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(54) Title: MODULATION OF DYRK1B EXPRESSION

(57) Abstract: Provided herein are methods, compounds, and compositions for reducing expression of DYRK1B in an animal. Such methods, compounds, and compositions are useful to treat, prevent, delay, or ameliorate a metabolic disease or disorder in an individual in need.



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MODULATION OF DYRK1B 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 BIOL0292WOSEQ_ST25.txt, created on March 14, 2017 which is 68 MB in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

Field of the Invention

Provided herein are methods, compounds, and compositions useful for reducing expression of dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1B (hereinafter referred to as DYRK1B) in an animal. Also, provided herein are methods, compounds, and compositions comprising DYRK1B inhibitors, which can be useful in reducing DYRK1B-related diseases or conditions in an animal. Such methods, compounds, and compositions can be useful, for example, to treat, prevent, delay or ameliorate metabolic disease in an animal.

Background

The metabolic abnormalities such as high glucose, blood lipids, blood pressure and obesity have caused severe health threats. Recently, a genetic analysis study has identified the dual specificity tyrosine phosphorylation regulated kinase 1B (DYRK1B) as a causative mutation for metabolic diseases. DYRK1B is a dual-specificity kinases that possesses both serine/threonine and tyrosin kinase activities. The substituting cysteine for arginine at position 102 (R102C) mutation in DYRK1B showed gain-of-function activities and association with metabolic disease (Keramati et al, New Engl. J. Med. 370: 1909-1919, 2014). In another finding, L28P variant in DYRK1B, assumed loss-of-function mutation, showed significant protective effects against type 2 diabetes as well as hypertension. GWAS studies of the DYRK1B locus has been linked to Type 2 diabetes (Sim et al., PLoS Genet. 7: e1001363, 2011 and Cho et al., Hum. Mol. Genet. 21: 947-957, 2012).

Summary

Provided herein are compositions, compounds and methods for modulating expression of DYRK1B associated with metabolic diseases or disorders. In certain embodiments, these compositions, compounds and methods are for modulating the expression of DYRK1B. In certain embodiments, the DYRK1B modulator is a DYRK1B-specific inhibitor. In certain embodiments, the DYRK1B-specific inhibitor decreases expression of a DYRK1B. In certain embodiments, DYRK1B-specific inhibitors include nucleic acids, proteins and small molecules. In certain embodiments, the DYRK1B-specific inhibitor is a nucleic acid. In certain embodiments, the nucleic acid is a compound. In certain embodiments, the compound comprises a modified

oligonucleotide. In certain embodiments, the modified oligonucleotide can be single stranded or double stranded.

Certain embodiments are directed to DYRK1B inhibitors useful for inhibiting a DYRK1B, which can be useful for treating, ameliorating, or slowing progression of a metabolic disease or disorder. Certain
5 embodiments relate to the novel findings of antisense inhibition of DYRK1B resulting in several metabolic endpoint lowering. Certain embodiments are directed to DYRK1B inhibitors useful in improving glucose tolerance. Certain embodiments are directed to DYRK1B inhibitors useful in reducing hyperglycemia. Certain embodiments are directed to DYRK1B inhibitors useful in improving insulin sensitivity. Certain
10 embodiments are directed to DYRK1B inhibitors useful in improving glucose homeostasis. Certain embodiments are directed to DYRK1B inhibitors useful in reducing hypertension. In certain embodiments, the DYRK1B inhibitor is specific to DYRK1B and does not inhibit DYRK1A expression. In certain embodiments, it is desirable to inhibit DYRK1B expression without inhibiting DYRK1A expression.

Detailed Description of the Invention

It is to be understood that both the foregoing general description and the following detailed
15 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
20 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
25 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 ISIS number (ISIS #) indicate a combination of nucleobase sequence, chemical modification, and motif.

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

30 “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(CH₂)₂-OCH₃) 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.

5 “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.

10 “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 $\pm 10\%$ of a value. For example, if it is stated, “the compounds affected about 70% inhibition of a DYRK1B”, it is implied that DYRK1B levels are inhibited within a range of 60% and
15 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.

20 “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
25 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
30 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.

“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.

“Cardiovascular disease” or “cardiovascular disorder” refers to a group of conditions related to the heart, blood vessels, or the circulation.

“Chemical modification” in a compound describes the substitutions or changes through chemical reaction, of any of the units in the compound. “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.

“Cholesterol” is a sterol molecule found in the cell membranes of all animal tissues. Cholesterol may be transported in an animal’s blood plasma by lipoproteins including very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), low density lipoprotein (LDL), and high density lipoprotein (HDL). “Plasma cholesterol” refers to cholesterol present in the plasma.

“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 (^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. 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.

“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.

“Diabetes mellitus” or “diabetes” is a syndrome characterized by disordered metabolism and abnormally high blood sugar (hyperglycemia) resulting from insufficient levels of insulin or reduced insulin sensitivity. The characteristic symptoms are excessive urine production (polyuria) due to high blood glucose levels, excessive thirst and increased fluid intake (polydipsia) attempting to compensate for increased urination, blurred vision due to high blood glucose effects on the eye's optics, unexplained weight loss, and lethargy.

“Diabetic dyslipidemia” or “type II diabetes with dyslipidemia” means a condition characterized by Type II diabetes, reduced HDL-C, elevated triglycerides, and elevated small, dense LDL particles.

“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” mean 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 compound” means a 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.

“DYRK1B” means dual specificity tyrosine phosphorylation regulated kinase 1B and refers to any nucleic acid of DYRK1B. For example, in certain embodiments, DYRK1B includes a DNA sequence encoding the DYRK1B, an RNA sequence transcribed from DNA encoding the DYRK1B (including genomic DNA comprising introns and exons). The target may be referred to in either upper or lower case.

5 “DYRK1B-specific inhibitor” refers to any agent capable of specifically inhibiting DYRK1B expression or activity at the molecular level. For example, DYRK1B-specific inhibitors include nucleic acids (including antisense compounds), peptides, antibodies, small molecules, and other agents capable of inhibiting the expression of DYRK1B.

10 “Dyslipidemia” refers to a disorder of lipid and/or lipoprotein metabolism, including lipid and/or lipoprotein overproduction or deficiency. Dyslipidemias may be manifested by elevation of lipids such as cholesterol and triglycerides as well as lipoproteins such as low-density lipoprotein (LDL) cholesterol.

15 “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.

20 “Elevated cholesterol” means cholesterol at a concentration in a subject at which lipid-lowering therapy is recommended, and includes, without limitation, elevated LDL-C”, “elevated VLDL-C,” “elevated IDL-C” and “elevated non-HDL-C.” In certain embodiments, cholesterol concentrations of less than 200 mg/dL, 200-239 mg/dL, and greater than 240 mg/dL are considered desirable, borderline high, and high, respectively. In certain embodiments, LDL-C concentrations of 100 mg/dL, 100-129 mg/dL, 130-159 mg/dL, 160-189 mg/dL, and greater than 190 mg/dL are considered optimal, near optimal/above optimal, borderline high, high, and very high, respectively.

25 “Elevated triglyceride” means a concentration of triglyceride in the serum or liver at which lipid-lowering therapy is recommended, and includes “elevated triglyceride” and “elevated liver triglyceride.” In certain embodiments, triglyceride concentration of 150-199 mg/dL, 200-499 mg/dL, and greater than or equal to 500 mg/dL is considered borderline high, high, and very high, respectively.

30 “Ensembl ID” is an identification number consisting of letters and numbers assigned to a gene sequence by Ensembl, which is a joint project between EMBL-EBI and the Wellcome Trust Sanger Institute to develop a software system that produces and maintains automatic annotation of selected eukaryotic genomes. Ensembl annotation helps identify a gene location in a particular genome and can be used to configure the equivalent gene on another species’ genome.

“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.”

“Glucose” is a monosaccharide used by cells as a source of energy and metabolic intermediate.

“Plasma glucose” refers to glucose present in the plasma or serum

“Glucose tolerance test” in medical practice is defined as the administration of glucose to determine how quickly it is cleared from the blood. The test is usually used to test for diabetes, insulin resistance, and sometimes reactive hypoglycemia. The glucose is most often given orally so the common test is technically an oral glucose tolerance test (OGTT).

“Hybridization” means 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.

“Hyperglycemia” means a condition characterized by elevated serum glucose levels and/or circulating (plasma) glucose levels.

“Hyperlipidemia” means a condition characterized by elevated serum lipid levels and/or circulating (plasma) lipid levels.

“Hypertriglyceridemia” means a condition characterized by elevated triglyceride or circulating (plasma) triglyceride levels.

“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).

“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.

“Insulin resistance” is defined as the condition in which normal amounts of insulin are inadequate to produce a normal insulin response from fat, muscle and liver cells. Insulin resistance in fat cells results in hydrolysis of stored triglycerides, which elevates free fatty acids in the blood plasma. Insulin resistance in muscle reduces glucose uptake whereas insulin resistance in liver reduces glucose storage, with both effects serving to elevate blood glucose. High plasma levels of insulin and glucose due to insulin resistance often leads to metabolic syndrome and type 2 diabetes.

“Insulin sensitivity” is a measure of how effectively an individual processes glucose. An individual having high insulin sensitivity effectively processes glucose whereas an individual with low insulin sensitivity does not effectively process glucose.

“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.

“Intraperitoneal administration” means administration through infusion or injection into the peritoneum.

“Intravenous administration” means administration into a vein.

“IPGTT” or “Intraperitoneal Glucose Tolerance Testing” in medical practice is defined as the administration of glucose through intraperitoneal injection to determine how quickly it is cleared from the blood. The test is usually used to test for diabetes, insulin resistance, and sometimes reactive hypoglycemia.

“ITT” or “Insulin Tolerance Test” in medical practice is defined as a test to measure insulin sensitivity through the hormone response to the stress of a low blood sugar level. The test is usually used to test for diabetes, insulin resistance, and sometimes reactive hypoglycemia.

“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.

“Metabolic disorder” refers to a condition characterized by an alteration or disturbance in metabolic function. Metabolic disorders include, but are not limited to, hyperglycemia, prediabetes, diabetes (type I and type II), obesity, insulin resistance and metabolic syndrome.

“Metabolic syndrome” is defined as a clustering of lipid and non-lipid cardiovascular risk factors of metabolic origin.

“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 a DYRK1B can mean to increase or decrease the level of the DYRK1B in a cell, tissue, organ or organism. A “modulator” effects the change in the cell, tissue, organ or organism. For example, a compound can be a modulator of DYRK1B that decreases the amount of DYRK1B 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.

“Obesity” means an excessively high amount of body fat or adipose tissue in relation to lean body mass. The amount of body fat (or adiposity) includes concern for both the distribution of fat throughout the body and the size of the adipose tissue deposits. Body fat distribution can be estimated by skin-fold
5 measures, waist-to-hip circumference ratios, or techniques such as ultrasound, computed tomography, or magnetic resonance imaging. According to the Center for Disease Control and Prevention, individuals with a body mass index (BMI) of 30 or more are considered obese.

“Oligomeric compound” means a compound comprising a single oligonucleotide and optionally one
10 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
15 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
20 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 animal. For example, a pharmaceutically acceptable carrier can be a sterile aqueous
25 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
30 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
5 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,
10 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)
15 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
20 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.

5 “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.

10 “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.

15 “Specifically inhibit” 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 and 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.

20 “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-
25 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.

30 “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 oligomeric compounds or nucleic acids.

“Subcutaneous administration” means administration just below the skin.

“Target gene” refers to a gene encoding a target.

“Targeting” means specific hybridization of a compound that to a target nucleic acid in order to induce a desired effect.

5 “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 described herein is targeted. “5’ target site” refers to the 5’-most nucleotide of a target segment. “3’ target
10 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.

15 “Total cholesterol” means all types of cholesterol, including, but not limited to, LDL-C, HDL-C, IDL-C and VLDL-C. Concentration of total cholesterol in serum (or plasma) is typically quantified in mg/dL or nmol/L.

“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.

20 “Triglycerides” means lipids that are the triesters of glycerol.

“Type I diabetes” (also known as insulin-dependent diabetes mellitus or IDDM—strikes people under age 35, typically appearing suddenly between the ages of 10 and 16. In this form of the illness, which affects 10 percent of diabetics, a virus or autoimmune reaction probably destroys the insulin-producing cells. Insulin normally enables sugar to pass from the blood into the body's cells. Since a person with type I
25 diabetes has completely stopped producing insulin, lifelong treatment means taking insulin several times daily.

“Type 2 diabetes,” (also known as “type 2 diabetes mellitus” or “diabetes mellitus, type 2”, and formerly called “diabetes mellitus type II”, “non-insulin-dependent diabetes (NIDDM)”, “obesity related diabetes”, or “adult-onset diabetes”) is a metabolic disorder that is primarily characterized by insulin
30 resistance, relative insulin deficiency, and hyperglycemia.

“White Adipose Tissue” or WAT refers to one of the two types of adipose tissue found in mammals. In humans, white adipose tissue composes as much as 20% of the body weight in men and 25% of the body weight in women. The white adipose tissue is used as a store of energy and also acts as a thermal insulator, helping to maintain body temperature.

5 *Certain Embodiments*

Certain embodiments provide methods, compounds, and compositions for modulating a metabolic condition, or a symptom thereof, in an animal or individual by administering a therapeutically effective amount of the compound or composition to the animal or individual, wherein the compound or composition comprises a DYRK1B modulator. Modulation of DYRK1B can lead to a decrease of DYRK1B level or
10 expression in order to treat, prevent, ameliorate or delay a metabolic disease or disorder, or a symptom thereof. In certain embodiments, the DYRK1B modulator is a DYRK1B-specific inhibitor. In certain embodiments, DYRK1B-specific inhibitors are nucleic acids (including antisense compounds), peptides, antibodies, small molecules, and other agents capable of inhibiting the expression of DYRK1B. In certain embodiments, DYRK1B-specific inhibitors do not inhibit DYRK1A. In certain embodiments, the animal or
15 individual is human.

Certain embodiments disclosed herein provide a method of treating, preventing, delaying or ameliorating a metabolic disease or disorder in an animal or individual comprising administering to the animal or individual a compound or composition comprising a DYRK1B-specific inhibitor. In certain
20 embodiments, the DYRK1B-specific inhibitor is a nucleic acid, peptide, antibody, small molecule or other agent capable of inhibiting the expression of DYRK1B. In certain embodiments, the DYRK1B-specific inhibitor comprises a compound described herein. In certain embodiments, the compound comprises an antisense compound or an oligomeric compound. In certain embodiments, the compound comprises a modified oligonucleotide. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides. In certain embodiments, the animal or individual is human. In certain embodiments, the
25 metabolic disease or disorder is diabetes mellitus, hyperglycemia, obesity, metabolic syndrome, essential hypertension, disorders of lipid metabolism, hypertensive heart disease, myocardial infarction, pulmonary heart disease, heart failure, and other symptoms involving the cardiovascular system. In certain embodiments, the animal or individual is human.

Certain embodiments disclosed herein provide a method of treating an animal or individual at risk for
30 a metabolic disease or disorder comprising administering to the animal or individual a compound or composition comprising a DYRK1B-specific inhibitor. In certain embodiments, the DYRK1B-specific inhibitor is a nucleic acid, peptide, antibody, small molecule or other agent capable of inhibiting the expression of DYRK1B. In certain embodiments, the DYRK1B-specific inhibitor comprises a compound. In certain embodiments, the compound comprises an antisense compound or an oligomeric compound. In

certain embodiments, the compound comprises a modified oligonucleotide. In certain embodiments, the metabolic disease or disorder is diabetes mellitus, hyperglycemia, obesity, metabolic syndrome, essential hypertension, disorders of lipid metabolism, hypertensive heart disease, myocardial infarction, pulmonary heart disease, heart failure, and other symptoms involving the cardiovascular system. In certain embodiments, the animal or individual is human.

Certain embodiments disclosed herein provide compounds or compositions comprising a DYRK1B modulator. In certain embodiments, the DYRK1B modulator is a DYRK1B-specific inhibitor. In certain embodiments, the DYRK1B-specific inhibitor is a nucleic acid, polypeptide, antibody, small molecules, or other agent capable of inhibiting the expression of DYRK1B. In certain embodiments, the nucleic acid is a compound or composition targeting DYRK1B. In certain embodiments, the compound or composition is single stranded. In certain embodiments, the compound or composition is double stranded. In certain embodiments, the compound is an antisense compound. In any of the foregoing embodiments, the compound can be an oligomeric compound. In certain embodiments, the compound or composition targeting DYRK1B comprises an oligonucleotide. In certain embodiments, the oligonucleotide is single stranded. In certain embodiments, the compound comprises deoxyribonucleotides. In certain embodiments, the compound is double-stranded and comprises ribonucleotides. In certain embodiments, the oligonucleotide is a modified oligonucleotide. In certain embodiments, the modified oligonucleotide is single stranded.

In any of the foregoing embodiments, the compound can comprise a modified oligonucleotide 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, these compounds are oligonucleotides.

In certain embodiments, at least one internucleoside linkage of said modified oligonucleotide is a modified internucleoside linkage. In certain embodiments, at least one internucleoside linkage is a phosphorothioate internucleoside linkage. In certain embodiments, the internucleoside linkages are phosphorothioate linkages and phosphodiester linkages. In certain embodiments, each internucleoside linkage is a phosphorothioate internucleoside linkage.

In certain embodiments, any of the foregoing oligonucleotides comprises at least one modified sugar. In certain embodiments, at least one modified sugar comprises a 2'-O-methoxyethyl group. In certain embodiments, at least one modified sugar is a bicyclic sugar, such as a 4'-CH(CH₃)-O-2' group, a 4'-CH₂-O-2' group, or a 4'-(CH₂)₂-O-2' group.

In certain embodiments, at least one nucleoside of said modified oligonucleotide comprises a modified nucleobase. In certain embodiments, the modified nucleobase is a 5-methylcytosine.

Certain embodiments disclosed herein provide a compound or composition comprising a modified oligonucleotide with: a) a gap segment consisting of linked deoxynucleosides; b) a 5' wing segment consisting of linked nucleosides; and c) a 3' wing segment consisting of linked nucleosides. The gap segment is positioned between the 5' wing segment and the 3' wing segment and each nucleoside of each wing

segment comprises a modified sugar. In certain embodiments, at least one internucleoside linkage is a phosphorothioate linkage. In certain embodiments, and at least one cytosine is a 5-methylcytosine.

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

5 In certain embodiments, the compound or composition is co-administered with a second agent. In certain embodiments, the compound or composition and the second agent are administered concomitantly.

Certain embodiments provide uses of the compounds and compositions described herein for inhibiting DYRK1B expression. In certain embodiments, the compounds or compositions inhibit DYRK1B expression by at least 5%, at least 10%, at least 20%, at least 30%, at least 35%, at least 40%, at least 45%, at
10 least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, or at least 90%. In certain embodiments, the compounds or compositions do not inhibit DYRK1A more than 30%, more than 25%, more than 20%, more than 15%, more than 10%, more than 5%. In certain embodiments, the compounds or compositions do not inhibit DYRK1A.

Certain embodiments provide uses of the compounds and compositions described herein for use in
15 therapy. In certain embodiments, the therapy is used in treating, preventing, delaying the onset or slowing progression of a disease related to elevated expression of DYRK1B. In certain embodiments, the disease is a metabolic disease or disorder. In certain embodiments, the disease is a cardiovascular disease or disorder. In certain embodiments, the metabolic disease or disorder is diabetes mellitus. In certain embodiments, the metabolic disease or disorder is hyperglycemia. In certain embodiments, the metabolic disease or disorder is
20 obesity. In certain embodiments, the metabolic disease or disorder is metabolic syndrome. In certain embodiments, the metabolic disease or disorder is essential hypertension. In certain embodiments, the metabolic disease or disorder is disorders of lipid metabolism. In certain embodiments, the metabolic disease or disorder is hypertensive heart disease. In certain embodiments, the metabolic disease or disorder is myocardial infarction. In certain embodiments, the metabolic disease or disorder is pulmonary heart disease.
25 In certain embodiments, the metabolic disease or disorder is heart failure. In certain embodiments, the compound or composition comprises a modified oligonucleotide 8 to 80 linked nucleosides in length. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides. In certain embodiments disclosed herein.

Certain embodiments disclosed herein provide uses of the compounds or compositions described
30 herein comprising a DYRK1B modulator. In certain embodiments, the DYRK1B modulator is a DYRK1B-specific inhibitor. In certain embodiments, the DYRK1B-specific inhibitor is a nucleic acid, polypeptide, antibody, small molecules, or other agent capable of inhibiting the expression of DYRK1B. In certain embodiments, the nucleic acid is a compound or composition targeting DYRK1B. In certain embodiments, the compound or composition is single stranded. In certain embodiments, the compound or composition is
35 double stranded. In certain embodiments, the compound is an antisense compound. In any of the foregoing embodiments, the compound can be an oligomeric compound. In certain embodiments, the compound or

composition targeting DYRK1B comprises an oligonucleotide. In certain embodiments, the oligonucleotide is single stranded. In certain embodiments, the compound comprises deoxyribonucleotides. In certain embodiments, the compound is double-stranded and comprises ribonucleotides. In certain embodiments, the oligonucleotide is a modified oligonucleotide. In certain embodiments, the modified oligonucleotide is single stranded.

In any of the foregoing embodiments provide uses of compounds or compositions described herein, wherein the compound can consist 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, these compounds are oligonucleotides.

In certain embodiments, at least one internucleoside linkage of said modified oligonucleotide is a modified internucleoside linkage. In certain embodiments, each internucleoside linkage is a phosphorothioate internucleoside linkage.

In certain embodiments, any of the foregoing oligonucleotides comprises at least one modified sugar. In certain embodiments, at least one modified sugar comprises a 2'-O-methoxyethyl group. In certain embodiments, at least one modified sugar is a bicyclic sugar, such as a 4'-CH(CH₃)-O-2' group, a 4'-CH₂-O-2' group, or a 4'-(CH₂)₂-O-2' group.

In certain embodiments, at least one nucleoside of said modified oligonucleotide comprises a modified nucleobase. In certain embodiments, the modified nucleobase is a 5-methylcytosine.

Certain embodiments disclosed herein provide use of a compound or composition comprising a modified oligonucleotide with: a) a gap segment consisting of linked deoxynucleosides; b) a 5' wing segment consisting of linked nucleosides; and c) a 3' wing segment consisting of linked nucleosides. The gap segment is positioned between the 5' wing segment and the 3' wing segment and each nucleoside of each wing segment comprises a modified sugar. In certain embodiments, at least one internucleoside linkage is a phosphorothioate linkage. In certain embodiments, and at least one cytosine is a 5-methylcytosine.

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

In certain embodiments, the animal is a human.

In certain embodiments, administration comprises parenteral administration. In certain embodiments, parenteral administration comprises subcutaneous administration. In certain embodiments, parenteral administration comprises intravenous administration.

In certain embodiments, the compounds or compositions disclosed herein are designated as a first agent and the methods or uses disclosed herein further comprise administering a second agent. In certain embodiments, the first agent and the second agent are co-administered. In certain embodiments, the first agent and the second agent are co-administered sequentially or concomitantly.

Certain Indications

Certain embodiments provided herein relate to methods of inhibiting DYRK1B expression or activity, which can be useful for treating, preventing, or ameliorating a disease associated with DYRK1B in an individual, by administration of a compound or composition that targets DYRK1B. In certain embodiments, the compound or composition does not target DYRK1A. In certain embodiments, such a
5 compound comprises a DYRK1B-specific inhibitor. In certain embodiments, such a compound does not inhibit DYRK1A. In certain embodiments, the compound comprises an antisense compound or an oligomeric compound targeted to DYRK1B. In certain embodiments, the compound comprises a modified oligonucleotide targeted to DYRK1B. In certain embodiments, the antisense compound, oligomeric compound, or modified oligonucleotide does not target DYRK1A.

10 Examples of diseases associated with a DYRK1B treatable, preventable, and/or ameliorable with the methods provided herein include diabetes mellitus, hyperglycemia, obesity, metabolic syndrome, essential hypertension, disorders of lipid metabolism, hypertensive heart disease, myocardial infarction, pulmonary heart disease, heart failure, and other symptoms involving the cardiovascular system.

Certain embodiments disclose a method of inhibiting expression or activity of DYRK1B in a cell
15 comprising contacting the cell with a compound or composition comprising a DYRK1B -specific inhibitor, thereby inhibiting expression or activity of DYRK1B in the cell. Certain embodiments disclose a method of inhibiting expression or activity of DYRK1B but not of DYRK1A in a cell, comprising contacting the cell with a compound or composition comprising a DYRK1B -specific inhibitor, thereby inhibiting expression or activity of DYRK1B but not of DYRK1A in the cell. In certain embodiments, the cell is in an individual who has, or is
20 at risk of having a disease, disorder, condition, symptom, or physiological marker associated with a metabolic disease or disorder. In certain embodiments, the metabolic disease or disorder is diabetes mellitus. In certain embodiments, the metabolic disease or disorder is hyperglycemia. In certain embodiments, the metabolic disease or disorder is obesity. In certain embodiments, the metabolic disease or disorder is metabolic syndrome. In certain embodiments, the metabolic disease or disorder is essential hypertension. In certain embodiments,
25 the metabolic disease or disorder is disorders of lipid metabolism. In certain embodiments, the metabolic disease or disorder is hypertensive heart disease. In certain embodiments, the metabolic disease or disorder is myocardial infarction. In certain embodiments, the metabolic disease or disorder is pulmonary heart disease. In certain embodiments, the metabolic disease or disorder is heart failure, and other symptoms involving the cardiovascular system. In certain embodiments, the DYRK1B-specific inhibitor is a nucleic acid, peptide,
30 antibody, small molecule or other agent capable of inhibiting the expression or activity of the DYRK1B. In certain embodiments, the the DYRK1B-specific inhibitor is a nucleic acid, peptide, antibody, small molecule or other agent capable of inhibiting the expression or activity of the DYRK1B but does not inhibit the expression or activity of DYRK1A. In certain embodiments, the DYRK1B-specific inhibitor is an antisense compound or an oligomeric compound targeted to DYRK1B. In certain embodiments, the DYRK1B -specific
35 inhibitor is oligonucleotide targeted to DYRK1B. In certain embodiments, the antisense compound, oligomeric compound, or modified oligonucleotide does not target DYRK1A. In certain embodiments, the compound or

composition comprises a modified oligonucleotide 8 to 80 linked nucleosides in length. In certain embodiments, the compound or composition comprises a modified oligonucleotide 10 to 30 linked nucleosides in length. In certain embodiments, the compound comprising a modified oligonucleotide can be single-stranded. In certain embodiments, the compound comprising a modified oligonucleotide can be double-stranded.

In certain embodiments, a method of treating, preventing, delaying the onset, slowing progression, or ameliorating one of more diseases, disorders, conditions, symptoms, or physiologic markers associated with a metabolic disease or disorder in an individual comprises administering to the individual a compound or composition comprising a specific inhibitor of DYRK1B, thereby treating, preventing, delaying the onset, slowing the progression, or ameliorating the disease, disorder, symptom, or physiological marker associated with the metabolic disease or disorder. In certain embodiments, the compound or composition does not inhibit DYRK1A. In some embodiments, the individual is identified as having, or at risk of having, the disease, disorder, condition, symptom, or physiological marker. In certain embodiments, the metabolic disease or disorder is diabetes mellitus. In certain embodiments, the metabolic disease or disorder is hyperglycemia. In certain embodiments, the metabolic disease or disorder is obesity. In certain embodiments, the metabolic disease or disorder is metabolic syndrome. In certain embodiments, the metabolic disease or disorder is essential hypertension. In certain embodiments, the metabolic disease or disorder is disorders of lipid metabolism. In certain embodiments, the metabolic disease or disorder is hypertensive heart disease. In certain embodiments, the metabolic disease or disorder is myocardial infarction. In certain embodiments, the metabolic disease or disorder is pulmonary heart disease. In certain embodiments, the metabolic disease or disorder is heart failure, and other symptoms involving the cardiovascular system. In certain embodiments, the DYRK1B-specific inhibitor is a compound targeted to DYRK1B, such as an oligonucleotide targeted to DYRK1B. In certain embodiments, the DYRK1B-specific inhibitor is a compound comprising a modified oligonucleotide consisting of 8 to 80 linked nucleosides. In any of the foregoing embodiments, the compound can be single-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 treats, ameliorates, or prevents a metabolic disease or disorder. In certain embodiments, the compound or composition comprises a modified oligonucleotide 8 to 80 linked nucleosides in length. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides. In certain embodiments, the animal is human.

Certain embodiments disclosed herein provide a method of reducing blood glucose levels in an animal comprising administering to the animal a therapeutically effective amount of a compound or composition comprising a DYRK1B-specific inhibitor. In certain embodiments, the compound or composition does not inhibit DYRK1A. In certain embodiments, the DYRK1B-specific inhibitor is a nucleic acid, peptide, antibody, small molecule or other agent capable of inhibiting the expression of the DYRK1B. In certain embodiments, the DYRK1B-specific inhibitor comprises a compound described herein. In certain

embodiments, the DYRK1B-specific inhibitor comprises an antisense compound or an oligomeric compound. In certain embodiments, the compound comprises a modified oligonucleotide. In certain embodiments, the antisense compound, oligomeric compound, or modified oligonucleotide does not target DYRK1A. In certain embodiments, the therapeutically effective amount of the compound or composition administered to the animal reduces glucose levels in the animal. In certain embodiments, the compound or composition comprises a modified oligonucleotide 8 to 80 linked nucleosides in length. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides. In certain embodiments, the animal is human.

Certain embodiments disclosed herein provide a method of regulates insulin levels in an animal comprising administering to the animal a therapeutically effective amount of a compound or composition comprising a DYRK1B-specific inhibitor. In certain embodiments, the compound or composition does not inhibit DYRK1A. In certain embodiments, the DYRK1B-specific inhibitor is a nucleic acid, peptide, antibody, small molecule or other agent capable of inhibiting the expression of the DYRK1B. In certain embodiments, the DYRK1B-specific inhibitor comprises a compound described herein. In certain embodiments, the DYRK1B-specific inhibitor comprises an antisense compound or an oligomeric compound. In certain embodiments, the compound comprises a modified oligonucleotide. In certain embodiments, the antisense compound, oligomeric compound, or modified oligonucleotide does not target DYRK1A. In certain embodiments, the therapeutically effective amount of the compound or composition administered to the animal reduces regulates insulin levels in the animal. In certain embodiments, the compound or composition comprises a modified oligonucleotide 8 to 80 linked nucleosides in length. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides. In certain embodiments, the animal is human.

Certain embodiments disclosed herein provide a method of increasing glucose tolerance in an animal comprising administering to the animal a therapeutically effective amount of a compound or composition comprising a DYRK1B-specific inhibitor. In certain embodiments, the compound or composition does not inhibit DYRK1A. In certain embodiments, the DYRK1B-specific inhibitor is a nucleic acid, peptide, antibody, small molecule or other agent capable of inhibiting the expression of the DYRK1B. In certain embodiments, the DYRK1B-specific inhibitor comprises a compound described herein. In certain embodiments, the DYRK1B-specific inhibitor comprises an antisense compound or an oligomeric compound. In certain embodiments, the compound comprises a modified oligonucleotide. In certain embodiments, the antisense compound, oligomeric compound, or modified oligonucleotide does not target DYRK1A. In certain embodiments, the therapeutically effective amount of the compound or composition administered to the animal increases glucose tolerance in the animal. In certain embodiments, the compound or composition comprises a modified oligonucleotide 8 to 80 linked nucleosides in length. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides. In certain embodiments, the animal is human.

Certain embodiments disclosed herein provide a method of increasing insulin sensitivity in an animal comprising administering to the animal a therapeutically effective amount of a compound or composition comprising a DYRK1B-specific inhibitor. In certain embodiments, the compound or composition does not inhibit DYRK1A. In certain embodiments, the DYRK1B-specific inhibitor is a nucleic acid, peptide, antibody, small molecule or other agent capable of inhibiting the expression of the DYRK1B. In certain embodiments, the DYRK1B-specific inhibitor comprises a compound described herein. In certain embodiments, the DYRK1B-specific inhibitor comprises an antisense compound or an oligomeric compound. In certain embodiments, the compound comprises a modified oligonucleotide. In certain embodiments, the antisense compound, oligomeric compound, or modified oligonucleotide does not target DYRK1A. In certain embodiments, the therapeutically effective amount of the compound or composition administered to the animal increases insulin sensitivity in the animal. In certain embodiments, the compound or composition comprises a modified oligonucleotide 8 to 80 linked nucleosides in length. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides. In certain embodiments, the animal is human.

Certain embodiments disclosed herein provide a method of reduces LDL cholesterol levels in an animal comprising administering to the animal a therapeutically effective amount of a compound or composition comprising a DYRK1B-specific inhibitor. In certain embodiments, the compound or composition does not inhibit DYRK1A. In certain embodiments, the DYRK1B-specific inhibitor is a nucleic acid, peptide, antibody, small molecule or other agent capable of inhibiting the expression of the DYRK1B. In certain embodiments, the DYRK1B-specific inhibitor comprises a compound described herein. In certain embodiments, the DYRK1B-specific inhibitor comprises an antisense compound or an oligomeric compound. In certain embodiments, the compound comprises a modified oligonucleotide. In certain embodiments, the antisense compound, oligomeric compound, or modified oligonucleotide does not target DYRK1A. In certain embodiments, the therapeutically effective amount of the compound or composition administered to the animal reduces LDL cholesterol in the animal. In certain embodiments, the compound or composition comprises a modified oligonucleotide 8 to 80 linked nucleosides in length. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides. In certain embodiments, the animal is human.

Certain embodiments disclosed herein provide a method of reduces triglyceride levels in an animal comprising administering to the animal a therapeutically effective amount of a compound or composition comprising a DYRK1B-specific inhibitor. In certain embodiments, the compound or composition does not inhibit DYRK1A. In certain embodiments, the DYRK1B-specific inhibitor is a nucleic acid, peptide, antibody, small molecule or other agent capable of inhibiting the expression of the DYRK1B. In certain embodiments, the DYRK1B-specific inhibitor comprises a compound described herein. In certain embodiments, the DYRK1B-specific inhibitor comprises an antisense compound or an oligomeric compound. In certain embodiments, the compound comprises a modified oligonucleotide. In certain embodiments, the

antisense compound, oligomeric compound, or modified oligonucleotide does not target DYRK1A. In certain embodiments, the therapeutically effective amount of the compound or composition administered to the animal reduces triglyceride levels in the animal. In certain embodiments, the compound or composition comprises a modified oligonucleotide 8 to 80 linked nucleosides in length. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides. In certain embodiments, the animal is human.

Certain embodiments disclosed herein provide a method of reduces blood pressure in an animal comprising administering to the animal a therapeutically effective amount of a compound or composition comprising a DYRK1B-specific inhibitor. In certain embodiments, the compound or composition does not inhibit DYRK1A. In certain embodiments, the DYRK1B-specific inhibitor is a nucleic acid, peptide, antibody, small molecule or other agent capable of inhibiting the expression of the DYRK1B. In certain embodiments, the DYRK1B-specific inhibitor comprises a compound described herein. In certain embodiments, the DYRK1B-specific inhibitor comprises an antisense compound or an oligomeric compound. In certain embodiments, the compound comprises a modified oligonucleotide. In certain embodiments, the antisense compound, oligomeric compound, or modified oligonucleotide does not target DYRK1A. In certain embodiments, the therapeutically effective amount of the compound or composition administered to the animal reduces blood pressure in the animal. In certain embodiments, the compound or composition comprises a modified oligonucleotide 8 to 80 linked nucleosides in length. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides. In certain embodiments, the animal is human.

Certain embodiments disclosed herein provide a method of reduces body-mass index in an animal comprising administering to the animal a therapeutically effective amount of a compound or composition comprising a DYRK1B-specific inhibitor. In certain embodiments, the compound or composition does not inhibit DYRK1A. In certain embodiments, the DYRK1B-specific inhibitor is a nucleic acid, peptide, antibody, small molecule or other agent capable of inhibiting the expression of the DYRK1B. In certain embodiments, the DYRK1B-specific inhibitor comprises a compound described herein. In certain embodiments, the DYRK1B-specific inhibitor comprises an antisense compound or an oligomeric compound. In certain embodiments, the compound comprises a modified oligonucleotide. In certain embodiments, the antisense compound, oligomeric compound, or modified oligonucleotide does not target DYRK1A. In certain embodiments, the therapeutically effective amount of the compound or composition administered to the animal reduces body-mass index in the animal. In certain embodiments, the compound or composition comprises a modified oligonucleotide 8 to 80 linked nucleosides in length. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides. In certain embodiments, the animal is human.

In certain embodiments, administering the compound or composition disclosed herein decreases blood glucose levels, regulates insulin levels, increases glucose tolerance, increases insulin sensitivity,

reduces LDL cholesterol levels, decreases triglyceride levels, reduces blood pressure and reduces body-mass index, or a combination thereof. In certain embodiments, blood glucose levels were independently reduced by at least 5%, at least 10%, at least 20%, at least 30%, at least 35%, at least 40%, at least 45% or at least 50%. In certain embodiments, insulin sensitivity was independently increased by at least 5%, at least 10%, at least 20%, at least 30%, at least 35%, at least 40%, at least 45% or at least 50%. In certain embodiments, glucose tolerance was independently increased by at least 5%, at least 10%, at least 20%, at least 30%, at least 35%, at least 40%, at least 45% or at least 50%. In certain embodiments, LDL cholesterol levels were independently decreased by at least 5%, at least 10%, at least 20%, at least 30%, at least 35%, at least 40%, at least 45% or at least 50%. In certain embodiments, triglyceride levels were independently decreased by at least 5%, at least 10%, at least 20%, at least 30%, at least 35%, at least 40%, at least 45% or at least 50%. In certain embodiments, blood pressure levels were independently decreased by at least 5%, at least 10%, at least 20%, at least 30%, at least 35%, at least 40%, at least 45% or at least 50%. In certain embodiments, body-mass index was independently decreased by at least 5%, at least 10%, at least 20%, at least 30%, at least 35%, at least 40%, at least 45% or at least 50%.

Certain embodiments are drawn to compounds or compositions described herein for use in therapy. Certain embodiments are drawn to a compound or composition comprising a DYRK1B-specific inhibitor for use in treating a metabolic disease or disorder. In certain embodiments, the compound or composition does not inhibit DYRK1A. In certain embodiments, the metabolic disease or disorder may be one or more of diabetes mellitus, hyperglycemia, obesity, metabolic syndrome, essential hypertension, disorders of lipid metabolism, hypertensive heart disease, myocardial infarction, pulmonary heart disease, heart failure, and other symptoms involving the cardiovascular system. In certain embodiments, the DYRK1B-specific inhibitor is a compound targeted to DYRK1B, such as an oligonucleotide targeted to a DYRK1B. In certain embodiments, the DYRK1B-specific inhibitor is a compound comprising a modified oligonucleotide consisting of 8 to 80 linked nucleosides. In any of the foregoing embodiments, the compound can be an antisense compound or oligomeric compound. In certain embodiments, the antisense compound, oligomeric compound, or modified oligonucleotide does not target DYRK1A. In any of the foregoing embodiments, the compound can be single-stranded or double-stranded. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides.

In certain embodiments, use of a compound or composition disclosed herein results in blood glucose levels independently reduced by at least 5%, at least 10%, at least 20%, at least 30%, at least 35%, at least 40%, at least 45% or at least 50%. In certain embodiments, use of a compound or composition disclosed herein results in insulin sensitivity independently increased by at least 5%, at least 10%, at least 20%, at least 30%, at least 35%, at least 40%, at least 45% or at least 50%. In certain embodiments, use of a compound or composition disclosed herein results in glucose tolerance independently increased by at least 5%, at least 10%, at least 20%, at least 30%, at least 35%, at least 40%, at least 45% or at least 50%. In certain

embodiments, use of a compound or composition disclosed herein results in LDL cholesterol levels independently decreased by at least 5%, at least 10%, at least 20%, at least 30%, at least 35%, at least 40%, at least 45% or at least 50%. In certain embodiments, use of a compound or composition disclosed herein results in triglyceride levels independently decreased by at least 5%, at least 10%, at least 20%, at least 30%, at least 35%, at least 40%, at least 45% or at least 50%. In certain embodiments, use of a compound or composition disclosed herein results in blood pressure levels independently decreased by at least 5%, at least 10%, at least 20%, at least 30%, at least 35%, at least 40%, at least 45% or at least 50%. In certain embodiments, use of a compound or composition disclosed herein results in body-mass index independently decreased by at least 5%, at least 10%, at least 20%, at least 30%, at least 35%, at least 40%, at least 45% or at least 50%.

Certain embodiments provide the use of a compound or composition as described herein in the manufacture or preparation of a medicament for treating, ameliorating, delaying or preventing one or more diseases, disorders, conditions, symptoms or physiological markers associated with DYRK1B. In certain embodiments, the use of the compound or composition does not inhibit DYRK1A. In certain embodiments, the compound or composition as described herein is used in the manufacture of a medicament for treating, ameliorating, delaying or preventing a metabolic disease or disorder, or a symptom or physiological marker thereof. In certain embodiments, the disease is a metabolic disease or disorder. In certain embodiments, the disease is a cardiovascular disease or disorder. In certain embodiments, the metabolic disease or disorder is diabetes mellitus. In certain embodiments, the metabolic disease or disorder is hyperglycemia. In certain embodiments, the metabolic disease or disorder is obesity. In certain embodiments, the metabolic disease or disorder is metabolic syndrome. In certain embodiments, the metabolic disease or disorder is essential hypertension. In certain embodiments, the metabolic disease or disorder is disorders of lipid metabolism. In certain embodiments, the metabolic disease or disorder is hypertensive heart disease. In certain embodiments, the metabolic disease or disorder is myocardial infarction. In certain embodiments, the metabolic disease or disorder is pulmonary heart disease. In certain embodiments, the metabolic disease or disorder is heart failure. In certain embodiments, the compound or composition comprises a modified oligonucleotide 8 to 80 linked nucleosides in length. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides. In certain embodiments, the modified oligonucleotide does not target DYRK1A. In certain embodiments disclosed herein, the animal is human.

Certain embodiments are drawn to use of a DYRK1B-specific inhibitor for the manufacture or preparation of a medicament for treating a metabolic disease or disorder. In certain embodiments, the use of the compound or composition does not inhibit DYRK1A. Examples of such metabolic diseases or disorders are diabetes mellitus, hyperglycemia, obesity, metabolic syndrome, essential hypertension, disorders of lipid metabolism, hypertensive heart disease, myocardial infarction, pulmonary heart disease, heart failure, and other symptoms involving the cardiovascular system. In certain embodiments, the DYRK1B-specific

inhibitor is a compound targeted to DYRK1B, such as an oligonucleotide targeted to DYRK1B. In certain embodiments, the DYRK1B-specific inhibitor is a compound comprising a modified oligonucleotide consisting of 8 to 80 linked nucleosides. In any of the foregoing embodiments, the compound can be an antisense compound or oligomeric compound. In certain embodiments, the antisense compound, oligomeric
5 compound, or modified oligonucleotide does not target DYRK1A. In any of the foregoing embodiments, the compound can be single-stranded or double-stranded. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides.

Certain embodiments are drawn to use of a DYRK1B-specific inhibitor for the manufacture of a medicament for decreasing blood glucose levels, regulating insulin levels, increasing glucose tolerance,
10 increasing insulin sensitivity, reducing LDL cholesterol levels, decreasing triglyceride levels, reducing blood pressure and reducing body-mass index, or a combination thereof in an individual having or at risk of having a metabolic disease or disorder. In certain embodiments, the disease is a cardiovascular disease or disorder. In certain embodiments, the metabolic disease or disorder is diabetes mellitus. In certain embodiments, the metabolic disease or disorder is hyperglycemia. In certain embodiments, the metabolic disease or disorder is
15 obesity. In certain embodiments, the metabolic disease or disorder is metabolic syndrome. In certain embodiments, the metabolic disease or disorder is essential hypertension. In certain embodiments, the metabolic disease or disorder is disorders of lipid metabolism. In certain embodiments, the metabolic disease or disorder is hypertensive heart disease. In certain embodiments, the metabolic disease or disorder is myocardial infarction. In certain embodiments, the metabolic disease or disorder is pulmonary heart disease.
20 In certain embodiments, the metabolic disease or disorder is heart failure. In certain embodiments, the DYRK1B-specific inhibitor is a compound targeted to DYRK1B, such as an oligonucleotide targeted to DYRK1B. In certain embodiments, the DYRK1B-specific inhibitor is a compound comprising a modified oligonucleotide consisting of 8 to 80 linked nucleosides. In any of the foregoing embodiments, the compound can be an antisense compound or oligomeric compound. In certain embodiments, the antisense compound,
25 oligomeric compound, or modified oligonucleotide does not target DYRK1A. In any of the foregoing embodiments, the compound can be single-stranded or double-stranded. In certain embodiments, the modified oligonucleotide consists of 10 to 30 linked nucleosides.

In any of the foregoing methods or uses, the compound can be an antisense compound targeted to DYRK1B. In certain embodiments, the compound comprises an oligonucleotide, for example an
30 oligonucleotide consisting of 8 to 80 linked nucleosides, 10 to 30 linked nucleosides, 12 to 30 linked nucleosides, or 20 linked nucleosides. In certain embodiments, the 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-
35 methylcytosine. In certain embodiments, the modified oligonucleotide comprises a gap segment consisting of linked 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 comprises or consists of a modified oligonucleotide 12 to 30 linked nucleosides in length, 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.

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.

Certain Compounds

In certain embodiments, compounds described herein are 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. 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, each modified oligonucleotide is 12-30 linked nucleosides in length.

In certain embodiments, compounds are double-stranded. Such double-stranded 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 compounds typically comprises or consists of a modified oligonucleotide. The oligonucleotide of the second oligomeric compound of such double-stranded compound may be modified or unmodified. The oligomeric compounds of double-stranded 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 10 to 30 linked subunits in length. In certain embodiments, compound described herein comprises an oligonucleotide is 12 to 30 linked subunits in length. In certain embodiments, compound described herein comprises an oligonucleotide is 12 to 22 linked subunits in length. In certain embodiments, compound described herein comprises an oligonucleotide is 14 to 30 linked subunits in length. In certain embodiments, compound described herein comprises an oligonucleotide is 14 to 20 linked subunits in length. In certain embodiments, compound described herein comprises an oligonucleotide is 15 to 30 linked subunits in length. In certain embodiments, compound described herein comprises an oligonucleotide is 15 to 20 linked subunits in length. In certain embodiments, compound described herein comprises an oligonucleotide is 16 to 30 linked subunits in length. In certain embodiments, compound described herein comprises an oligonucleotide is 16 to 20 linked subunits in length. In certain embodiments, compound described herein comprises an oligonucleotide is 17 to 30 linked subunits in length. In certain embodiments, compound described herein comprises an oligonucleotide is 17 to 20 linked subunits in length. In certain embodiments, compound described herein comprises an oligonucleotide is 18 to 30 linked subunits in length. In certain embodiments, compound described herein comprises an oligonucleotide is 18 to 21 linked subunits in length. In certain embodiments, compound described herein comprises an oligonucleotide is 18 to 20 linked subunits in length. In certain embodiments, compound described herein comprises an oligonucleotide is 20 to 30 linked subunits in length. In other words, such oligonucleotides are from 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

14 linked subunits in length. In certain embodiments, a compound described herein comprises an oligonucleotide 16 linked subunits in length. In certain embodiments, a compound described herein comprises an oligonucleotide 17 linked subunits in length. In certain embodiments, compound described herein comprises an oligonucleotide 18 linked subunits in length. In certain embodiments, a compound
5 described herein comprises an oligonucleotide 19 linked subunits in length. In certain embodiments, a compound described herein comprises an oligonucleotide 20 linked subunits in length. In other embodiments, a compound described herein comprises an oligonucleotide 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
10 comprises an oligonucleotide 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 in length, or a range defined by any two of the above values. In some embodiments the linked subunits are nucleotides, nucleosides, or nucleobases.

15 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 a DYRK1B 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.

20 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.

25 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 89:7305-7309, 1992; Gautschi et al. *J. Natl. Cancer Inst.* 93:463-471, March 2001; Maher and Dolnick *Nuc. Acid. Res.* 16:3341-3358, 1988). 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
30 (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
35 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 double-stranded compound comprises a first strand comprising the nucleobase sequence complementary to a target region of a DYRK1B nucleic acid and a second strand. In certain embodiments, the double-stranded compound comprises ribonucleotides in which the first strand has uracil (U) in place of thymine (T) and is complementary to a target region. In certain embodiments, a double-stranded compound comprises (i) a first strand comprising a nucleobase sequence complementary to a target region of a DYRK1B nucleic acid, and (ii) a second strand. In certain embodiments, the double-stranded 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 double-stranded 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 double-stranded compound comprises one or more linkages between adjacent nucleotides other than a naturally-occurring phosphodiester linkage. Examples of such linkages include phosphoramidate, phosphorothioate, and phosphorodithioate linkages. The double-stranded compounds may also be chemically modified nucleic acid molecules as taught in U.S. Pat. No. 6,673,661. In other embodiments, the dsRNA 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 double-stranded compound is an siRNA guide strand and the second strand of the double-stranded compound is an siRNA passenger strand. In certain embodiments, the second strand of the double-stranded compound is complementary to the first strand. In certain embodiments, each strand of the double-stranded compound consists of 16, 17, 18, 19, 20, 21, 22, or 23 linked nucleosides.

In certain embodiments, a single-stranded compound described herein can comprise any of the oligonucleotide sequences targeted to a DYRK1B described herein. In certain embodiments, such a single-stranded compound is a single-stranded RNAi (ssRNAi) compound. In certain embodiments, a ssRNAi compound comprises the nucleobase sequence complementary to a target region of a DYRK1B nucleic acid. In certain embodiments, the ssRNAi compound comprises ribonucleotides in which uracil (U) is in place of thymine (T). In certain embodiments, ssRNAi compound comprises a nucleobase sequence complementary to a target region of a DYRK1B nucleic acid. In certain embodiments, a ssRNAi 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, a ssRNAi

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 ssRNAi compound. In certain embodiments, the ssRNAi compound comprises one or more linkages between adjacent nucleotides other than a naturally-occurring phosphodiester linkage. Examples of such linkages include phosphoramidate, phosphorothioate, and phosphorodithioate linkages. The ssRNAi compounds may also be chemically modified nucleic acid molecules as taught in U.S. Pat. No. 6,673,661. In other embodiments, the ssRNAi contains a capped strand, as disclosed, for example, by WO 00/63364, filed Apr. 19, 2000. In certain embodiments, the ssRNAi compound consists of 16, 17, 18, 19, 20, 21, 22, or 23 linked nucleosides.

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.

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, such antisense 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 selective 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 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 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. In certain embodiments, the target region is an lncRNA.

Human gene sequences that encode a DYRK1B include, without limitation, the following gene sequences: the complement of RefSeqNo. NT_011109.17 truncated from nucleotides 12584000 to 12594000 (SEQ ID NO: 2); RefSeqNo. NM_004714.2 (SEQ ID NO: 3); RefSeqNo. NM_006483.2 (SEQ ID NO: 4); and RefSeqNo. NM_006484.2 (SEQ ID NO: 5). Murine sequences that encode a DYRK1B include, without limitation, the following gene sequences: RefSeqNo. NT_187034.1 truncated from nucleotides 25178000 to 25189000 (SEQ ID NO: 6); RefSeqNo. NM_001037957.3 (SEQ ID NO: 7); RefSeqNo. NM_001271370.1 (SEQ ID NO: 8); and RefSeqNo. NM_010092.2 (SEQ ID NO: 9).

Hybridization

In some embodiments, hybridization occurs between a compound disclosed herein and a DYRK1B 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 DYRK1B 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 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 DYRK1B 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 DYRK1B 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, or are at least, 70%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% complementary to a DYRK1B 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 is 18 nucleobases in length 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 and would thus fall within the scope of the present invention. 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 DYRK1B 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 capable of precise base pairing with the corresponding nucleobases 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.

5 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.

10 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 DYRK1B nucleic acid, or specified portion thereof.

15 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 DYRK1B nucleic acid, or specified portion thereof.

20 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
25 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
30 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 Isis 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 Isis 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 are antisense compounds. In certain embodiments, a portion of the 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 are 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 modified 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'-OCH₃ ("OMe" or "O-methyl"), and 2'-O(CH₂)₂OCH₃ ("MOE"). In certain embodiments, 2'-substituent groups are selected from among: halo, allyl, amino, azido, SH, CN, OCN, CF₃, OCF₃, O-C₁-C₁₀ alkoxy, O-C₁-C₁₀ substituted alkoxy, O-C₁-C₁₀ alkyl, O-C₁-C₁₀ 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(CH₂)₂SCH₃, O(CH₂)₂ON(R_m)(R_n) or OCH₂C(=O)-N(R_m)(R_n), where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C₁-C₁₀ 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 (NO₂), 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., WO 2008/101157 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, NH₂, N₃, OCF₃, OCH₃, O(CH₂)₃NH₂, CH₂CH=CH₂, OCH₂CH=CH₂, OCH₂CH₂OCH₃, O(CH₂)₂SCH₃, O(CH₂)₂ON(R_m)(R_n),

$\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$, and N-substituted acetamide ($\text{OCH}_2\text{C}(=\text{O})-\text{N}(\text{R}_m)(\text{R}_n)$), where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ 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 ,

$\text{OCH}_2\text{CH}_2\text{OCH}_3$, $\text{O}(\text{CH}_2)_2\text{SCH}_3$, $\text{O}(\text{CH}_2)_2\text{ON}(\text{CH}_3)_2$, $\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$, and $\text{OCH}_2\text{C}(=\text{O})-\text{N}(\text{H})\text{CH}_3$ ("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 $\text{OCH}_2\text{CH}_2\text{OCH}_3$.

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 modified 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($=\text{CH}_2$)-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 $\text{C}_1\text{-C}_{12}$ 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: $-\text{C}(\text{R}_a)(\text{R}_b)]_n-$, $-\text{C}(\text{R}_a)(\text{R}_b)]_n\text{-O-}$, $-\text{C}(\text{R}_a)=\text{C}(\text{R}_b)-$, $-\text{C}(\text{R}_a)=\text{N-}$, $-\text{C}(=\text{NR}_a)-$, -

$\text{C}(=\text{O})-$, $-\text{C}(=\text{S})-$, $-\text{O-}$, $-\text{Si}(\text{R}_a)_2-$, $-\text{S}(=\text{O})_x-$, and $-\text{N}(\text{R}_a)-$;

wherein:

x is 0, 1, or 2;

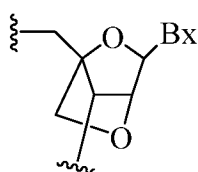
n is 1, 2, 3, or 4;

each R_a and R_b is, independently, H, a protecting group, hydroxyl, $\text{C}_1\text{-C}_{12}$ alkyl, substituted $\text{C}_1\text{-C}_{12}$ alkyl, $\text{C}_2\text{-C}_{12}$ alkenyl, substituted $\text{C}_2\text{-C}_{12}$ alkenyl, $\text{C}_2\text{-C}_{12}$ alkynyl, substituted $\text{C}_2\text{-C}_{12}$ alkynyl, $\text{C}_5\text{-C}_{20}$ aryl, substituted $\text{C}_5\text{-C}_{20}$ aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl,

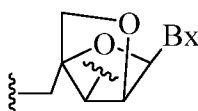
C₅-C₇ alicyclic radical, substituted C₅-C₇ alicyclic radical, halogen, OJ₁, NJ₁J₂, SJ₁, N₃, COOJ₁, acyl (C(=O)-H), substituted acyl, CN, sulfonyl (S(=O)₂-J₁), or sulfoxyl (S(=O)-J₁); and each J₁ and J₂ is, independently, H, C₁-C₁₂ alkyl, substituted C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, substituted C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, substituted C₂-C₁₂ alkynyl, C₅-C₂₀ aryl, substituted C₅-C₂₀ aryl, acyl (C(=O)-H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C₁-C₁₂ aminoalkyl, substituted C₁-C₁₂ 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.*, 20017, 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 91999/014226; 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; and U.S. Patent Publication Nos. 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'-CH₂-O-2'



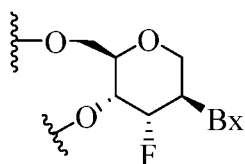
α -L-LNA (α -L-configuration)
bridge = 4'-CH₂-O-2'

α -L-methyleneoxy (4'-CH₂-O-2') or α -L-LNA bicyclic nucleosides have been incorporated into oligonucleotides that showed antisense activity (Frieden *et al.*, *Nucleic Acids Research*, 2003, 31, 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).

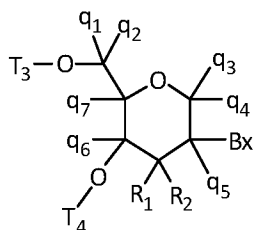
In certain embodiments, modified sugar moieties are sugar surrogates. In certain such embodiments, the oxygen atom of the sugar moiety is replaced, *e.g.*, with a sulfur, carbon or nitrogen atom. In certain such embodiments, such modified sugar moieties also comprise bridging and/or non-bridging substituents as described herein. For example, certain sugar surrogates comprise a 4'-sulfur atom and a substitution at the 2'-
 5 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"),
 10 manitol nucleic acid ("MNA") (*see e.g.*, Leumann, C.J. *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; Swayze et al., U.S.; 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
 15 nucleosides comprising additional modified THP compounds having the formula:

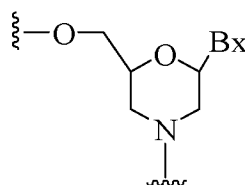


wherein, independently, for each of said modified THP nucleoside: Bx is a nucleobase moiety; T₃ and T₄ are each, independently, an internucleoside linking group linking the modified THP nucleoside to the remainder of an oligonucleotide or one of T₃ and T₄ is an internucleoside linking group linking the modified THP nucleoside to the remainder of an oligonucleotide and the other of T₃ and T₄ is H, a hydroxyl protecting group, a linked conjugate group, or a 5' or 3'-terminal group; q₁, q₂, q₃, q₄, q₅, q₆ and q₇ are each, independently, H, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, substituted C₂-C₆ alkenyl, C₂-C₆ alkynyl, or substituted C₂-C₆ alkynyl; and each of R₁ and R₂ is independently selected from among:

hydrogen, halogen, substituted or unsubstituted alkoxy, NJ_1J_2 , SJ_1 , N_3 , $\text{OC}(=\text{X})\text{J}_1$, $\text{OC}(=\text{X})\text{NJ}_1\text{J}_2$, $\text{NJ}_3\text{C}(=\text{X})\text{NJ}_1\text{J}_2$, and CN , wherein X is O , S or NJ_1 , and each J_1 , J_2 , and J_3 is, independently, H or $\text{C}_1\text{-C}_6$ 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 referred to herein as “modified morpholinos.”

In certain embodiments, sugar surrogates comprise acyclic moieties. 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., WO2011/133876.

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

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 impart nuclease stability, binding affinity or some other beneficial biological property to compounds described herein.

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 that does not comprise a nucleobase, referred to as an abasic nucleoside.

In certain embodiments, modified nucleobases are selected from: 5-substituted pyrimidines, 6-azapyrimidines, 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, 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-benzoyladenine, 2-N-isobutrylguanine, 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 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 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., 6,166,199; and Matteucci et al., U.S. 6,005,096.

In certain embodiments, compounds targeted to a DYRK1B 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.

Modified Internucleoside Linkages

The naturally occurring internucleoside linkage of RNA and DNA is a 3' to 5' phosphodiester linkage. In 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.

In certain embodiments, compounds targeted to a DYRK1B 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 the 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 of the present invention 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 one block of at least 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 methylphosphonate linkages. In certain embodiments, oligonucleotides having a gapmer nucleoside motif comprise a linkage motif

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

5 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
10 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.

15 *B. 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
20 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
25 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).

1. Certain Sugar Motifs

In certain embodiments, compounds described herein comprise oligonucleotides. In certain
30 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
35 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
5 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
10 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,
15 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
20 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
25 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
30 modified oligonucleotide. In certain embodiments, each nucleoside of a uniformly modified comprises the same 2'-modification.

2. Certain Nucleobase Motifs

In certain embodiments, compounds described herein comprise oligonucleotides. In certain
embodiments, oligonucleotides comprise modified and/or unmodified nucleobases arranged along the
35 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.

5 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.

10 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.

15 3. 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, 20 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 25 linkages. In certain embodiments, the terminal internucleoside linkages are modified.

C. 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 30 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 35 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.

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.

In certain embodiments, the present invention provides 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.

5 A compound described herein targeted to a DYRK1B 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 a DYRK1B nucleic acid and a pharmaceutically acceptable diluent. In certain embodiments, the pharmaceutically acceptable diluent is water. In certain embodiments,
10 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
15 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.

20 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.

Certain Combinations and Combination Therapies

25 In certain embodiments, a first agent comprising the 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
30 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, the secondary agent is a glucose-lowering agent. In certain embodiments, one or more compounds or compositions provided herein and one or more glucose-lowering agents are administered at different times. In certain embodiments, one or more compounds or compositions provided herein and one or more glucose-lowering agents are prepared together in a single formulation. In certain embodiments, one or more compounds or compositions provided herein and one or more glucose-lowering agents are prepared separately. In certain embodiments, a glucose-lowering agent is selected from a PPAR agonist, a dipeptidyl peptidase (IV) inhibitor, a GLP-I analog, insulin or an insulin analog, an insulin secretagogue, a SGLT2 inhibitor, a human amylin analog, a biguanide, an alpha-glucosidase inhibitor, or a combination thereof. In certain embodiments, a glucose-lowering agent is selected from metformin, sulfonylurea, rosiglitazone, or a combination thereof. In certain embodiments, a glucose-lowering agent is selected from acetohexamide, chlorpropamide, tolbutamide, tolazamide, glimepiride, a glipizide, a glyburide, or a gliclazide. In certain embodiments, a glucose-lowering agent is selected from a meglitinide selected from nateglinide or repaglinide. In certain embodiments, a glucose-lowering agent is selected from a thiazolidinedione selected from pioglitazone or rosiglitazone. In certain embodiments, a glucose-lowering agent is selected from an alpha-glucosidase inhibitor selected from acarbose or miglitol. In certain embodiments, a glucose-lowering agent is selected from insulin or an insulin-analog.

Certain embodiments are directed to the use of a compound targeted to DYRK1B as described herein in combination with a glucose-lowering agent. In particular embodiments such use is in a method of treating a patient suffering from a metabolic disease or disorder or in the preparation or manufacture of a medicament for treating the metabolic disease or disorder. In certain embodiments the metabolic disease or disorder is selected from: diabetes mellitus, hyperglycemia, obesity, metabolic syndrome, essential hypertension, disorders of lipid metabolism, hypertensive heart disease, myocardial infarction, pulmonary heart disease, heart failure, and other symptoms involving the cardiovascular system. In certain embodiments, a glucose-lowering agent is selected from a PPAR agonist, a dipeptidyl peptidase (IV) inhibitor, a GLP-I analog, insulin or an insulin analog, an insulin secretagogue, a SGLT2 inhibitor, a human amylin analog, a biguanide, an alpha-glucosidase inhibitor, or a combination thereof. In certain embodiments, a glucose-lowering agent is selected from metformin, sulfonylurea, rosiglitazone, or a combination thereof. In certain embodiments, a glucose-lowering agent is selected from acetohexamide, chlorpropamide, tolbutamide, tolazamide, glimepiride, a glipizide, a glyburide, or a gliclazide. In certain embodiments, a glucose-lowering agent is selected from a meglitinide selected from nateglinide or repaglinide. In certain embodiments, a glucose-lowering agent is selected from a thiazolidinedione selected from pioglitazone or

rosiglitazone. In certain embodiments, a glucose-lowering agent is selected from an alpha-glucosidase inhibitor selected from acarbose or miglitol. In certain embodiments, a glucose-lowering agent is selected from insulin or an insulin-analog.

Certain embodiments are drawn to a combination of a compound targeted to DYRK1B as described herein and a glucose-lowering agent, such as a glucose-lowering agent is selected from: a PPAR agonist, a dipeptidyl peptidase (IV) inhibitor, a GLP-I analog, insulin or an insulin analog, an insulin secretagogue, a SGLT2 inhibitor, a human amylin analog, a biguanide, an alpha-glucosidase inhibitor, metformin, sulfonylurea, rosiglitazone, acetohexamide, chlorpropamide, tolbutamide, tolazamide, glimepiride, a glipizide, a glyburide, or a gliclazide, nateglinide or repaglinide, a thiazolidinedione selected from pioglitazone or rosiglitazone, an alpha-glucosidase inhibitor selected from acarbose or miglitol, insulin or an insulin-analog. In certain embodiments, such a combination of a compound targeted to DYRK1B as described herein and a glucose-lowering agent, such as a glucose-lowering agent is selected from: a PPAR agonist, a dipeptidyl peptidase (IV) inhibitor, a GLP-I analog, insulin or an insulin analog, an insulin secretagogue, a SGLT2 inhibitor, a human amylin analog, a biguanide, an alpha-glucosidase inhibitor, metformin, sulfonylurea, rosiglitazone, acetohexamide, chlorpropamide, tolbutamide, tolazamide, glimepiride, a glipizide, a glyburide, or a gliclazide, nateglinide or repaglinide, a thiazolidinedione selected from pioglitazone or rosiglitazone, an alpha-glucosidase inhibitor selected from acarbose or miglitol, insulin or an insulin-analog, is useful for decreasing blood glucose levels, regulating insulin levels, increasing glucose tolerance, increasing insulin sensitivity, reducing LDL cholesterol levels, decreasing triglyceride levels, reducing blood pressure and reducing body-mass index, or a combination thereof and/or treating a metabolic disease or disorder.

In certain embodiments the compound targeted to DYRK1B, 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).

ADVANTAGES OF CERTAIN EMBODIMENTS

Provided herein, for the first time, are methods and compositions for the modulation of a DYRK1B nucleic acid that can treat, delay, prevent and/or ameliorate a metabolic disease, disorder or condition, or a physiological marker thereof. In a particular embodiment, for the first time, DYRK1B inhibitors (e.g., oligonucleotides targeting a nucleic acid encoding DYRK1B) are provided for decreases blood glucose levels, regulates insulin levels, increases glucose tolerance, increases insulin sensitivity, reduces LDL

cholesterol levels, decreases triglyceride levels, reduces blood pressure and reduces body-mass index, or a combination thereof in an animal.

EXAMPLES

Non-limiting disclosure and incorporation by reference

5 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: Antisense inhibition of mouse DYRK1B in TCMK-1 cells

10 Three hundred antisense oligonucleotides were screened in TCMK-1 and HEPA1-6 cells and the top 10 oligonucleotides were evaluated in vivo. The studies described below are a representative of these extensive experiments.

Antisense oligonucleotides were designed targeting a DYRK1B nucleic acid and were tested for their effects on DYRK1B mRNA in vitro. Cultured TCMK-1 cells at a density of 20,000 cells per well were
 15 transfected using electroporation with 7,000 nM antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and DYRK1B mRNA levels were measured by quantitative real-time PCR. Mouse primer probe set RTS34826 (forward sequence GATGAACCAGCATGATACAGAGA, designated herein as SEQ ID NO: 10; reverse sequence CGTACAGGTTGTAGGACAGC, designated herein as SEQ ID NO: 11; probe sequence
 20 CACCTTAAGCGGCACTTCATGTTCC, designated herein as SEQ ID NO: 12) was used to measure mRNA levels. DYRK1B mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of DYRK1B, relative to untreated control cells.

The chimeric antisense oligonucleotides in the Table below were designed as 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the central gap segment comprises of ten 2'-
 25 deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising five nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a 2'-MOE modification. The internucleoside linkages throughout each gapmer are phosphorothioate (P=S) linkages. All cytosine residues throughout each gapmer are 5-methylcytosines.

“Start site” indicates the 5'-most nucleoside to which the gapmer is targeted in the mouse gene
 30 sequence. “Stop site” indicates the 3'-most nucleoside to which the gapmer is targeted mouse gene sequence. Each gapmer listed in the Tables below is targeted to the mouse DYRK1B genomic sequence, designated herein as SEQ ID NO: 1 (RefSeq No. NT_187034.1 truncated from nucleotides 25178000 to 25189000).

Table 1

Inhibition of mouse DYRK1B mRNA by 5-10-5 MOE gapmers targeting SEQ ID NO: 1

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO
793673	8385	8404	ATCGGTAGGCTCTGTTGTCG	0	13
793684	9066	9085	CCTCTCCCTTGACCCCCTGC	0	14
793686	9180	9199	AATCTCCCCTCTACCGGACC	23	15
793688	2317	2336	GGTGGCGGCGGCGATGAGGA	0	16
793691	1789	1808	CCCTCGGGCTCAGCCTCTTC	8	17
793693	2314	2333	GGCGGCGGCGATGAGGAGGT	0	18
793694	2534	2553	CTTGTCAGATCCCCTTCTAT	0	19
793695	2664	2683	CTACGCTGGGTCATTCCACA	40	20
793696	2921	2940	CTATAGATGTTTCAACCACC	15	21
793697	3154	3173	AGGCAGAAACCGTGTAGAGT	0	22
793698	3697	3716	CCCTTCAATCCTCAGGCAGG	10	23
793762	9073	9092	CCAAACTCCTCTCCCTTGAC	12	24
793771	2475	2494	CACAGATAAACAACCTCTTC	3	25
793773	2704	2723	TTTCTTCTTTACCCTGAGGT	29	26
793774	2972	2991	ATGGACCTCCCAGCAAACCC	41	27
793775	3247	3266	GGAGCCATCAGAGCCAGACA	20	28
793704	4967	4986	TCACATCCCTTATACTGGAT	35	29
793705	5375	5394	CGTCCCTCACCAGCTGCGGG	0	30
793706	5633	5652	AAGCAAAACCTCCAAAAGTA	0	31
793707	5892	5911	GTCAAAACAGCTCCACATTT	2	32
793777	3903	3922	TGTTGTGAACCTTCAGACCT	13	33
793778	4151	4170	TTCCATTCTGCCCCAGGTCA	18	34
793710	6693	6712	TCAGCTTCATCCTTTCTCTT	4	35
793783	5532	5551	TGTCCTCTACAGAGTCCCTT	30	36
793712	8483	8502	CCACCCTCTTCCAAAATTTC	0	37

Example 2: Dose-dependent antisense inhibition of mouse DYRK1B in HEPA1-6 cells

5 Gapmers from Example 1 exhibiting significant *in vitro* inhibition of DYRK1B mRNA were selected and tested at various doses in HEPA1-6 cells. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.7 μ M, 2.2 μ M, 6.7 μ M, and 20.0 μ M concentrations of antisense oligonucleotide. After a treatment period of approximately 16 hours, RNA was isolated from the cells and DYRK1B mRNA levels were measured by quantitative real-time PCR. Mouse primer probe set RTS34826

10 was used to measure mRNA levels. DYRK1B mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. The half maximal inhibitory concentration (IC₅₀) of each oligonucleotide is

presented. DYRK1B mRNA levels were significantly reduced in a dose-dependent manner in antisense oligonucleotide treated cells.

Table 2
Efficacy of mouse oligonucleotides targeting DYRK1B

IsisNo	IC ₅₀ (μ M)
793686	<0.7
793695	0.7
793696	3.8
793704	3.8

Example 3: Effect antisense inhibition of DRYK1B in the ob/ob mouse model of obesity

Leptin is a hormone produced by fat that regulates appetite. Deficiency of this hormone in both humans and in non-human animals, leads to obesity. ob/ob mice have a mutation in the leptin gene which results in obesity and hyperglycemia. As such, these mice are a useful model for the investigation of obesity and diabetes and related conditions provided herein. These mice models are also useful for testing compounds, compositions and methods designed to treat, prevent or ameliorate such conditions.

Treatment

In accordance with the present invention, the effects of antisense inhibition of DYRK1B were investigated in the ob/ob mouse model of obesity. C57Bl/6J-Lep^{ob}/Lep^{ob} (ob/ob) mice at 4 weeks of age were purchased from Jackson Laboratories (Bar Harbor, ME). During a 1 week acclimation period and throughout the study, mice were fed a diet with added cocoa butter, cholesterol, and sodium cholate and a fat content of 10-15% (Labdiets #5015, Purina, St. Louis, MO).

The mice were divided into 4 groups of 6 mice each based on body weight and body fat content. Two groups of mice was treated with 25 mg/kg or 50 mg/kg of ISIS 793695 administered subcutaneously weekly for 5 weeks. The third group of mice was treated with 50 mg/kg control oligonucleotide, ISIS 141923 (CCTTCCCTGAAGGTTCTCC, 5-10-5 MOE gapmer with no known murine target; SEQ ID NO: 38) administered subcutaneously weekly for 5 weeks. A control group of mice was treated with PBS administered subcutaneously weekly for 5 weeks.

RNA analysis

RNA was extracted from the liver, white adipose tissue (WAT), and quadricep muscle (Quad) for RT-PCR analysis of murine DYRK1B expression. The data was normalized to the housekeeping gene, cyclophilin. The results are presented in the Table below and demonstrate the in vivo inhibition of DYRK1B by antisense oligonucleotide.

Table 3
Dose-dependent in vivo inhibition (%) of mouse DYRK1B

Dose (mg/kg)	Liver	WAT	Quad
25	75	66	21
50	82	77	32

Effect on glucose tolerance

Glucose tolerance was measured via the intraperitoneal glucose tolerance test at week 3. The mice were fasted overnight and then an intraperitoneal administration of glucose at 0.50 g/kg was given. Blood glucose levels were measured before the glucose challenge and at different time points after challenge up to 120 min. The results for the area under the curve (AUC values) are also presented below and are found to be statistically different for mice treated with ISIS 793695 at 50 mg/dl compared to the PBS control as well as the oligo control.

As presented in the Tables below, in antisense oligonucleotide treated mice, initial glucose levels were lower and the increase in glucose levels during the IPGTT assay was less than in the saline control. Therefore, antisense oligonucleotide treated mice had better glucose tolerance as compared to the saline controls.

Table 4
Glucose (mg/dL) in ob/ob mice

	Dose (mg/kg)	0 min	15 min	30 min	60 min	90 min	120 min
PBS		219	388	392	340	305	331
ISIS 141923	50	231	447	433	346	314	334
ISIS 793695	25	224	354	395	278	246	278
	50	192	394	350	287	294	277

Table 5
AUC values in ob/ob mice

PBS	43932
ISIS 141923	44639
ISIS 793695	35149

Fed glucose level analysis

Plasma levels of glucose were measured using an automated clinical chemistry analyzer (Olympus Clinical Analyzer). The results are presented in the Table below, expressed in mg/d/L. Treatment with ISIS oligonucleotide resulted in lowering of fed glucose levels in the plasma over the PBS control at weeks 2 and

5. Therefore, antisense inhibition of DRK1B resulted in significant reduction of fed glucose levels in mice compared to the control.

Table 6
Fed glucose levels (mg/dL) in ob/ob mice

	Dose (mg/kg)	Week 2	Week 5
PBS		523	503
ISIS 141923	50	438	500
ISIS 793695	25	364	416
	50	335	330

5 *Body weight*

Weekly body weights were measured and are presented in the Table below. The data indicates that antisense inhibition of DYRK1B had no adverse effects on body weight outside the expected range for antisense oligonucleotides.

Table 7
Weekly body weights (g)

	Dose (mg/kg)	Week 0	Week 1	Week 2	Week 3	Week 4
PBS		39	43	47	51	53
ISIS 141923	50	39	44	48	53	54
ISIS 793695	25	38	44	47	52	53
	50	38	43	47	52	53

In addition, plasma levels of transaminases, bilirubin, triglycerides, and cholesterol were measured. The data indicates that antisense inhibition of DYRK1B had no adverse effects on these plasma chemistry markers outside the expected range for antisense oligonucleotides.

15 **Example 4: Antisense inhibition of DYRK1B in the Diet-Induced Model of Obesity (DIO)**

The C57BL/6 mouse strain is reported to be prone to diet-induced obesity and is accepted as a model for diet-induced obesity for human (C. Gallou-Kabani et al, *Obesity* (2007) 15, 1996–2005). To induce obesity, these mice were fed a high-fat diet and used in the following studies to evaluate the effect of antisense inhibition of DRK1B.

20 *Treatment*

C57BL/6 mice were fed for a 60% high fat diet for 16 weeks. The start weights of the mice were 32–40 g. The mice were then divided into 3 groups of 3 mice each based on body weight and body fat content. One group of mice was treated with 37.5 mg/kg of ISIS 793695 administered subcutaneously twice weekly (75 mg/kg/week) for 7 weeks. Another group of mice was treated with 37.5 mg/kg of control oligonucleotide,

ISIS 141923 administered subcutaneously twice weekly (75 mg/kg/week) for 7 weeks. A control group of mice was treated with PBS administered subcutaneously twice weekly for 7 weeks.

Fed glucose level analysis

After 2 weeks of treatment, plasma levels of glucose were measured using an automated clinical chemistry analyzer (Olympus Clinical Analyzer). The results are presented in the Table below, expressed in mg/d/L. Treatment with ISIS oligonucleotide resulted in lowering of fed glucose levels in the plasma over the PBS control. Therefore, antisense inhibition of DRK1B resulted in significant reduction of fed glucose levels in mice compared to the control.

Table 8
Fed glucose levels (mg/dL) in DIO mice

	Glucose
PBS	214
ISIS 141923	191
ISIS 793695	179

Insulin sensitivity analysis

After 7 weeks of treatment, insulin sensitivity in the mice was measured by the intraperitoneal insulin tolerance test (IPITT). The mice were fasted overnight, injected intraperitoneally with human recombinant insulin at 0.75 U/kg and tested for blood glucose levels over a period of 2 hours. The blood glucose levels (mg/dL) are shown below in the Table below. The glucose levels in mice treated with ISIS 793695 were significantly lower than controls during ITT. The results for the area under the curve (AUC values) are also presented below and are found to be statistically different for mice treated with ISIS 793695 at 50 mg/dl compared to the PBS control as well as the oligo control.

Table 9
Glucose levels (mg/dL) in DIO mice

	0 min	15 min	30 min	60 min	90 min	120 min
PBS	72	89	61	41	42	54
ISIS 141923	76	87	62	45	46	59
ISIS 793695	68	76	53	37	32	44

Table 10
AUC values in DIO mice

PBS	6650
ISIS 141923	6993
ISIS 793695	5580

In addition, plasma levels of transaminases, bilirubin, triglycerides, and cholesterol were measured. The data indicates that antisense inhibition of DYRK1B had no adverse effects on these plasma chemistry markers outside the expected range for antisense oligonucleotides.

These data support the role of DYRK1B in glucose homeostasis and suggest that antisense inhibition of DYRK1B may be a novel approach for treating hyperglycemia and metabolic diseases.

Example 5: Specificity of inhibition of DYRK1B but not of DYRK1A in vivo

In order to demonstrate the specificity of Ionis oligonucleotides to DYRK1B, C57BL/6 mice were dosed with oligonucleotides targeting DYRK1B, and the expression levels of DYRK1B and DYRK1A were evaluated.

Additional antisense oligonucleotides were designed targeting a DYRK1B nucleic acid. The chimeric antisense oligonucleotides in the Table below were designed as 3-10-3 cEt gapmers. The gapmers are 16 nucleosides in length, wherein the central gap segment comprises of ten 2'-deoxynucleosides and 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. All cytosine residues throughout each gapmer are 5-methylcytosines.

"Start site" indicates the 5'-most nucleoside to which the gapmer is targeted in the mouse gene sequence. "Stop site" indicates the 3'-most nucleoside to which the gapmer is targeted mouse gene sequence. Each gapmer listed in the Table below is targeted to the mouse DYRK1B genomic sequence, designated herein as SEQ ID NO: 1 (RefSeq No. NT_187034.1 truncated from nucleotides 25178000 to 25189000).

Table 11
3-10-3 cEt gapmers targeting SEQ ID NO: 1

ISIS No	Start Site	Stop Site	Sequence	SEQ ID NO
860464	2584	2599	CTAAAAGTGTCTTCG	39
860466	2601	2616	GCACAAGACTTCACTC	40
860471	2613	2628	TCCCTAAATATCGCAC	41
860491	2726	2741	TCTAAGAGTCACGGTC	42
860492	2728	2743	CATCTAAGAGTCACGG	43
860493	2729	2744	ACATCTAAGAGTCACG	44
860521	2923	2938	ATAGATGTTTCAACCA	45
860597	4011	4026	AGTTACAAAGCTCCTG	46

Treatment

Groups of C57BL/6 mice were treated with 50 mg/kg of ISIS 860464, ISIS 860466, ISIS 860471, ISIS 860491, ISIS 860492, ISIS 860493, ISIS 860521, or ISIS 860597, administered subcutaneously weekly for 4 weeks. Another group of mice was treated with 50 mg/kg of control oligonucleotide, ISIS 549144 (GGCCAATACGCCGTCA; SEQ ID NO: 47; 3-10-3 cEt apmer with no known target) administered subcutaneously weekly for 4 weeks. A control group of mice was treated with PBS administered subcutaneously weekly for 4 weeks. DYRK1B and DYRK1A expressions were measured and normalized to RIBOGREEN®. The results are presented in the Table below and demonstrate that most Ionis oligonucleotides inhibit DYRK1B expression levels in a number of tissues, but not DYRK1A expression levels. Hence, Ionis oligonucleotides are highly specific in inhibiting DYRK1B mRNA expression.

Table 12
% inhibition in the liver compared to PBS control

ISIS No	DYRK1B	DYRK1A
549144	28	21
860464	48	0
860466	74	1
860471	52	0
860491	53	0
860492	64	0
860493	72	27
860521	61	0
860597	4	0

Table 13
% inhibition in the quadricep muscle compared to PBS control

ISIS No	DYRK1B	DYRK1A
549144	0	5
860464	31	0
860466	35	0
860471	32	0
860491	31	0
860492	35	0
860493	47	0
860521	46	1
860597	19	14

Table 14
% inhibition in the white adipose tissue compared to PBS control

ISIS No	DYRK1B	DYRK1A
549144	30	0
860464	33	0
860466	45	0
860471	55	0
860491	44	0
860492	64	0
860493	71	0
860521	70	0
860597	41	0

What is claimed is:

1. A method of treating, preventing, delaying the onset of, slowing the progression on, or ameliorating a metabolic disease or disorder in an individual having, or at risk of having, a metabolic disease or disorder comprising administering a compound comprising a DYRK1B specific inhibitor to the individual, thereby treating, preventing, delaying the onset of, slowing the progression on, or ameliorating the metabolic disease or disorder in the individual.
2. The method of claim 1, wherein the metabolic disease or disorder is diabetes, obesity, hypertension, hyperglycemia, or metabolic syndrome.
3. The method of claim 2, wherein the diabetes is Type 2 diabetes.
4. The method of claim 1, wherein the metabolic disease or disorder is disorders of lipid metabolism.
5. The method of any preceding claim, wherein the specific inhibitor of DYRK1B reduces plasma glucose levels.
6. The method of any preceding claim, wherein the specific inhibitor of DYRK1B regulates insulin levels.
7. A method of inhibiting expression or activity of DYRK1B in a cell comprising contacting the cell with a compound comprising a DYRK1B specific inhibitor, thereby inhibiting expression or activity of DYRK1B in the cell.
8. The method of claim 7, wherein the cell is in an individual.
9. The method of claim 8, wherein the individual has, or is at risk of a metabolic disease or disorder.
10. The method of claim 9, wherein the metabolic disease or disorder is diabetes, obesity, or metabolic syndrome.
11. A method of inhibiting the expression or activity of DYRK1B but not of DRK1A in a cell comprising contacting the cell with a compound comprising a DYRK1B specific inhibitor, thereby inhibiting expression or activity of DYRK1B but not of DYRK1A in the cell.
12. The method of any preceding claim, wherein the individual is human.
13. The method of any preceding claim, wherein the DYRK1B-specific inhibitor selected from any of a nucleic acid, a polypeptide, an antibody, and a small molecule.
14. The method of any preceding claim, wherein the compound comprises a modified oligonucleotide targeting DYRK1B.
15. The method of claim 14, wherein the compound is single-stranded.
16. The method of claim 14, wherein the compound is double-stranded.
17. The method of any one of claims 14-16, wherein the modified oligonucleotide is 12 to 30 linked nucleosides in length.
18. The method of any one of claims 14-17, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage, at least one modified sugar moiety, or at least one modified nucleobase.

19. The method of claim 18, wherein the at least one modified internucleoside linkage of the modified oligonucleotide is a phosphorothioate internucleoside linkage, the at least one modified sugar is a bicyclic sugar or 2'-O-methoxyethyl and the at least one modified nucleobase is a 5-methylcytosine.
20. The method of claim 18 or 19, wherein at least one modified sugar comprises a 4'-CH(CH₃)-O-2' bridge or a 4'-(CH₂)_n-O-2' bridge, wherein n is 1 or 2.
21. The method of any one of claims 14-20, wherein the modified oligonucleotide comprises:
 - a gap segment consisting of linked deoxynucleosides;
 - a 5' wing segment consisting of linked nucleosides;
 - a 3' wing segment consisting 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.
22. The method of any one of the preceding claims, wherein compound is administered parenterally.
23. The method of claim 22, wherein the compound is administered parenterally by subcutaneous or intravenous administration.
24. The method of any one of the preceding claims, comprising co-administering a DYRK1B inhibitor and at least one additional therapy.
25. The method of claim 24, wherein the DYRK1B inhibitor and the additional therapy are administered concomitantly.
26. The method of claim 24, wherein the DYRK1B inhibitor and the additional therapy are administered consecutively.
27. The method of any one of claims 22-26, wherein the additional therapy is a glucose-lowering agent.
28. Use of a compound comprising a DYRK1B-specific inhibitor for the manufacture or preparation of a medicament for treating a metabolic disease or disorder.
29. Use of a compound comprising a DYRK1B-specific inhibitor for the treatment of a metabolic disease or disorder.
30. The use of claims 28 or 29, wherein the metabolic disease or disorder is diabetes, obesity, hypertension, hyperglycemia, or metabolic syndrome.
31. The use of claim 30, wherein the diabetes is Type 2 diabetes.
32. The use of claim 30, wherein the metabolic disease or disorder is disorders of lipid metabolism.
33. The use of any of claims 28-32, wherein the compound is capable of reducing plasma glucose levels or regulating insulin levels.
34. The use of claim 28 or 29, wherein the DYRK1B specific inhibitor is selected from any of a nucleic acid, a polypeptide, an antibody, and a small molecule.
35. The use of any of claims 28-34, wherein the compound comprises a modified oligonucleotide targeted to DYRK1B.

36. The use of claim 35, wherein the compound is single-stranded.
37. The use of claim 35, wherein the compound is double-stranded
38. The use of any one of claims 35-37, wherein the modified oligonucleotide is 12 to 30 linked nucleosides in length.
39. The use of any one of claims 35-38, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage, at least one modified sugar moiety, or at least one modified nucleobase.
40. The use of claim 39, wherein the at least one modified internucleoside linkage of the modified oligonucleotide is a phosphorothioate internucleoside linkage, the at least one modified sugar is a bicyclic sugar or 2'-O-methoxyethyl and the at least one modified nucleobase is a 5-methylcytosine.
41. The use of any one of claims 35-39, wherein at least one modified sugar comprises a 4'-CH(CH₃)-O-2' bridge or a 4'-(CH₂)_n-O-2' bridge, wherein n is 1 or 2.
42. The use of any one of claims 35-41, wherein the modified oligonucleotide comprises:
 - a gap segment consisting of linked deoxynucleosides;
 - a 5' wing segment consisting of linked nucleosides;
 - a 3' wing segment consisting 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.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2017/022782

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/473; A61P 35/00; C07D 471/04; C12P 19/34; C12Q 1/6883 (2017.01)

CPC - A61K 31/437; A61K 31/506; C07D 471/04; C12Q 1/68; C12Q 1/6883 (2017.05)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History documentDocumentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/183; 514/1.1; 514/253.03 (keyword delimited)Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	WO 2015/196068 A2 (GEISINGER CLINIC) 23 December 2015 (23.12.2015) entire document	1-4, 7-10, 28-32, 34
X	ASHFORD et al. "A Novel DYRK1B Inhibitor AZ191 Demonstrates that DYRK1B Acts Independently of GSK3 β to Phosphorylate Cyclin D1 at Thr286, not Thr288," Biochem J, 01 January 2014 (01.01.2014), Vol. 457, Iss. 1, Pgs. 43-56. entire document	5 11
Y	US 2015/246913 A1 (DANA-FARBER CANCER INSTITUTE, INC et al) 03 September 2015 (03.09.2015) entire document	5
A	US 2014/0371251 A1 (4SC DISCOVERY GMBH) 18 December 2014 (18.12.2014) entire document	1-5, 7-11, 28-32, 34
A	KERAMATI et al. "A Form of the Metabolic Syndrome Associated with Mutations in DYRK1B," The New England Journal of Medicine, 15 May 2014 (15.05.2014), Vol. 370, Iss. 20, Pgs. 1909-1919. entire document	1-5, 7-11, 28-32, 34

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

01 May 2017

Date of mailing of the international search report

05 JUN 2017

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2017/022782

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 6, 12-27, 33, 35-42
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

Remark on Protest

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