTGCCGACCTCAC	74	2598
1157392	2892	2907	3092	3107	TTACACCTCAGTACGA	85	2599
1157425	2970	2985	3170	3185	CAAGATTCATGAGTAT	66	2600
1157457	3121	3136	3321	3336	ATACAAACTGCTTACA	130	2601
1157491	3233	3248	3433	3448	CCCGCCTCAGTTACAC	96	2602
1157524	3332	3347	3532	3547	GAGTCATTTGCCTTTA	27	2603

1157558	3445	3460	3645	3660	GGACATCTCTTCCACA	76	2604
1157590	3627	3642	3827	3842	TACTATAGCATCTGTG	107	2605
1157623	3694	3709	3894	3909	AGTCCCTGAAGGTGTT	72	2606
1157657	3822	3837	4022	4037	CTTCAACATTTGGCCT	82	2607
1157690	3940	3955	4140	4155	AATTACCTAAACCCAC	100	2608
1157724	4049	4064	4249	4264	TAAATCATTGGGAGTT	62	2609
1157757	4183	4198	4383	4398	CTCTATACTTTGAAGG	80	2610
1157790	4261	4276	4461	4476	GCATTTCCCATAATTG	54	2611
1157824	4426	4441	4626	4641	GAATCTTACTTGATAA	87	2612
1157857	4613	4628	4812	4827	CTCTAAGAGACATTCA	77	2613
1157923	4814	4829	5013	5028	GAATCTCAGGGTTATG	43	2614
1157957	4902	4917	5101	5116	AAATGGTAGATTCCGT	40	2615
1157991	5049	5064	5248	5263	GGATTAATGTAGTGTA	14	2616
1158024	5135	5150	5334	5349	CAAACGAAACATTGGC	69	2617
1158057	5219	5234	5418	5433	TATCTGTTAACAGCTG	59	2618
1158090	5285	5300	5484	5499	AACTCCACAGCTCTTA	N.D.	2619
1158122	5387	5402	5586	5601	GAACAAGTCCTACAAT	68	2620
1158155	5485	5500	5684	5699	GCATCAAGGCACTGAT	65	2621
1158189	5574	5589	5773	5788	TAGCAGTAACATCTGA	54	2622
1158222	5772	5787	5971	5986	GTGTTCGCAGACAAAG	90	2623
1158255	5894	5909	6093	6108	CTCTATTGCCATGTGC	43	2624
1158288	5991	6006	6190	6205	ACCCCTGACTTTCTGG	82	2625
1158322	6079	6094	6278	6293	TACCACTCTAAGATTG	95	2626
1158356	6194	6209	6393	6408	CAAAATCCTGAATGGC	90	2627
1158389	6323	6338	6522	6537	GTAAGCCCCACCCCCT	135	2628
1158422	6435	6450	6634	6649	AGCAGCGGGATCAGAA	81	2629
1158454	6536	6551	6735	6750	TTTATCACTCAGCTGG	47	2630
1158487	6694	6709	6893	6908	TTAAGGTTGCATCTGG	35	2631
1158518	6966	6981	7165	7180	TAGTGGTTCCCAATCC	86	2632
1158551	7060	7075	7259	7274	GAAAAAGCTTGTTCAC	72	2633
1158585	7151	7166	7350	7365	AGTTTGCTCACATGCC	35	2634
1158617	7305	7320	7504	7519	ACCTTAGGATAATAGC	61	2635
1158651	7398	7413	7597	7612	CAAGCATTCCTTCGGA	75	2636
1158684	7521	7536	7720	7735	AAAGTGGTTGCCCGCT	85	2637
1158718	7653	7668	7852	7867	CCAAGCTACTGGCTGC	77	2638
1158752	7707	7722	7906	7921	GACCTCGACACCATCG	56	2639
1158784	7774	7789	7973	7988	AATACCCTTCTGTTAA	84	2640
1158818	7870	7885	8069	8084	TTACAGTTCTTGAACA	75	2641
1158851	7947	7962	8146	8161	ATTCCCACCCAAAAGC	N.D.	2642
1158884	8039	8054	8238	8253	CTGAAGAGCATTGGAG	50	2643
1158949	8327	8342	8526	8541	AAGGATGTATATAGTT	79	2644
1158983	8422	8437	8621	8636	GCAGGCTATTACCTGA	81	2645
1159016	1005	1020	N/A	N/A	CACCTTCCGCCGCCTC	72	2646

Example 14: Design of gapmers with 2'-O methyl modifications complementary to human MALAT1 RNA

Modified oligonucleotides complementary to human a MALAT1 nucleic acid were designed. The modified oligonucleotides in the table below are 3-10-3 cET gapmers. The gapmers are 16 nucleosides in length, wherein the central gap segment comprises of a combination of one 2'-O-methyl nucleoside and nine 2'-deoxynucleosides. The central gap segment is flanked by wing segments on the 5' direction and the 3' direction comprising three nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a cEt sugar modification. The internucleoside linkages throughout each gapmer are phosphorothioate (P=S) linkages. The sequence and chemical notation column specifies the sequence, including 5-methylcytosines, sugar chemistry, and the internucleoside linkage chemistry; wherein subscript 'd' represents a 2'-β-D-deoxyribosyl sugar moiety, subscript 'k' represents a cET sugar moiety, subscript 's' represents to a phosphorothioate internucleoside linkage, superscript 'm' before the cytosine residue represents a 5-methylcytosine, and subscript 'y' represents a 2'-OMe sugar moiety. "Start site" indicates the 5'-most nucleoside to which the gapmer is complementary in the human nucleic acid sequence. "Stop site" indicates the 3'-most nucleoside to which the gapmer is complementary in the human nucleic acid sequence.

Each modified oligonucleotide listed in the table below is complementary to human MALAT1 nucleic acid sequence SEQ ID NO: 1 (GENBANK Accession No: XR_001309.1).

Table 65

cET gapmers with 2'-OMe sugars complementary to human MALAT1

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence (5' to 3')	Chemistry Notation (5' to 3')	SEQ ID No.
1304879	2033	2048	GTTACCAATAATTTCC	$G_{ks}T_{ks}T_{ks}A_{ds}C_{ys}{}^{m}C_{ds}A_{ds}A_{ds}T_{ds}A_{ds}A_{ds}T_{ds}T_{ds}T_{ks}{}^{m}C_{ks}{}^{m}C_{k}$	1592
1304880	5078	5093	TCTCATTTATTTCGGC	$T_{ks}{}^{m}C_{ks}T_{ks}{}^{m}C_{ds}A_{ys}T_{ds}T_{ds}T_{ds}A_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}G_{ks}G_{ks}{}^{m}C_{k}$	1077
1304881	5494	5509	CCTTAGTTGGCATCAA	${}^{m}C_{ks}{}^{m}C_{ks}T_{ks}T_{ds}A_{ys}G_{ds}T_{ds}T_{ds}G_{ds}G_{ds}{}^{m}C_{ds}A_{ds}T_{ds}{}^{m}C_{ks}A_{ks}A_{k}$	6
1304882	5419	5434	GAAGUGTACTATCCCA	$G_{ks}A_{ks}A_{ks}G_{ds}U_{ys}G_{ds}T_{ds}A_{ds}{}^{m}C_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ks}{}^{m}C_{ks}A_{k}$	2647
1304883	5074	5089	ATTTATTTCGGCTTCT	$A_{ks}T_{ks}T_{ks}T_{ds}A_{ys}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}G_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{ks}T_{k}$	850
1304885	4938	4953	TTTTUGTGGTTATAGC	$T_{ks}T_{ks}T_{ks}T_{ds}U_{ys}G_{ds}T_{ds}G_{ds}G_{ds}T_{ds}T_{ds}A_{ds}T_{ds}A_{ks}G_{ks}{}^{m}C_{k}$	2648
1304886	4903	4918	AAAAUGGTAGATTCCG	$A_{ks}A_{ks}A_{ks}A_{ds}U_{ys}G_{ds}G_{ds}T_{ds}A_{ds}G_{ds}A_{ds}T_{ds}T_{ds}{}^{m}C_{ks}{}^{m}C_{ks}G_{k}$	2649
1304887	4935	4950	TTGTGGTTATAGCTTG	$T_{ks}T_{ks}G_{ks}T_{ds}G_{ys}G_{ds}T_{ds}T_{ds}A_{ds}T_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{ks}T_{ks}G_{k}$	1232
1304888	4933	4948	GTGGUTATAGCTTGAC	$G_{ks}T_{ks}G_{ks}G_{ds}U_{ys}T_{ds}A_{ds}T_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{ds}G_{ks}A_{ks}{}^{m}C_{k}$	2650
1304889	4808	4823	CAGGGTTATGCTTATT	${}^{m}C_{ks}A_{ks}G_{ks}G_{ds}G_{ys}T_{ds}T_{ds}A_{ds}T_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{ds}A_{ks}T_{ks}T_{k}$	2152
1304891	2034	2049	GGTTACCAATAATTTC	$G_{ks}G_{ks}T_{ks}T_{ds}A_{ys}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}A_{ds}T_{ds}A_{ds}A_{ds}T_{ds}T_{ks}T_{ks}{}^{m}C_{k}$	3
1304892	2341	2356	TGGTAATTACTCTTGA	$T_{ks}G_{ks}G_{ks}T_{ds}A_{ys}A_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ks}G_{ks}A_{k}$	4
1304893	1533	1548	CGGTUTAATCTCTTTT	${}^{m}C_{ks}G_{ks}G_{ks}T_{ds}U_{ys}T_{ds}A_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ks}T_{ks}T_{k}$	2651
1304894	7290	7305	CGCTUTGTTGTCTCTC	${}^{m}C_{ks}G_{ks}{}^{m}C_{ks}T_{ds}U_{ys}T_{ds}G_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ks}T_{ks}{}^{m}C_{k}$	2652
1304895	7835	7850	GGTTUAAGTTGGTTTT	$G_{ks}G_{ks}T_{ks}T_{ds}U_{ys}A_{ds}A_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ds}T_{ds}T_{ks}T_{ks}T_{k}$	2653
1304896	7825	7840	GGTTUTAGTCACTGGA	$G_{ks}G_{ks}T_{ks}T_{ds}U_{ys}T_{ds}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}T_{ds}G_{ks}G_{ks}A_{k}$	2654
1304897	7289	7304	GCTTUGTTGTCTCTCC	$G_{ks}{}^{m}C_{ks}T_{ks}T_{ds}U_{ys}G_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ks}{}^{m}C_{ks}{}^{m}C_{k}$	2655

1304898	5495	5510	TCCTUAGTTGGCATCA	$T_{ks}{}^{m}C_{ks}{}^{m}C_{ks}T_{ds}U_{ys}A_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ds}{}^{m}C_{ds}A_{ds}T_{ks}{}^{m}C_{ks}A_{k}$	2656
1304899	6700	6715	CTGAUTTTAAGGTTGC	$^{m}C_{ks}T_{ks}G_{ks}A_{ds}U_{ys}T_{ds}T_{ds}T_{ds}A_{ds}A_{ds}G_{ds}G_{ds}T_{ds}T_{ks}G_{ks}{}^{m}C_{k}$	2657
1304900	6699	6714	TGATUTTAAGGTTGCA	$T_{ks}G_{ks}A_{ks}T_{ds}U_{ys}T_{ds}T_{ds}A_{ds}A_{ds}G_{ds}G_{ds}T_{ds}T_{ds}G_{ks}{}^{m}C_{ks}A_{k}$	2658
1304901	5525	5540	AGCCUTCAGAGATTCA	$A_{ks}G_{ks}{}^{m}C_{ks}{}^{m}C_{ds}U_{ys}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}A_{ds}G_{ds}A_{ds}T_{ds}T_{ks}{}^{m}C_{ks}A_{k}$	2659
1304902	5050	5065	AGGAUTAATGTAGTGT	$A_{ks}G_{ks}G_{ks}A_{ds}U_{ys}T_{ds}A_{ds}A_{ds}T_{ds}G_{ds}T_{ds}A_{ds}G_{ds}T_{ks}G_{ks}T_{k}$	2660
1304903	5051	5066	CAGGATTAATGTAGTG	$^{m}C_{ks}A_{ks}G_{ks}G_{ds}A_{ys}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}G_{ds}T_{ds}A_{ds}G_{ks}T_{ks}G_{k}$	161
1304904	4821	4836	GTAGUAAGAATCTCAG	$G_{ks}T_{ks}A_{ks}G_{ds}U_{ys}A_{ds}A_{ds}G_{ds}A_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ks}A_{ks}G_{k}$	2661
1304905	1564	1579	GTCAUGGATTTCAAGG	$G_{ks}T_{ks}{}^{m}C_{ks}A_{ds}U_{ys}G_{ds}G_{ds}A_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}A_{ks}G_{ks}G_{k}$	2662
1304907	1535	1550	TTCGGTTTAATCTCTT	$T_{ks}T_{ks}{}^{m}C_{ks}G_{ds}G_{ys}T_{ds}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ks}T_{ks}T_{k}$	2
1304908	4932	4947	TGGTUATAGCTTGACA	$T_{ks}G_{ks}G_{ks}T_{ds}U_{ys}A_{ds}T_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}A_{ks}{}^{m}C_{ks}A_{k}$	2663

Example 15: Antisense inhibition of human MALAT1 in HepG2 cells by 3-10-3 cEt gapmers

Modified oligonucleotides complementary to a MALAT1 nucleic acid were synthesized and tested for their effect on MALAT1 RNA levels *in vitro* in comparison with comparator compounds 395240 and 556089 described above. The modified oligonucleotides were tested in a series of experiments using the same culture conditions. The results for each separate experiment are presented in separate tables below.

Except for comparator compound 395240, which is a 5-10-5 MOE gapmer (i.e., it has a central gap segment of ten 2'-deoxynucleosides flanked on each side by wing segments, each comprising five 2'-O-methoxyethyl modified nucleosides), the modified oligonucleotides are all 3-10-3 cEt gapmers (i.e., they have a central gap segment of ten 2'-deoxynucleosides flanked on each side by wing segments, each comprising three cEt modified nucleosides). The internucleoside linkages throughout each modified oligonucleotide are phosphorothioate (P=S) linkages. All cytosine nucleobases throughout each modified oligonucleotide are 5-methylcytosines.

"Start site" indicates the 5'-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. "Stop site" indicates the 3'-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. As shown in the tables below, the modified oligonucleotides are 100% complementary to either the human MALAT1 RNA transcript, designated herein as SEQ ID NO: 1 (GENBANK Accession No. XR_001309.1) or the human MALAT1 RNA transcript designated here in as SEQ ID NO: 2824 (GENBANK Accession No. EF177381.1). 'N/A' indicates that the modified oligonucleotide is not complementary to that particular target sequence with 100% complementarity.

Cultured HepG2 cells at a density of 20,000 cells per well were transfected using electroporation with 300 nM of modified oligonucleotide. After an overnight incubation, RNA was isolated from the cells and MALAT1 RNA levels were measured by quantitative real-time RTPCR. Human primer probe set RTS2738 (forward sequence GAATTGCGTCATTTAAAGCCTAGTT, designated herein as SEQ ID NO: 2820; reverse sequence TCATCCTACCACTCCCAATTAATCT, designated herein as SEQ ID NO: 2821; probe sequence ACGCATTTACTAAACGCAGACGAAAATGGA, designated herein as SEQ ID NO: 2822) was used to measure RNA levels. MALAT1 RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Results are presented as percent change of MALAT1 RNA, relative to PBS control. The symbol "ǂ" indicates that the modified

oligonucleotide is complementary to the target transcript within the amplicon region of the primer probe set and so the associated data is not reliable. In such instances, additional assays using alternative primer probes must be performed to accurately assess the potency and efficacy of such modified oligonucleotides.

Table 66

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395240	3320	3339	3520	3539	TGCCTTTAGGATTCTAGACA	51	11
556032	3310	3325	3510	3525	TAGACAGACCTAAGGG	22	2664
556089	6445	6460	6644	6659	GCATTCTAATAGCAGC	6	31
556130	8007	8022	8206	8221	ATGCTAGCTTGGCCAA	17	2665
559466	36	51	2	17	GGGCCCCAGTCCTTTA	86	2666
559467	177	192	143	158	CGTCCCAAGGACTCTG	105	2667
559468	281	296	247	262	ACCCCAAGACCAAACT	93	2668
559469	412	427	378	393	AAGTGTTTACACTGCT	74	2669
559470	522	537	488	503	ATCGCCATGGAAAGCG	95	2670
559471	636	651	602	617	GTGGCCCACTCTGATC	87	2671
559472	760	775	726	741	TCGGAGCAGCACGGGC	77	2672
559473	868	883	834	849	CAGGGACGGTTGAGAA	91	2673
559474	968	983	934	949	CTTGAGGGACAGTAGG	84	2674
559475	N/A	N/A	1051	1066	TTGAGCTGCAAACTTT	119	2675
559476	N/A	N/A	1162	1177	GGTTAAAAATAGGTTC	73	2676
559477	1063	1078	1263	1278	ACAGCTCGGGCGAGGC	74	2677
559478	1199	1214	1399	1414	ACCTATTGACTATATT	33	2678
559479	1415	1430	1615	1630	TTGGTATTAATTCGGG	8	2679
559480	1561	1576	1761	1776	ATGGATTTCAAGGTCT	7	2680
559481	1690	1705	1890	1905	GTTTTCCACTTCAAAC	35	2681
559482	1953	1968	2153	2168	CAATACTTGTCTTAGC	13	2682
559484	2178	2193	2378	2393	GTGATTTTTAACCAAC	7	2683
559485	2399	2414	2599	2614	TAGTCCTCAGGATTTA	21	2684
559486	2503	2518	2703	2718	CTAGCTTCATCAAACA	22	2685
559487	2626	2641	2826	2841	CTTCACCACCAAATCG	20	2686
559488	2752	2767	2952	2967	GCATGCTGGTCTAGGA	22	2687
559489	2789	2804	2989	3004	ACCAACCACTCGCTTT	22	2688
559490	2889	2904	3089	3104	CACCTCAGTACGAAAC	42	2689
559491	2985	3000	3185	3200	CTCAAAAGCTTCAGAC	29	2690
559492	2997	3012	3197	3212	TGGCAGTCTGCCCTCA	22	2691
559493	3166	3181	3366	3381	GTCATCTATTCACAAA	8	2692
559494	3322	3337	3522	3537	CCTTTAGGATTCTAGA	17	2693

559495	3435	3450	3635	3650	TCCACAGACCTCAACG	17	2694
559496	3502	3517	3702	3717	AAAGTCTGATTAAGGG	18	2695
559497	3629	3644	3829	3844	AGTACTATAGCATCTG	8	32
559498	3720	3735	3920	3935	ACTCTTCCAAGGATAA	17	2696
559499	3766	3781	3966	3981	GAACCAAAGCTGCACT	17	2697
559500	3884	3899	4084	4099	GCCAATATTTGCCCCT	22	2698
559501	4022	4037	4222	4237	TGGAAGTTGATATTTC	10	2699
559502	4080	4095	4280	4295	GCTTCCCAATTCAAAC	37	2700
559503	4182	4197	4382	4397	TCTATACTTTGAAGGA	33	2701
559504	4295	4310	4495	4510	GAGAACCACACACTAC	23	2702
559505	4405	4420	4605	4620	AAGCTACCATCAGAAG	29	2703
559506	4575	4590	4774	4789	ATCAGTTACAATTTAC	12	2704
559507	4629	4644	4828	4843	TCAACAAAAGCCCACC	48	2705
559508	4687	4702	4886	4901	CTCAGAAGATGTTATC	19	2706
559509	4748	4763	4947	4962	CAATTCACCAAGGAGC	10	2707
559510	4845	4860	5044	5059	CATATGCAGATAATGT	12	2708
559511	4976	4991	5175	5190	GACATTGCCTCTTCAT	4	2709
559512	5041	5056	5240	5255	GTAGTGTAACATTTTC	3	2710
559513	5131	5146	5330	5345	CGAAACATTGGCACAC	10	2711
559514	5142	5157	5341	5356	TCTGAGGCAAACGAAA	37	2712
559515	5229	5244	5428	5443	AAGTTAAACTTATCTG	38	2713
559516	5257	5272	5456	5471	TATCCCTAACATGCAA	28	2714
559517	5359	5374	5558	5573	CGATGGAAAAATTTCT	20	2715
559518	5466	5481	5665	5680	TTTAGAGGCTTTTAAG	60	2716
559519	5569	5584	5768	5783	GTAACATCTGATTCTA	9	2717
559520	5721	5736	5920	5935	TGCCCCAACACTGAAC	42	2718
559521	5795	5810	5994	6009	ATCCTGATCTGGTCCA	27	2719
559523	5830	5845	6029	6044	TCCTGCCTTAAAGTTA	61	2720
559525	5928	5943	6127	6142	GTCTAAGAGGTTATTT	29	2721
559527	6061	6076	6260	6275	AGCATTTAAAGTTAAC	19	2722
559529	6169	6184	6368	6383	GATGAAATGCCTCTGC	14	2723
559531	6259	6274	6458	6473	AACTCACTGCAAGGTC	15	2724
559533	6385	6400	6584	6599	ACCTGAAGTCAAGACA	18	2725
559535	6532	6547	6731	6746	TCACTCAGCTGGATTT	16	2726
559537	6582	6597	6781	6796	CAAATACGACTGCTTA	62	2727
559539	6849	6864	7048	7063	TGTTCCTGCATGTAAG	47	2728
559541	6964	6979	7163	7178	GTGGTTCCCAATCCCC	21	2729
559543	7143	7158	7342	7357	CACATGCCAGTTACTC	12	2730
559545	7231	7246	7430	7445	GTGCCTTTAGTGAGGG	23	2731
559547	7404	7419	7603	7618	GTACTTCAAGCATTCC	8	2732
559549	7519	7534	7718	7733	AGTGGTTGCCCGCTTT	16	2733
559551	7748	7763	7947	7962	GCAAATTAATGGCCTT	8	2734
559553	7871	7886	8070	8085	ATTACAGTTCTTGAAC	28	2735

559556	8158	8173	8357	8372	TGCCAACCACCAGCAT	81	2736
559557	8209	8224	8408	8423	GTCAAAGCAAAGACGC	82	2737
559559	8378	8393	8577	8592	CGTGTAAATATGAATA	55	2738

Table 67

Inhibition of MALAT1 RNA by 3-10-3 cEt gapmers

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2824 Start Site	SEQ ID NO: 2824 Stop Site	Sequence (5' to 3')	MALAT1 (% UTC)	SEQ ID No.
395240	3320	3339	3520	3539	TGCCTTTAGGATTCTAGACA	49	11
556057	4700	4715	4899	4914	AGGCTGGTTATGACTC	10	2739
559522	84	99	50	65	GTTGCTAAAATGGCGC	82	2740
559524	229	244	195	210	TGGAATGGCCAGCCTA	79	2741
559526	337	352	303	318	ATGAGCTTCAGACCTT	78	2742
559528	472	487	438	453	CGAATGGCTTTGTCTC	84	2743
559530	579	594	545	560	GAAATTTTTCTACCGT	92	2744
559532	710	725	676	691	CACTCTTGGAAAACGC	91	2745
559534	816	831	782	797	CAGTCCTGCGACTTGC	98	2746
559536	918	933	884	899	GTGATAGTTCAGGGCT	103	2747
559538	N/A	N/A	1001	1016	GGTCATCAAACACCTC	70	2748
559540	N/A	N/A	1110	1125	GGAACTTGAATGCAAA	75	2749
559542	N/A	N/A	1200	1215	TCCGCCGCCTTTGTGA	69	2750
559544	1131	1146	1331	1346	CGGTTTCCTCAAGCTC	4	2751
559546	1326	1341	1526	1541	CGTCATGTTTTAGAAA	11	2752
559548	1509	1524	1709	1724	CGCCTTCAAATTATTT	8	2753
559550ǂ	1660	1675	1860	1875	AATTGTTTCATCCTAC	47	2754
559552	1852	1867	2052	2067	ACATTTTGCCCTTAGC	10	2755
559554	2006	2021	2206	2221	GTGCTATTTTATCCAA	4	2756
559555	2116	2131	2316	2331	GTAAACACCCTCATCT	27	2757
559558	2267	2282	2467	2482	TAAGGCCTTCCAAATT	27	2758
559560	2448	2463	2648	2663	TCACTGAATCCACTTC	12	2759
559561	2576	2591	2776	2791	CAAATCGCACTGGCTC	10	2760
559562	2679	2694	2879	2894	GCTACCTTCATCACCA	32	2761
559563	2758	2773	2958	2973	ACACTGGCATGCTGGT	20	2762
559564	2839	2854	3039	3054	CCATAAGTAAGTTCCA	7	36
559565	2939	2954	3139	3154	AAACCTACAACACCCG	26	2763
559566	2992	3007	3192	3207	GTCTGCCCTCAAAAGC	19	2764
559567	3063	3078	3263	3278	GTTTTCCTCAAATTCG	9	2765
559568	3225	3240	3425	3440	AGTTACACATCCAAAC	22	2766
559569	3315	3330	3515	3530	GATTCTAGACAGACCT	79	2767

559570	3370	3385	3570	3585	ATCCTGATATTGGATT	65	2768
559571	3467	3482	3667	3682	AACTACCAGCCATTTC	31	2769
559572	3555	3570	3755	3770	ATCCCAAAATGCTTCA	22	2770
559573	3695	3710	3895	3910	CAGTCCCTGAAGGTGT	20	2771
559574	3743	3758	3943	3958	ACTTTTCAGCTTCAAC	18	2772
559575	3814	3829	4014	4029	TTTGGCCTACTCAAGC	20	2773
559577	4038	4053	4238	4253	GAGTTACTTGCCAACT	21	2774
559578	4131	4146	4331	4346	GCCCAAATTAATGCAC	32	2775
559579	4232	4247	4432	4447	CCCAGTAGGCCAGACC	15	2776
559580	4350	4365	4550	4565	CAGTTTCTATAGTAGT	11	2777
559581	4495	4510	4694	4709	GCAGTTAAACAATGGA	6	2778
559582	4624	4639	4823	4838	AAAAGCCCACCCTCTA	60	2779
559583	4634	4649	4833	4848	CCTCATCAACAAAAGC	55	2780
559584	4798	4813	4997	5012	CTTATTCCCCAATGGA	14	2781
559585	4899	4914	5098	5113	TGGTAGATTCCGTAAC	6	2782
559586	5004	5019	5203	5218	GCTTTTGTAAAAGCAG	66	2783
559587	5092	5107	5291	5306	GATCCCAACTCATCTC	8	2784
559588	5136	5151	5335	5350	GCAAACGAAACATTGG	8	2785
559589	5178	5193	5377	5392	AATGAAGCAACTCTTC	42	2786
559590	5250	5265	5449	5464	AACATGCAATACTGCA	8	2787
559591	5303	5318	5502	5517	CCATGGTTGATATTTA	16	2788
559592	5411	5426	5610	5625	CTATCCCATCACTGAA	19	2789
559593	5516	5531	5715	5730	AGATTCAATGCTAAAC	13	2790
559594	5658	5673	5857	5872	GTATACATTCTCTAAT	52	2791
559595	5771	5786	5970	5985	TGTTCGCAGACAAAGT	14	2792
559596	5824	5839	6023	6038	CTTAAAGTTACATTCG	9	2793
559597	5875	5890	6074	6089	GAATTATTATATGCTC	12	2794
559598	5994	6009	6193	6208	TAGACCCCTGACTTTC	8	2795
559599	6111	6126	6310	6325	CCTATATAAGGTCAAT	39	2796
559600	6241	6256	6440	6455	ATACACTCACTAGAAC	55	2797
559601	6327	6342	6526	6541	ACAAGTAAGCCCCACC	75	2798
559602	6428	6443	6627	6642	GGATCAGAACAGTACT	15	2799
559603	6452	6467	6651	6666	TCACAATGCATTCTAA	28	2800
559604	6554	6569	6753	6768	TTTCCTCAACACTCAG	19	2801
559605	6677	6692	6876	6891	AAAGACTAAAGGCTTC	19	2802
559606	6921	6936	7120	7135	TTAAAGTAAATAGGCT	38	2803
559607	7032	7047	7231	7246	TTTTGTCCACTGGTGA	16	2804
559609	7303	7318	7502	7517	CTTAGGATAATAGCGC	6	2805
559610	7454	7469	7653	7668	TAAGAGCTGCTATAAA	85	2806
559611	7641	7656	7840	7855	CTGCATCGAGGTGAGG	19	2807
559612	7799	7814	7998	8013	AATAGAGCTACTTAGC	28	2808

559613	7974	7989	8173	8188	GAAAAAGTCTTAGCAG	33	2809
559614	8054	8069	8253	8268	ACCTTCATGACCCTAC	65	2810
559615	8181	8196	8380	8395	AACCCCGTCCTGGAAA	83	2811
559616	8316	8331	8515	8530	TAGTTCAAAGATATTG	93	2812
559617	8446	8461	8645	8660	GTAGGGCTTCTCAAAA	111	2813

Example 16: Dose-dependent inhibition of human MALAT1 in A431 cells by 3-10-3 cEt gapmers

Certain modified oligonucleotides described in the studies above exhibiting significant *in vitro* inhibition of MALAT1 RNA were selected and tested at various doses in A431 cells in comparison with comparator compounds 395240, 395243, 395244, 395248, 395253, 395254, 395255, 395256, 395280, 556089, and 559497 described above.

The modified oligonucleotides were tested in a series of experiments using the same culture conditions. The results for each experiment are presented in separate tables shown below. Cultured A431 cells at a density of 10,000 cells per well were transfected using free uptake with modified oligonucleotides diluted to different concentrations as specified in the tables below. After a treatment period of approximately 48 hours, RNA levels were measured as previously described using the Human primer-probe set RTS2736. MALAT1 RNA levels were normalized to total RNA, as measured by RIBOGREEN®. Results are presented as percent change of MALAT1 RNA, relative to PBS control.

The half maximal inhibitory concentration (IC_{50}) of each modified oligonucleotide was calculated using a linear regression on a log/linear plot of the data in excel and is also presented in the tables below. The %UTC values for modified oligonucleotides marked with a triple asterisk in the tables below has been previously presented in Example 3 (Table 3) herein above. The %UTC and IC_{50} data for modified oligonucleotides marked with a triple asterisk (⁂) in the tables below is identical to the data presented in Example 3 as the data is from the same experiments.

Table 68

Dose-dependent percent reduction of human MALAT1 RNA in A431 cells by modified oligonucleotides

Compound Number	MALAT1 (% UTC)					
	0.4 nM	2 nM	10 nM	50 nM	250 nM	IC_{50} nM
395240	177	217	122	22	4	57
395243	117	65	74	86	23	92
395244	93	103	74	37	9	25
395248	106	110	95	44	17	50
395253	103	90	79	20	8	19
395254	97	85	57	16	6	12
395255	67	84	81	60	29	98
395256	110	93	85	26	7	23
395280	80	77	73	46	21	28
556089	112	79	103	40	19	44
559497	90	94	75	40	11	25
559590	116	118	82	34	8	32

Table 69

Dose-dependent percent reduction of human MALAT1 RNA in A431 cells by modified oligonucleotides

Compound Number	MALAT1 (% UTC)					
	0.4 nM	2 nM	10 nM	50 nM	250 nM	IC_{50} nM
395240	93	77	46	19	10	9
395253	89	74	31	8	6	6
395254	84	59	23	11	7	3
395256	87	77	48	24	7	9
556089	101	85	71	34	14	22
559497	92	84	64	33	12	17
559564	85	67	30	8	2	4
1157124	99	69	31	8	3	6
1157190	71	28	13	4	2	1
1157958	85	47	15	3	1	2
1157992	67	24	6	2	1	0.4
1158618	76	60	22	5	3	3

Example 17: Dose-dependent inhibition of human MALAT1 in A431 cells by 3-10-3 cEt gapmers

Certain modified oligonucleotides described in the studies above exhibiting significant *in vitro* inhibition of MALAT1 RNA were selected and tested at various doses in A431 cells.

The modified oligonucleotides were tested in a series of experiments using the same culture conditions. The results for each experiment are presented in separate tables shown below. Cultured A431 cells at a density of 10,000 cells per well were transfected using free uptake with modified oligonucleotides diluted to different concentrations as specified in the tables below. After a treatment period of approximately 48 hours, RNA levels were measured as previously described using the Human primer-probe set RTS2736. MALAT1 RNA levels were normalized to total RNA, as measured by RIBOGREEN®. Results are presented as percent change of MALAT1 RNA, relative to PBS control.

The half maximal inhibitory concentration (IC_{50}) of each modified oligonucleotide was calculated using a linear regression on a log/linear plot of the data in excel and is also presented in the tables below. The %UTC values for modified oligonucleotides marked with a triple asterisk in the tables below has been previously presented in Example 3 (Table 3) herein above. The %UTC and IC_{50} data for modified oligonucleotides marked with a triple asterisk (⁂) in the tables below is identical to the data presented in Example 3 as the data is from the same experiments.

Table 70

Dose-dependent percent reduction of human MALAT1 RNA in A431 cells by modified oligonucleotides

Compound Number	MALAT1 (% UTC)				
	0.3 nM	1 nM	5 nM	20 nM	IC_{50} nM
559564	112	96	74	30	11
1156957	91	75	50	20	4
1157124	99	89	82	25	11
1157190⁂	89	93	58	18	6

1157191	140	99	69	29	9
1157224	102	110	88	35	20
1157525	102	94	92	46	>20
1157826	137	113	101	86	>20
1157924	96	89	66	26	8
1157925	88	96	68	28	9
1157958	114	88	58	20	6
1157959	97	60	49	14	3
1157992	70	86	44	12	3
1157993	87	78	43	12	3
1158157	97	62	72	33	8
1158618	95	89	43	21	5
1158652	107	106	73	33	13
1158820	92	93	62	25	7
1158886	106	98	77	29	12

Table 71

Dose-dependent percent reduction of human MALAT1 RNA in A431 cells by modified oligonucleotides

Compound Number	MALAT1 (% UTC)				
	0.3 nM	1 nM	5 nM	20 nM	IC_{50} nM
559564	170	98	54	16	6
1156959	78	71	35	9	2
1156960	165	118	59	22	8
1156993	88	101	79	26	12
1157092	118	112	62	24	8
1157093	91	78	55	15	4
1157127	102	94	72	23	9
1157926	93	87	59	20	6
1157960	94	84	47	17	4
1157994	92	63	45	11	3
1158158	85	71	31	6	2
1158159	95	75	30	5	3
1158359	96	98	68	30	10
1158490	98	102	62	26	8
1158491	95	70	33	6	3
1158492	84	52	14	3	1
1158622	144	129	70	22	10
1158821	98	76	50	15	4
1158855	123	129	104	38	>20

Table 72

Dose-dependent percent reduction of human MALAT1 RNA in A431 cells by modified oligonucleotides

Compound Number	MALAT1 (% UTC)				
	0.3 nM	1 nM	5 nM	20 nM	IC_{50} nM
559564	145	123	63	23	9
1157095	114	101	78	27	11
1157128	96	130	83	37	>20
1157130	101	90	63	18	6
1157431	82	66	63	46	14
1157597	121	84	58	16	6
1157831	94	90	67	28	9
1157895	102	113	88	56	>20
1157928	104	106	76	33	13
1157929⁂	81	76	29	10	2
1158161⁂	83	77	37	9	3
1158162⁂	82	78	32	10	3
1158227	83	86	61	24	6
1158228	106	91	56	25	7
1158429	144	101	60	29	8
1158459	113	114	104	52	>20
1158623	79	82	56	24	5
1158789	107	121	98	43	>20
1158857	105	107	60	23	8

Table 73

Dose-dependent percent reduction of human MALAT1 RNA in A431 cells by modified oligonucleotides

Compound Number	MALAT1 (% UTC)				
	0.3 nM	1 nM	5 nM	20 nM	IC_{50} nM
559564	151	92	57	19	6
1156996	96	87	51	24	6
1157096	107	112	66	45	18
1157097	79	70	39	9	2
1157131	59	67	36	10	1
1157366	87	82	39	10	3
1157697	73	80	51	19	4
1157698	71	41	36	13	1
1157897	98	102	66	29	10
1157931	101	84	47	13	4
1158000	146	83	74	25	8
1158163	103	84	41	12	4
1158164	97	81	45	11	4
1158230	78	62	31	10	2
1158231	115	82	53	21	5

1158263	102	99	68	28	9
1158495	104	90	42	12	4
1158625	80	68	48	21	3
1158859	99	96	58	18	6

Table 74

Dose-dependent percent reduction of human MALAT1 RNA in A431 cells by modified oligonucleotides

Compound Number	MALAT1 (% UTC)				
	0.3 nM	1 nM	5 nM	20 nM	IC_{50} nM
559564	115	91	44	14	5
1157032	86	103	35	8	5
1157033	93	67	43	27	4
1157064	86	75	43	16	3
1157065	93	75	56	21	5
1157099	89	78	55	25	5
1157534	79	75	62	36	9
1157535	105	90	45	19	5
1157600	93	100	45	14	5
1157701	102	96	61	18	6
1157898	89	88	59	23	6
1158001	85	106	74	35	12
1158002	90	73	34	10	3
1158067	88	79	54	23	5
1158165	93	68	27	7	2
1158232	79	80	61	21	5
1158431	107	89	74	32	11
1158497	94	95	56	20	6
1158626	79	86	56	36	9

Table 75

Dose-dependent percent reduction of human MALAT1 RNA in A431 cells by modified oligonucleotides

Compound Number	MALAT1 (% UTC)				
	0.3 nM	1 nM	5 nM	20 nM	IC_{50} nM
559564	143	83	48	15	5
1157001	100	76	36	8	3
1157034⁂	72	57	26	6	1
1157035	115	89	46	11	4
1157101	95	83	48	13	4
1157102	113	65	25	8	3
1157836	95	83	56	28	6
1157900	105	93	51	19	5
1157901	56	83	62	16	6
1157902	109	86	34	13	4

1157934	108	80	46	11	4
1157936	91	59	24	5	2
1157969	119	96	53	17	6
1157970	89	60	19	5	2
1158003	89	82	43	10	3
1158004	90	62	30	7	2
1158069	88	78	47	19	4
1158167	95	88	51	15	5
1158168	84	63	33	9	2

Table 76

Dose-dependent percent reduction of human MALAT1 RNA in A431 cells by modified oligonucleotides

Compound Number	MALAT1 (% UTC)				
	0.3 nM	1 nM	5 nM	20 nM	IC_{50} nM
559564	135	84	58	17	6
946404	107	73	44	12	4
1157036	99	76	42	21	4
1157103	95	86	56	30	7
1157171	129	89	41	11	5
1157571	128	101	80	24	10
1157703	91	84	50	23	5
1157871	94	87	48	17	5
1157938	95	69	38	11	3
1157971	83	60	16	5	2
1157972	93	71	22	7	2
1158005	98	68	24	7	2
1158135	88	91	63	29	8
1158136	63	80	46	19	5
1158137	85	67	28	9	2
1158170	87	72	33	10	3
1158236	99	102	78	34	12
1158435	120	91	59	25	7
1158631	99	112	81	70	>20

Table 77

Dose-dependent percent reduction of human MALAT1 RNA in A431 cells by modified oligonucleotides

Compound Number	MALAT1 (% UTC)				
	0.3 nM	1 nM	5 nM	20 nM	IC_{50} nM
559564	129	95	55	18	6
1157139	89	69	44	14	3
1157306	104	61	63	17	5
1157474	148	129	78	28	11
1157575	102	61	29	9	3

1157807	85	77	77	31	11
1157872	117	104	57	20	7
1157905	117	91	47	22	6
1157940	121	88	43	12	5
1157973	108	87	34	7	4
1157974	128	106	47	12	6
1158006	94	77	44	16	4
1158138	91	80	44	14	4
1158139	93	66	25	7	2
1158171	102	81	28	8	3
1158172	95	72	38	12	3
1158337	97	84	43	14	4
1158338	96	92	57	17	5
1158568	117	77	47	18	5

Table 78

Dose-dependent percent reduction of human MALAT1 RNA in A431 cells by modified oligonucleotides

Compound Number	MALAT1 (% UTC)				
	0.3 nM	1 nM	5 nM	20 nM	IC_{50} nM
559564	132	103	68	22	8
1157009	151	100	54	23	7
1157108	114	74	30	9	3
1157109	137	78	52	16	5
1157142	111	96	88	28	13
1157150	107	100	74	35	13
1157207	129	102	65	22	8
1157750	122	113	92	58	>20
1157841	111	93	68	43	14
1157941	102	85	44	17	4
1157942	113	96	72	19	8
1157943	142	102	67	20	8
1158140	89	68	31	12	2
1158141	100	97	16	28	4
1158373	108	105	79	41	19
1158569	123	84	44	15	5
1158570	96	82	58	18	5
1158736	111	97	79	39	16
1158737	135	113	76	43	15

Table 79

Dose-dependent percent reduction of human MALAT1 RNA in A431 cells by modified oligonucleotides

Compound Number	MALAT1 (% UTC)				
	0.3 nM	1 nM	5 nM	20 nM	IC_{50} nM
559564	138	125	74	32	12
1156942	108	91	71	30	10
1157042	93	102	93	72	20
1157044	116	93	64	19	7
1157075	85	87	64	28	8
1157076	134	113	80	32	12
1157077	103	102	82	26	10
1157110	107	93	50	13	5
1157111⁂	108	73	6	7	2
1157279	127	111	99	74	>20
1157478	134	114	74	13	8
1157546	200	149	107	40	17
1157644	90	94	60	24	7
1157711	74	109	75	32	11
1157712	128	93	51	19	6
1158012	111	101	90	44	27
1158142	113	111	75	23	10
1158175	105	112	109	130	20
1158738	98	92	72	30	10

Table 80

Dose-dependent percent reduction of human MALAT1 RNA in A431 cells by modified oligonucleotides

Compound Number	MALAT1 (% UTC)				
	0.3 nM	1 nM	5 nM	20 nM	IC_{50} nM
559564	127	129	73	27	10
1156978	112	106	71	45	17
1157179	104	93	65	36	10
1157180	95	94	60	31	9
1157181	124	78	45	13	4
1157246	93	91	72	32	11
1157247	104	107	78	42	20
1157282	128	98	62	25	8
1157448	96	92	20	23	4
1157612	96	99	57	43	12
1157780	97	110	81	34	12
1157880	102	100	69	41	15
1157912	87	92	52	19	5
1157946	112	97	68	37	11
1157947	93	91	50	15	5

1158013	95	104	97	56	>20
1158312	96	99	77	33	13
1158541	102	96	68	43	16
1158839	95	81	82	44	>20

Table 81

Dose-dependent percent reduction of human MALAT1 RNA in A431 cells by modified oligonucleotides

Compound Number	MALAT1 (% UTC)				
	0.3 nM	1 nM	5 nM	20 nM	IC_{50} nM
559564	145	127	69	22	9
1157014	99	83	62	23	6
1157016	85	70	39	10	3
1157048	99	73	12	11	2
1157080	90	76	47	15	4
1157081	88	78	43	13	3
1157251	115	78	51	16	5
1157450	100	82	43	16	4
1157718	131	90	54	15	6
1157782	98	79	46	14	4
1157915	95	101	49	15	6
1157948	110	92	60	18	6
1157951	102	74	29	8	3
1157982	83	78	37	15	3
1157983	87	80	41	8	3
1158381	113	88	74	35	11
1158809	87	92	46	11	4
1158810	90	53	20	5	2
1158812	86	49	13	3	1

Table 82

Dose-dependent percent reduction of human MALAT1 RNA in A431 cells by modified oligonucleotides

Compound Number	MALAT1 (% UTC)				
	0.3 nM	1 nM	5 nM	20 nM	IC_{50} nM
559564	129	101	66	25	8
568503	95	78	21	21	3
1156951	94	84	47	14	4
1157153	102	91	64	25	7
1157185	156	109	65	23	8
1157186	85	83	44	15	4
1157318	96	97	73	41	18
1157454	81	81	36	11	3
1157519	105	101	75	36	14
1157752	110	61	39	12	3

1157886	95	101	48	15	6
1157919	95	89	34	10	3
1157953	109	94	46	13	5
1157987	93	82	38	12	3
1158051	113	120	137	81	20
1158084	112	93	60	30	8
1158183	90	84	51	20	5
1158645	107	98	49	22	6
1158814	98	88	66	23	7

Table 83

Dose-dependent percent reduction of human MALAT1 RNA in A431 cells by modified oligonucleotides

Compound Number	MALAT1 (% UTC)				
	0.3 nM	1 nM	5 nM	20 nM	IC_{50} nM
559564	142	106	57	17	7
1156950	97	78	47	15	4
1157015	94	80	37	11	3
1157017	89	75	43	11	4
1157084	82	86	51	12	3
1157518	74	71	29	9	4
1157717	87	66	27	9	7
1157754	99	82	54	19	7
1157783	95	83	58	12	2
1157918	96	76	40	9	3
1157920	131	79	41	11	3
1157950	94	78	10	8	2
1157984	50	59	28	4	2
1158021	174	131	60	19	2
1158150	85	82	53	14	5
1158614	82	45	16	3	1
1158780	85	99	67	19	5
1158811	105	65	40	8	4
1158813	100	110	67	12	8

Table 84

Dose-dependent percent reduction of human MALAT1 RNA in A431 cells by modified oligonucleotides

Compound Number	MALAT1 (% UTC)				
	0.3 nM	1 nM	5 nM	20 nM	IC_{50} nM
559564	179	119	67	17	8
1156954	93	85	59	25	6
1156987	118	80	39	7	4
1156988	113	81	52	17	5
1157021	106	86	17	24	4

1157188	106	93	58	28	8
1157290	115	81	71	27	8
1157489	100	88	35	6	3
1157922	91	90	63	19	7
1157954	98	82	48	18	5
1158055	103	85	43	10	4
1158056	91	80	57	24	6
1158186	77	82	57	22	6
1158187	98	84	45	12	4
1158285	90	73	57	24	5
1158386	119	92	56	13	6
1158388	134	137	87	29	12
1158615	93	43	8	1	1
1158616	93	83	49	17	4

Table 85

Dose-dependent percent reduction of human MALAT1 RNA in A431 cells by modified oligonucleotides

Compound Number	MALAT1 (% UTC)				
	0.3 nM	1 nM	5 nM	20 nM	IC_{50} nM
395254	112	67	73	35	10
559564	146	119	84	30	12
1156481	109	103	87	87	20
1156989	83	85	59	25	7
1157123	128	112	58	32	9
1157223	99	88	54	24	6
1157357	95	95	70	82	20
1157524	105	103	52	15	6
1157726	106	86	69	36	11
1157756	102	86	86	45	>20
1157923	89	83	24	18	3
1157957	82	96	38	17	5
1157991	88	80	25	4	2
1158090	128	118	115	59	20
1158255	90	84	74	26	9
1158487	115	91	74	22	8
1158585	62	78	47	17	4
1158717	80	97	80	66	20
1158851	89	84	95	83	20

Example 18: Dose-dependent inhibition of human MALAT1 in MDA-MB-436 cells by cEt gapmers

Modified oligonucleotides described in the studies above were tested at various doses in MDA-MB-436 cells. Cultured MDA-MB-436 cells at a density of 5,000-12,000 cells per well were treated using free uptake with modified oligonucleotides diluted to concentrations described in the tables below. After approximately 48 hours, MALAT1 RNA

levels were measured as previously described using the Human MALAT1 primer-probe set RTS2736. MALAT1 RNA levels were normalized to b-actin, measured using human primer-probe set HTS5002 (described herein above). Results are presented in the tables below as percent control of the amount of MALAT1 RNA relative to untreated control cells (%UTC). IC50s were calculated using the "log(inhibitor) vs. response – variable slope (4 parameters)" formula using Prism6 software. The %UTC values for modified oligonucleotides marked with a triple asterisk in the tables below has been previously presented in Example 4 (Table 4) herein above. The %UTC data for modified oligonucleotides marked with a triple asterisk (⁂) in the tables below is identical to the data presented in Table 4 as the data is from the same experiments.

Table 86

Dose-dependent inhibition of human MALAT1 RNA expression by modified oligonucleotides in MDA-MB-436 cells

Compound Number	%control				IC50 (nM)
	0.8 nM	4.0 nM	20.0 nM	100.0 nM	
559564	105	93	54	12	22.9
568503	90	76	34	20	12.2
1157044	138	84	51	20	22.9
1157131	102	52	47	6	9.6
1157150	92	80	53	27	25.0
1157190⁂	56	39	15	5	1.4
1157726	82	58	53	14	11.1
1157929⁂	58	51	33	5	2.6
1157936	34	30	18	6	0.2
1157943	64	49	39	10	3.6
1157958	50	32	21	6	0.9
1157959	83	52	27	5	4.9
1157992	51	44	9	2	1.2
1157993	67	28	14	3	1.6
1158002	49	62	49	12	3.7
1158005	49	34	17	3	0.8
1158161⁂	36	48	27	3	0.5
1158230	65	57	63	12	8.9
1158263	61	59	52	29	9.3
1158490	78	54	32	15	5.7
1158491	58	40	20	9	1.6
1156959	68	55	33	6	4.2
1158618	56	55	28	9	2.6
1158821	50	53	28	8	1.8
1158886	58	57	53	21	6.4
1157021	70	46	50	19	5.8
1157032	94	51	20	3	4.8
1157034⁂	50	25	17	5	0.7
1157048	57	41	28	9	1.7
1157097	56	63	27	4	3.2

1157108	51	37	18	3	1.0
1157110	51	48	17	5	1.4
1157111⁂	98	30	13	8	2.9
1157181	104	56	30	7	7.0
1157448	77	89	43	17	16.8
1157575	101	64	21	6	6.8
1157698	99	81	51	16	20.0
1157752	77	89	49	11	18.2
1157912	43	61	32	12	1.6
1157919	84	38	32	5	3.8
1157923	72	53	34	8	4.6
1157947	90	61	27	6	6.6
1157950	108	104	48	12	20.2
1157951	106	85	33	6	12.8
1157970	59	58	24	4	3.0
1157971	57	40	19	4	1.5
1157972	91	34	10	3	2.8
1157973	71	55	11	2	3.3
1157974	83	72	24	5	7.7
1157984	80	74	52	13	15.1
1157991	67	65	19	2	4.3
1158004	68	57	26	3	4.0
1158056	52	99	67	23	34.9
1158137	65	37	35	4	2.3
1158139	62	59	35	10	4.4
1158140	59	67	38	10	5.4
1158159	112	85	27	10	11.6
1158162⁂	57	37	22	6	1.5
1158163	118	51	16	7	4.0
1158164	90	52	19	6	4.7
1158165	79	36	10	3	2.5
1158168	45	37	19	6	0.7
1158171	78	31	16	6	2.4
1158492	41	29	12	5	0.4
1158614	45	36	26	8	0.6
1158615	31	19	14	6	0.1
1158810	40	23	11	4	0.4
1158812	47	29	15	2	0.7

Example 19: Tolerability of modified oligonucleotides targeting human MALAT1 in CD-1 mice

BALB/c mice are a multipurpose mouse model frequently utilized for safety and efficacy testing. The mice were treated with modified oligonucleotides selected from studies described above and evaluated for changes in the levels of various plasma chemistry markers.

Study 1

Groups of four 6-to-8-week-old male BALB/c mice were injected subcutaneously twice a week for 4 weeks (for a total of 8 treatments) with 50 mg/kg of modified oligonucleotides. One group of four male CD-1 mice was injected with PBS. Mice were euthanized 24 hours following the final administration.

To evaluate the effect of modified oligonucleotides on liver and kidney function, plasma levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL), and blood urea nitrogen (BUN) were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400c, Melville, NY). The results are presented in the table below. Assays include four animals in a group, except where an asterisk (*) indicates that 3 animals or less was used for a specific assay. Modified oligonucleotides that caused changes in the levels of any of the liver or kidney function markers outside the expected range for modified oligonucleotides were excluded in further studies.

Table 87

Plasma chemistry markers in male BALB/c mice

Compound Number	ALT (IU/L)	AST (IU/L)	BUN (mg/dL)
PBS	126	112	23
556057	6377	4060	29
556089	120	127	19
559479	511	521	24
559482	65	89	25
559484	2728	1760	24
559497*	43	72	28
559509	2535	2366	28
559511	2226	1626	25
559512	304	261	28
559519	912	470	24
559547	2213	839	32
559548	3279	1520	28
559551	374	215	21
559554	1921	1649	24
559564	88	116	24
559567	2832	5557	24
559581	1301	842	23
559585	1038	1053	25
559587	716	490	24
559588	2706	2201	18
559590*	195	158	24
559596	51	114	24
559598	1301	999	25
559609*	390	356	24

Body weight was measured on day 25, and the average body weight for each group is presented in the table below. Liver, kidney and spleen weights were measured at the end of the study and are presented in the table below. Modified oligonucleotides that caused any changes in organ weights outside the expected range for modified oligonucleotides were excluded from further studies.

Table 88

Body and organ weights (in grams)

Compound Number	Body Weight (g)	Liver (g)	Kidney (g)	Spleen (g)
PBS	25	1.3	0.4	0.1
556057	20	2.2	0.3	0.1
556089	25	1.7	0.4	0.1
559479	24	1.8	0.4	0.1
559482	26	1.5	0.4	0.2
559484	26	2.1	0.4	0.2
559497*	24	1.3	0.4	0.1
559509	25	1.2	0.4	0.1
559511	22	1.4	0.3	0.1
559512	25	1.7	0.4	0.1
559519	24	1.8	0.3	0.1
559547	20	1	0.3	0.1
559548	25	3.4	0.3	0.2
559551	23	1.2	0.3	0.1
559554	27	2.2	0.4	0.2
559564	25	1.5	0.4	0.2
559567	17	1	0.3	0
559581	23	1.7	0.3	0.1
559585	24	1.6	0.4	0.1
559587	26	2.2	0.4	0.2
559588	22	1.4	0.3	0.2
559590*	26	1.9	0.4	0.2
559596	24	1.4	0.4	0.1
559598	25	1.9	0.4	0.1
559609	25	1.8	0.4	0.3

Study 2

Groups of four 4-to-6-week-old male CD-1 mice were injected subcutaneously twice a week for 4 weeks (for a total of 8 treatments) with 50 mg/kg/dose of modified oligonucleotides. One group of four male CD-1 mice was injected with PBS. Mice were euthanized 24 hours following the final administration. The values for modified oligonucleotides marked with a triple asterisk in the tables below have been previously presented in Tables 7 and 8 herein above. The data

for modified oligonucleotides marked with a triple asterisk (⁂) in the tables below is identical to the data presented in Table 7 and Table 8 as the data is from the same experiments.

To evaluate the effect of modified oligonucleotides on liver and kidney function, plasma levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), total bilirubin (TBIL), and albumin (ALB) were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400c, Melville, NY). The results are presented in the table below. Assays include four animals in a group, except where an asterisk (*) indicates that 3 animals or less was used for a specific assay. Modified oligonucleotides that caused changes in the levels of any of the liver or kidney function markers outside the expected range for modified oligonucleotides were excluded in further studies.

Table 89

Plasma chemistry markers in CD-1 Male mice

Compound Number	ALT (IU/L)	AST (IU/L)	BUN (mg/dL)	TBIL (mg/dL)	ALB (g/dL)
PBS	20	46	24	0.2	2.5
1157190	78	95	26	0.2	2.6
1157919	388	269	30	0.3	2.3
1157929⁂	330	225	24	0.2	2.3
1157936	220	171	25	0.2	2.2
1157958	38	50	22	0.2	2.4
1157970	195	250	25	6.1	3.1
1157972	1172	824	23	2.9	2.9
1157991	343	264	25	0.2	2.2
1157992	1168	2608	18	1.9	2.5
1157993	630	545	23	0.2	1.9
1158002	963	737	26	0.2	2.2
1158005	115	149	25	0.2	1.9
1158161⁂	86	128	29	0.2	2.3
1158162	178	199	25	0.2	2.5
1158491	598	684	24	0.2	2.2
1158492	451	417	20	0.2	1.9
1158810	1589*	1409*	37*	0.3*	2.3*
1158812	4795*	4273*	30*	1.4*	4.5*

Body weights of CD-1 mice were measured at the end of the study, and the average body weight for each group is presented in the table below. Liver, kidney and spleen weights were measured at the end of the study and are presented in the table below. Modified oligonucleotides that caused any changes in organ weights outside the expected range for modified oligonucleotides were excluded from further studies.

Table 90

Body and organ weights (in grams)

Compound Number	Body Weight (g)	Liver (g)	Kidney (g)	Spleen (g)
PBS	32	1.7	0.5	0.1
1157190	36	2.2	0.5	0.2
1157919	38	2.9	0.5	0.4
1157929⁂	34	2.3	0.5	0.2
1157936	33	2	0.5	0.1
1157958	35	2.1	0.5	0.2
1157970	31	2.2	0.4	0.2
1157972	31	2.7	0.5	0.2
1157991	37	2.6	0.5	0.2
1157992	29	2.3	0.5	0.1
1157993	37	2.7	0.6	0.3
1158002	31	2.2	0.5	0.2
1158005	35	2.2	0.5	0.2
1158161⁂	34	2.3	0.5	0.2
1158162	34	2.3	0.6	0.2
1158491	34	2.1	0.5	0.2
1158492	36	2.1	0.5	0.2
1158810	28	1.7	0.4	0.1
1158812	27	2	0.4	0.1

Study 3

Groups of four 4-to-6-week-old male CD-1 mice were injected subcutaneously twice a week for 4 weeks (for a total of 8 treatments) with 50 mg/kg/dose of modified oligonucleotides. One group of four male CD-1 mice was injected with PBS. Mice were euthanized 24 hours following the final administration.

To evaluate the effect of modified oligonucleotides on liver and kidney function, plasma levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), and total bilirubin (TBIL) were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400c, Melville, NY). The results are presented in the table below. Assays include four animals in a group, except where an asterisk (*) indicates that 3 animals or less was used for a specific assay. Modified oligonucleotides that caused changes in the levels of any of the liver or kidney function markers outside the expected range for modified oligonucleotides were excluded in further studies.

The values for modified oligonucleotides marked with a triple asterisk in the tables below have been previously presented in Tables 13 and 14 herein above. The data for modified oligonucleotides marked with a triple asterisk (⁂) in the tables below is identical to the data presented in Table 13 and Table 14 as the data is from the same experiments

Table 91

Plasma chemistry markers in CD-1 Male mice

ION NO.	ALT (IU/L)	AST (IU/L)	BUN (mg/dL)	TBIL (mg/dL)
PBS	20	51	21	0.2
1157032	1933	746	20	0.1
1304893	52	106	19	0.2
1157919	389	271	30	0.2
1304889	57	80	25	0.2
1157936	86	87	18	0.2
1304906***	59	78	22	0.2
1157970	224	305	21	0.2
1304890***	33	51	21	0.2
1157972	1477	785	28	0.3
1304888	59	94	21	0.2
1157993	455	428	20	0.2
1304903	194	157	19	0.2
1158002	861	734	26	0.1
1304883	203	271	26	0.2
1158162	240	243	24	0.2
1304898	310	335	24	0.2
1158491	131	155	27	0.2
1304900	61	140	27	0.3
1158492	422	358	20	0.2
1304899	66	96	21	0.2
1158812	3116	2358	25	0.5
1304895	35	98	24	0.2
1158139	326	256	22	0.2
1304882	1931	797	23	0.2
1158168	1492	880	31	0.2
1304901	1790	1477	34	4.3
1157974	1664	1935	23	2.5
1304885	98	107	18	0.2

Body weights of CD-1 male mice were measured at days 1 and 25, and the average body weight for each group is presented in the table below. Liver, kidney and spleen weights were measured at the end of the study and are presented in the table below. Modified oligonucleotides that caused any changes in organ weights outside the expected range for modified oligonucleotides were excluded from further studies.

Table 92

Body and organ weights (in grams)

ION No.	Body Weight (g)	Liver (g)	Kidney (g)	Spleen (g)
PBS	32	1.6	0.5	0.1
1157032	32	2	0.5	0.2
1304893	35	2	0.5	0.1
1157919	34	2.4	0.4	0.2
1304889	35	1.9	0.5	0.2
1157936	38	2.1	0.6	0.1
1304906***	34	1.8	0.5	0.1
1157970	33	2.2	0.4	0.2
1304890***	36	2	0.5	0.2
1157972	30	2.4	0.4	0.1
1304888	35	1.9	0.5	0.1
1157993	36	2.5	0.5	0.3
1304903	36	2.3	0.5	0.2
1158002	34	2.1	0.5	0.2
1304883	35	2	0.6	0.2
1158162	35	2	0.5	0.1
1304898	37	2.4	0.6	0.2
1158491	36	2.1	0.5	0.2
1304900	34	1.9	0.6	0.3
1158492	36	2	0.6	0.2
1304899	35	2	0.5	0.2
1158812	27	1.9	0.4	0.1
1304895	37	1.9	0.5	0.2
1158139	34	2.6	0.5	0.1
1304882	32	3.1	0.5	0.1
1158168	37	5.4	0.5	0.2
1304901	32	5	0.5	0.2
1157974	26	1.2	0.5	0.1
1304885	36	2.3	0.6	0.2

Study 4

Groups of four 4-to-6-week-old male CD-1 mice were injected subcutaneously twice a week for 4 weeks (for a total of 8 treatments) with 50 mg/kg/dose of modified oligonucleotides. One group of four male CD-1 mice was injected with PBS. Mice were euthanized 72 hours following the final administration. The values for modified oligonucleotides marked with a triple asterisk in the tables below have been previously presented in Tables 15 and 16 herein above. The

data for modified oligonucleotides marked with a triple asterisk (⁂) in the tables below is identical to the data presented in Table 15 and Table 16 as the data is from the same experiments.

To evaluate the effect of modified oligonucleotides on liver and kidney function, plasma levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), and total bilirubin (TBIL) were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400c, Melville, NY). The results are presented in the table below. Assays include four animals in a group, except where an asterisk (*) indicates that 3 animals or less was used for a specific assay. Modified oligonucleotides that caused changes in the levels of any of the liver or kidney function markers outside the expected range for modified oligonucleotides were excluded in further studies.

Table 93

Plasma chemistry markers in CD-1 Male mice

Compound Number	ALT (IU/L)	AST (IU/L)	BUN (mg/dL)	TBIL (mg/dL)
PBS	19	56	16	0.2
1304879	36	48	14	0.1
1304880	129	153	16	0.1
1304881	103	80	14	0.2
1304884⁂	33	55	15	0.1
1304886	27	71	17	0.1
1304887	1531	1672	20	1.5
1304891	242	143	17	0.1
1304892	79	94	17	0.2
1304894	1009	569	19	0.2
1304896	51	54	15	0.2
1304897	99*	106*	16*	0.1*
1304902	34	47	16	0.1
1304904	29	52	15	0.1
1304905	737	389	16	0.1
1304907	102	84	14	0.1
1304908	71	69	17	0.1

Body weights of CD-1 male mice were measured at days 1 and 25, and the average body weight for each group is presented in the table below. Liver, kidney and spleen weights were measured at the end of the study and are presented in the table below. Modified oligonucleotides that caused any changes in organ weights outside the expected range for modified oligonucleotides were excluded from further studies.

Table 94

Body and organ weights (in grams)

Compound Number	Body Weight (g)	Liver (g)	Kidney (g)	Spleen (g)
PBS	34	2	0.5	0.1
1304879	34	2.2	0.5	0.1
1304880	36	2.5	0.5	0.2
1304881	34	2.2	0.5	0.2
1304884⁂	37	2.2	0.5	0.2
1304886	38	2.2	0.6	0.1
1304887	33	2.9	0.4	0.1
1304891	37	3.2	0.5	0.2
1304892	35	2.3	0.5	0.2
1304894	33	1.7	0.4	0.1
1304896	35	2.1	0.5	0.1
1304897	35	2.2*	0.5*	0.2*
1304902	39	2.4	0.6	0.2
1304904	37	2.2	0.5	0.2
1304905	38	2.6	0.5	0.2
1304907	36	1.9	0.5	0.1
1304908	37	2.3	0.6	0.3

Study 5

Groups of four 4-to-6-week-old male CD-1 mice were injected subcutaneously twice a week for 4 weeks (for a total of 8 treatments) with 50 mg/kg/dose of modified oligonucleotides. One group of four male CD-1 mice was injected with PBS. Mice were euthanized 24 hours following the final administration. The values for modified oligonucleotides marked with a triple asterisk in the tables below have been previously presented in Tables 9 and 10 herein above. The data for modified oligonucleotides marked with a triple asterisk (⁂) in the tables below is identical to the data presented in Table 9 and Table 10 as the data is from the same experiments.

To evaluate the effect of modified oligonucleotides on liver and kidney function, plasma levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN) and total bilirubin (TBIL) were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400c, Melville, NY). The results are presented in the table below. Assays include four animals in a group, except where an asterisk (*) indicates that 3 animals or less was used for a specific assay. Modified oligonucleotides that caused changes in the levels of any of the liver or kidney function markers outside the expected range for modified oligonucleotides were excluded in further studies.

Table 95

Plasma chemistry markers in CD-1 Male mice

Compound Number	ALT (IU/L)	AST (IU/L)	BUN (mg/dL)	TBIL (mg/dL)
PBS	43	71	26	0.2
1157034	891	641	23	0.2
1157032	579	652	20	0.2
1157048	2247	2324	20	4.2
1157110	1408	966	25	0.3
1157111⁂	341	200	22	0.2
1158139	651	307	25	0.2
1158614	8358*	6909*	37*	4.6*
1158615	1699	1170	30	0.3
1158168	3846	1734	27	10.7
1157974	1399	1957	16*	1.1

Body weights of CD-1 male mice were measured at days 1 and 25, and the average body weight for each group is presented in the table below. Liver, kidney and spleen weights were measured at the end of the study and are presented in the table below. Modified oligonucleotides that caused any changes in organ weights outside the expected range for modified oligonucleotides were excluded from further studies.

Table 96

Body and organ weights (in grams)

Compound Number	Body Weight (g)	Liver (g)	Kidney (g)	Spleen (g)
PBS	37	2	0.6	0.1
1157032	35	2.3	0.4	0.2
1157034	33	2	0.4	0.1
1157048	31	2.7	0.4	0.1
1157110	32	1.8	0.5	0.2
1157111⁂	38	2.8	0.5	0.2
1157974	30	1.6	0.5	0.2
1158139	34	3	0.4	0.1
1158168	31	5.1	0.4	0.1
1158614	27	3.2	0.4	0
1158615	26	1.6	0.3	0.1

Example 20: Tolerability of modified oligonucleotides targeting human MALAT1 in Sprague-Dawley rats

Sprague-Dawley rats are a multipurpose model used for safety and efficacy evaluations. The rats were treated with Ionis modified oligonucleotides from the studies described in the Examples above and evaluated for changes in the levels of various plasma chemistry markers.

Study 1

Groups of 4 Sprague-Dawley rats each were weekly injected subcutaneously with 50 mg/kg of Ionis oligonucleotide for 6 weeks (total 7 doses). The rats were euthanized; and organs, urine and plasma were harvested for further analysis 2 days after the last dose.

Plasma chemistry markers

To evaluate the effect of modified oligonucleotides on liver and kidney function, plasma levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN) and total bilirubin (TBIL) were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400c, Melville, NY). The results are presented in the table below. Assays include four animals in a group, except where an asterisk (*) indicates that 3 animals or less was used for a specific assay. Modified oligonucleotides that caused changes in the levels of any of the liver or kidney function markers outside the expected range for modified oligonucleotides were excluded in further studies.

Table 97

Plasma chemistry markers in Sprague-Dawley rats

Compound Number	ALT (IU/L)	AST (IU/L)	BUN (mg/dL)	TBIL (mg/dL)
PBS	65	133	16	0.7
1157034*	333	292	195	0.8
1157111	37	73	31	0.2
1157190	47	83	19	0.2
1157929	42	74	20	0.2
1158161	92	117	22	0.2
1158162	882	700	96	1.7

Blood obtained from rat groups at the end of the study, day 43, were sent to IDEXX BioAnalytics for measurement of blood cell counts. Counts taken include red blood cell (RBC) count, Hemoglobin (HGB), Hematocrit (HCT), platelet count (PLT), total white blood cell count (WBC), neutrophil counts (NEU), lymphocyte counts (LYM), and monocyte counts (MON). The results are presented in the tables below. Ionis oligonucleotides that caused changes in the blood cell count outside the expected range for modified oligonucleotides were excluded in further studies.

Table 98

Blood Cell Count in Sprague-Dawley Rats

Compound No.	RBC (x106/µL)	HGB (g/dL)	HCT (%)	PLT (10^3/µL)	WBC (x10^3/µL)	NEU (%)	LYM (%)	MON (%)
PBS	8	15	44	667	8	18	75	5

1157034*	6	11	32	836	15	42	53	5
1157111	6	11	34	677	17	32	62	5
1157190	6	12	35	632	10	19	76	4
1157929	7	12	36	771	9	25	69	5
1158161	7	13	36	1068	10	28	65	7
1158162	7	11	33	743	21	33	60	7

To evaluate the effect of Ionis oligonucleotides on kidney function, urinary levels of micro total protein (MTP) and creatinine were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400c, Melville, NY). The ratios of MTP to creatinine (MTP/C ratio) are presented in the table below. Ionis oligonucleotides that caused changes in the levels of the ratio outside the expected range for modified oligonucleotides were excluded in further studies.

Table 99

MTP to creatinine ratio in Sprague-Dawley rats

Compound Number	MTP/C Ratio
PBS	3
1157034*	837
1157111	77
1157190	11
1157929	15
1158161	13
1158162	161

Body weights of rats were measured at on day 41, and the average body weight for each group is presented in the table below. Liver, spleen and kidney weights were measured at the end of the study, and are presented in the table below. Ionis oligonucleotides that caused any changes in organ weights outside the expected range for modified oligonucleotides were excluded from further studies.

Table 100

Body and organ weights (g)

Compound Number	Body Weight (g)	Liver (g)	Kidney (g)	Spleen (g)
PBS	469	17	3.5	1.1
1157034*	338	13	7.1	1.3
1157111	348	16	3.2	1.8
1157190	358	16	3.7	2.2
1157929	389	16	3.2	1.8

1158161	422	16	3.3	1.7
1158162	306	13	4.1	1.2

Study 2

Groups of 4 Sprague-Dawley rats each were weekly injected subcutaneously with 50 mg/kg of Ionis oligonucleotide for 6 weeks (total 7 doses). The rats were euthanized; and organs, urine and plasma were harvested for further analysis 1 day after the last dose.

Plasma chemistry markers

To evaluate the effect of modified oligonucleotides on liver and kidney function, plasma levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN) and total bilirubin (TBIL) were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400c, Melville, NY). The results are presented in the table below. Modified oligonucleotides that caused changes in the levels of any of the liver or kidney function markers outside the expected range for modified oligonucleotides were excluded in further studies.

Table 101

Plasma chemistry markers in Sprague-Dawley rats

Compound Number	ALT (IU/L)	AST (IU/L)	BUN (mg/dL)	TBIL (mg/dL)
PBS	70	66	15	0.12
1304884	70	85	19	0.11
1304890	49	78	18	0.11
1304906	77	103	18	0.15

Blood obtained from rat groups at the end of the study, day 43, were sent to IDEXX BioAnalytics for measurement of blood cell counts. Counts taken red blood cell (RBC) count, Hemoglobin (HGB), Hematocrit (HCT), platelet count (PLT), total white blood cell count (WBC), neutrophil counts (NEU), lymphocyte counts (LYM), and monocyte counts (MON).. The results are presented in the tables below. Ionis oligonucleotides that caused changes in the blood cell count outside the expected range for modified oligonucleotides were excluded in further studies.

Table 102

Blood Cell Count in Sprague-Dawley Rats

Compound No.	RBC (x106/µL)	HGB (g/dL)	HCT (%)	PLT (10^3/µL)	WBC (x10^3/µL)	NEU (%)	LYM (%)	MON (%)
PBS	7	14	39	351	8	13	81	5
1E+06	7	14	39	450	11	17	79	4
1E+06	8	14	40	578	8	7	86	6
1E+06	8	15	41	545	10	15	78	7

To evaluate the effect of Ionis oligonucleotides on kidney function, urinary levels of micro total protein (MTP) and creatinine were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400c, Melville,

NY). The ratios of MTP to creatinine (MTP/C ratio) are presented in the table below. Ionis oligonucleotides that caused changes in the levels of the ratio outside the expected range for modified oligonucleotides were excluded in further studies.

Table 103

MTP to creatinine ratio in Sprague-Dawley rats

Compound Number	MTP/C
PBS	3
1304884	15
1304890	16
1304906	12

Body weights of rats were measured at days 1 and 38 and the average body weight for each group is presented in the table below. Liver, spleen and kidney weights were measured at the end of the study, and are presented in the table below. Ionis oligonucleotides that caused any changes in organ weights outside the expected range for modified oligonucleotides were excluded from further studies.

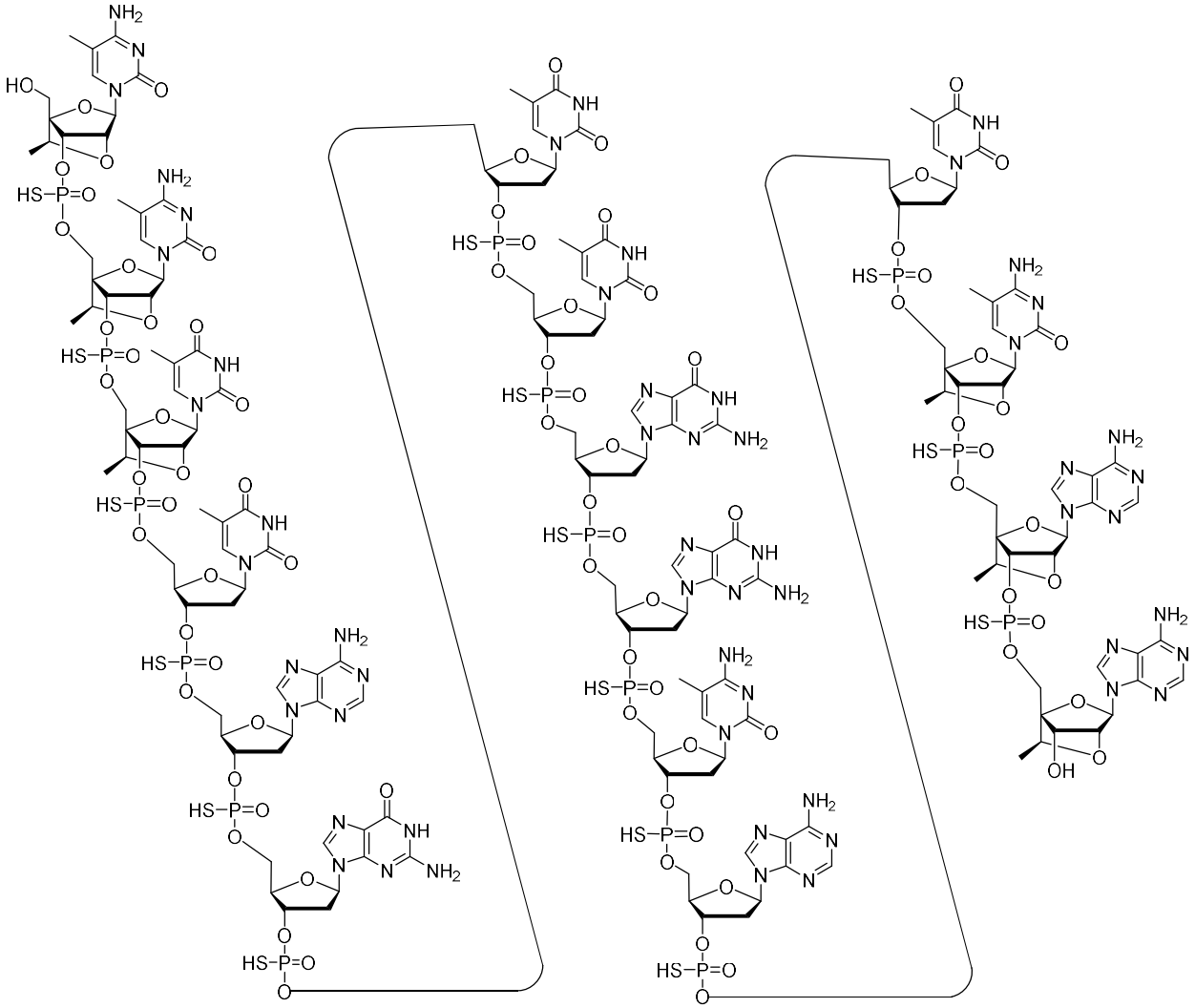
Table 104

Body and organ weights (g)

Compound Number	Body Weight (g)	Liver (g)	Kidney (g)	Spleen (g)
PBS	474	17.4	3.7	0.8
1E+06	385	15.5	3.3	1.9
1E+06	385	15	3.4	1.5
1E+06	404	15.1	3.4	2.1

WHAT IS CLAIMED:

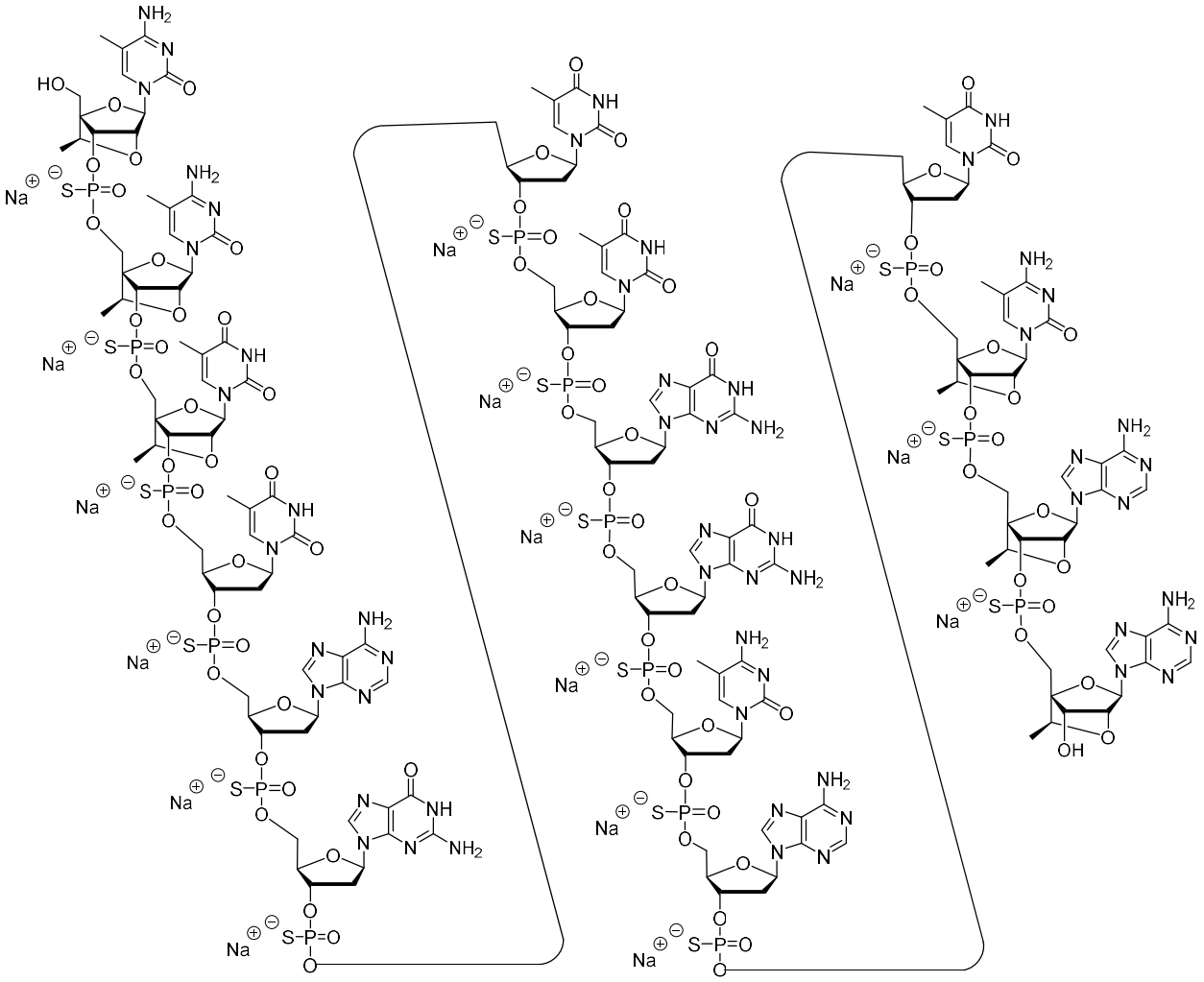
1. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 6), or a salt thereof.

2. The modified oligonucleotide of claim 1, wherein the modified oligonucleotide is the sodium salt or the potassium salt.

3. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 6).

4. A composition comprising the modified oligonucleotide of any one of claims 1-3, and a pharmaceutically acceptable diluent or carrier.

5. A composition comprising the modified oligonucleotide of any one of claims 1-3, and water.

6. Use of the modified oligonucleotide of any one of claims 1-3 in the manufacture of a medicament for treating, preventing or ameliorating a cancer.

7. The use of claim 6, wherein the cancer is cancer associated with MALAT1.

8. The use of claim 6 or 7, wherein the cancer is breast cancer; inflammatory breast cancer; breast ductal carcinoma; breast lobular carcinoma; luminal A breast cancer; luminal B breast cancer; basal-like breast cancer; HER2 positive (HER2+) breast cancer; HER2 negative (HER2-) breast cancer; Estrogen Receptor negative (ER-) breast cancer; Estrogen Receptor positive (ER+) breast cancer; Progesterone Receptor negative (PR-) breast cancer; Progesterone Receptor positive (PR+) breast cancer; ER positive (ER+) and PR positive (PR+) breast cancer; ER positive (ER+) and PR negative (PR-) breast cancer; ER negative (ER-) and PR

positive (PR+) breast cancer; ER positive (ER+) and HER2 negative (HER2-) breast cancer; ER-, PR-, and HER2- triple negative breast cancer (ER-, PR-, HER2-; TNBC); hormone receptor negative breast cancer (ER- and PR-); ER+, PR+, and HER2+ triple positive breast cancer (ER+, PR+, HER2+; TPBC); hepatocellular carcinoma (HCC); head and neck squamous cell carcinoma (HNSCC); oral tongue squamous cell carcinoma (OTSCC); sarcomas (e.g. epitheloid, rhabdoid and synovial); esophageal cancer; gastric cancer; ovarian cancer; pancreatic cancer; lung cancer; non-small cell lung carcinoma (NSCLC); small-cell lung carcinoma (SCLC); squamous cell carcinoma (SCC); head and neck cancer; head and neck squamous cell carcinoma (HNSCC); gastrointestinal cancer; large intestinal cancer; small intestinal cancer; stomach cancer; colon cancer; colorectal cancer; bladder cancer; liver cancer; biliary tract cancer; urothelial cancer; endometrial cancer; cervical cancer; prostate cancer; mesothelioma; chordoma; renal cancer; renal cell carcinoma (RCC); brain cancer; neuroblastoma; glioblastoma; skin cancer; melanoma; basal cell carcinoma; merkel cell carcinoma; blood cancer; hematopoetic cancer; myeloma; multiple myeloma (MM); B cell malignancies; lymphoma; B cell lymphoma; Hodgkin lymphoma; T cell lymphoma; leukemia; or acute lymphocytic leukemia (ALL).

9. The use of any one of claims 6-8, wherein the modified oligonucleotide is to be administered parenterally.

10. The use of any one of claims 6-9, wherein the modified oligonucleotide inhibits or reduces cancer cell proliferation, cancer cell migration, cancer cell branching morphogenesis, tumor progression, tumor growth, or metastasis.

11. The use of any one of claims 6-10, wherein the modified oligonucleotide increases or induces cancer cell differentiation, cancer cell adhesion, or tumor differentiation.

12. The use of any one of claims 6-11, wherein the modified oligonucleotide induces a cancer cell or tumor to have a cystic, ductular, or acinar phenotype or morphology.

13. The use of any one of claims 6-12, wherein the modified oligonucleotide induces a cancer cell or tumor to have a more differentiated phenotype or structure.

14. The use of claim 13, wherein the more differentiated phenotype or structure comprises presence of secretory lipid droplets, increased desmosomal structures, polarized ductal structures, or increased levels of E-cadherin or casein.

15. Use of the modified oligonucleotide of any one of claims 1-3 in the manufacture of a medicament for

inhibiting expression of MALAT1 in a cancer cell;

reducing or inhibiting cancer cell proliferation, cancer cell migration, cancer cell branching morphogenesis, tumor progression, tumor growth, or metastasis in an individual having cancer;

increasing or inducing cancer cell differentiation, cancer cell adhesion, or tumor differentiation in an individual having cancer;

inducing a cancer cell or tumor to have a cystic, ductular, or acinar phenotype or morphology in an individual; or

inducing a cancer cell or tumor to have a more differentiated phenotype or structure, optionally wherein the more differentiated phenotype or structure comprises presence of secretory lipid droplets, increased desmosomal structures, polarized ductal structures, or increased levels of E-cadherin or casein.

16. The modified oligonucleotide of any one of claims 1-3 for use in therapy.