INHIBIN SUBUNIT BETA E-RELATED DOUBLE STRANDED OLIGONUCLEOTIDE COMPOSITIONS AND METHODS RELATING THERETO

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 63/581,620, filed September 8, 2023, and U.S. Provisional Application No. 63/586,079, filed September 28, 2023, the contents of each of which are incorporated herein by reference herein in their entirety.

TECHNICAL FIELD

Among other things, the present disclosure provides double stranded (ds) oligonucleotides, compositions and methods (e.g., of preparation, use, etc.) thereof. In some embodiments, provided technologies are useful for preventing and/or treating various conditions, disorders, or diseases associated with inhibin subunit beta E (INHBE) expression.

BACKGROUND

Metabolic disorders, e.g., metabolic syndrome, and related diseases, e.g., obesity, cardiovascular disease, diabetes, and hypertension are an increasing medical concern. Typical treatment for such disorders and diseases involves targeted approaches and/or changes in diet and lifestyle, e.g., increased physical activity. Particularly, treatment for obesity, which is a disorder involving excess body fat, entails exercise and a healthy, balanced diet leading to weight loss. There exists, however, a need for alternate treatment methods for metabolic diseases, particularly weight loss.

Double stranded (ds) oligonucleotides are useful in various applications, e.g., therapeutic, diagnostic, and/or research applications. Inhibin subunit beta E (INHBE), which is primarily expressed in the liver, has been linked with both body mass index and insulin resistance. As such, ds oligonucleotides targeting disorders or diseases associated with expression of INHBE can be useful treatment of such conditions including metabolic disorders, e.g., metabolic syndrome, and related diseases, e.g., obesity, cardiovascular disease, diabetes, and hypertension.

SUMMARY

In some embodiments, the present disclosure provides ds oligonucleotides targeting INHBE and compositions thereof that have significantly improved properties and/or high activities. Among other things, the present disclosure provides technologies for designing, manufacturing and utilizing such ds oligonucleotides and compositions. Particularly, in some

embodiments, the present disclosure provides ds oligonucleotides comprising useful patterns of internucleotidic linkages and/or patterns of sugar modifications, which, when combined with one or more other structural elements, e.g., base sequence (or portion thereof), nucleobase modifications (and patterns thereof), additional chemical moieties, etc., can provide ds oligonucleotides targeting INHBE and compositions thereof with high activities and/or desired properties, including but not limited to effective and efficient reduction of expression, levels and/or activities of INHBE transcripts and products encoded thereby. In some embodiments, ds oligonucleotides targeting INHBE and compositions reduce levels of a INHBE transcript, and are useful for treating and/or preventing INHBE-associated condition, disorder, or disease, including, but not limited to metabolic disorders, e.g., metabolic syndrome, and related diseases, e.g., obesity, cardiovascular disease, diabetes, and hypertension.

In some embodiments, a ds oligonucleotide targeting INHBE is capable of mediating knockdown of INHBE, wherein the level, expression and/or activity of INHBE or a product thereof are decreased. In some embodiments, a ds oligonucleotide targeting INHBE is capable of mediating pan-specific knockdown of INHBE, wherein the level, expression and/or activity of multiple or all INHBE alleles are decreased. In some embodiments, a ds oligonucleotide targeting INHBE has a base sequence that is complementary to a sequence which is common in multiple or all INHBE alleles.

In certain embodiments, such structural elements include one or more of: (1) chemical modifications (*e.g.*, modifications of a sugar, base and/or internucleotidic linkage) and patterns thereof; and (2) alterations in stereochemistry (*e.g.*, stereochemistry of a backbone chiral internucleotidic linkage) and patterns thereof. One or more of such structural elements can, in certain embodiments, be independently present in one or both oligonucleotides of a ds oligonucleotide. In certain embodiments, the properties and/or activities impacted by such structural elements include, but are not limited to, participation in, direction of a decrease in expression, activity or level of a gene or a gene product thereof, mediated, for example, by RNA interference (RNAi interference).

In certain embodiments, the present disclosure demonstrates that compositions comprising ds oligonucleotides (e.g., dsRNAi oligonucleotides, also referred to as dsRNAi agents) with controlled structural elements provide unexpected properties and/or activities.

In certain embodiments, a dsRNAi agent capable of directing INHBE (Inhibin subunit βE)-specific RNA interference to induce lipolysis while preserving muscle mass, the dsRNAi agent comprises a guide strand and a passenger strand, wherein:

a) the guide strand is complementary or substantially complementary to an INHBE target RNA sequence;

b) the guide strand comprises:

i. a non-negatively charged internucleotidic linkage in the *S*p configuration between the +3 nucleotide relative to the 5' terminal nucleotide and the immediately downstream (+4) nucleotide;

ii. a non-negatively charged internucleotidic linkage in the *R*p configuration between the +10 nucleotide and the immediately downstream (+11) nucleotide;

iii. phosphorothioate internucleotidic linkages in *S*p configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide; and/or

iv. phosphorothioate internucleotidic linkages in *R*p, *S*p, or alternating configurations between the 5' terminal (+1) nucleotide and the immediately downstream (+2) nucleotide and between the +2 nucleotide and the immediately downstream (+3) nucleotide;

c) the guide strand further comprises a 5' phosphate modification;

d) the passenger strand comprises one or more chiral internucleotidic linkages in *R*p or *S*p configuration; and

e) the guide strand and the passenger strand each independently has a length of 15-49 nucleotides.

In alternative embodiments, the present disclosure encompasses the recognition that stereochemistry, e.g., stereochemistry of backbone chiral centers, can unexpectedly maintain or improve properties of ds oligonucleotides. For example, but not by way of limitation, the instant disclosure relates, in part, to ds oligonucleotides comprising one or more of:

(1) a guide strand comprising backbone non-negatively charged internucleotidic linkage in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction;

(2) a guide strand comprising backbone non-negatively charged internucleotidic linkage in the Rp configuration between the +10 nucleotide and the immediately downstream (+11) nucleotide, i.e., in the 3' direction;

(3) a guide strand comprising backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream, i.e., in the 5' direction, (N-2) nucleotide;

(4) a guide strand comprising backbone phosphorothioate chiral centers in Rp, Sp, or alternating configurations between the 5' terminal (+1) nucleotide and the immediately downstream, i.e., in the 3' direction, (+2) nucleotide and between the +2 nucleotide and the immediately downstream (+3) nucleotide;

(5) a guide strand comprising one or more backbone phosphorothioate chiral centers upstream, i.e., in the 5' direction, relative to backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide, where the upstream backbone phosphorothioate chiral centers are in Rp or Sp configuration;

(6) a guide strand comprising one or more backbone phosphorothioate chiral centers in Rp or Sp configuration between the N-2 nucleotide and the immediately upstream (N-3) nucleotide, i.e., in the 5' direction;

(7) a guide strand comprising a 5' terminal modification, e.g. 5' phosphate modification, e.g. 5' triazole phosphate modification;

(8) a passenger strand in combination with one or more of the aforementioned guide strands, comprising one or more backbone chiral centers in Rp or Sp configuration; and

(9) a passenger strand in combination with one or more of the aforementioned guide strands, comprising backbone phosphorothioate chiral centers in the Sp configuration between the 5' terminal (+1) nucleotide and the immediately downstream, i.e., in the 3' direction, (+2) nucleotide and between the 3' terminal nucleotide and the penultimate (N-1) nucleotide;

wherein the ds oligonucleotide further comprises one or more of:

(1) a guide strand where one or both of the 5' and 3' terminal dinucleotides are ***not*** linked by a Rp, Sp, or stereorandom non-negatively charged internucleotidic linkages, i.e., the guide strand comprises one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkages downstream, i.e., in the 3' direction, relative to the

linkage between the 5' terminal dinucleotide and/or upstream, i.e., in the 5' direction, relative to the linkage between the 3' terminal dinucleotide;

(2) a guide strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide;

(3) a guide strand where an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between the third (+3) and fourth (+4) nucleotides, relative to the 5' terminal nucleotide, of the guide strand and/or between the tenth (+10) and eleventh (+11) nucleotides, relative to the 5' terminal nucleotide;

(4) a passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs upstream, i.e., in the 5' direction, relative to the central nucleotide of the passenger strand; and

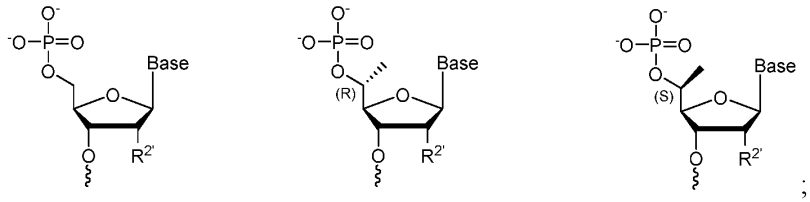
(5) Passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs downstream, i.e., in the 3' direction, relative to the central nucleotide of the passenger strand, and

wherein the ds oligonucleotide further comprises a 2' modification, e.g., a 2'-F modification, of the 3' nucleotide of a nucleotide pair linked by a Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide or passenger strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

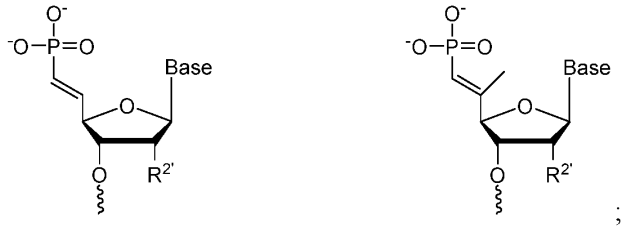
In certain embodiments, the present disclosure encompasses the recognition that stereochemistry, e.g., stereochemistry of chiral centers at a 5' terminal modification, e.g. 5' phosphate modification, e.g. 5' triazole phosphate *modification* of guide strands, can unexpectedly maintain or improve properties of the ds oligonucleotides described herein. For example, but not by way of limitation, the instant disclosure relates, in part, to ds oligonucleotides comprising a guide stranding comprising: (1) a phosphorothioate chiral center

in Rp or Sp configuration; (2) an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage where the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage comprises a 2' modification, e.g., a 2' F; and (3) a 5' terminal modification, e.g. 5' phosphate modification, e.g. 5' triazole phosphate modification selected from: a

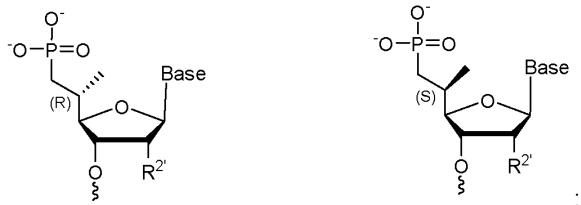
(a) 5' PO modifications, such as, but not limited to:


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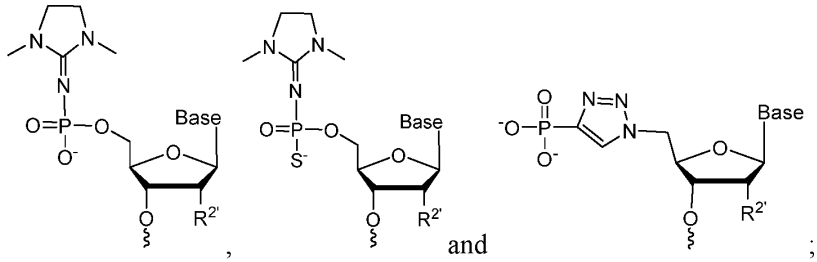
(b) 5' VP modifications, such as, but not limited to:


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(c) 5' MeP modifications, such as, but not limited to:

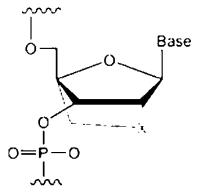

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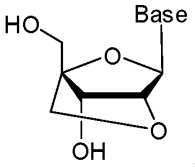
(d) 5' PN and 5' triazole-P modifications, such as, but not limited to:


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wherein Base is selected from A, C, G, T, U, abasic and modified nucleobases;

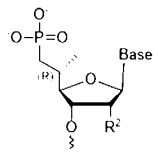
$R^{2'}$ is selected from H, OH, O-alkyl, F, MOE, locked nucleic acid (LNA) bridges and bridged nucleic acid (BNA) bridges to the 4' C, such as, but not limited to:

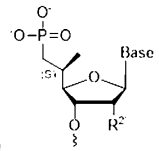


, and 

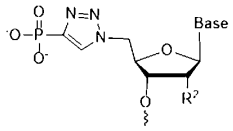
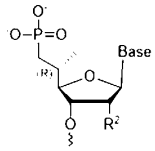
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In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage. In certain embodiments, the guide strand comprises, a backbone phosphorothioate chiral center in Sp configuration between the 5' terminal (+1) nucleotide and the immediately downstream, i.e., in the 3' direction, (+2) nucleotide, and a backbone phosphorothioate chiral center in the Rp configuration between the +2 nucleotide and the immediately downstream (+3) nucleotide.

In certain embodiments, the guide strand comprises a 5' terminal modification, e.g. 5' phosphate modification, e.g. 5' triazole phosphate modification selected from, but not limited to, 5' MeP modifications and 5' triazole-P modifications. In certain embodiments, the 5' terminal modification, e.g. 5' phosphate modification, e.g. 5' triazole phosphate modification is 

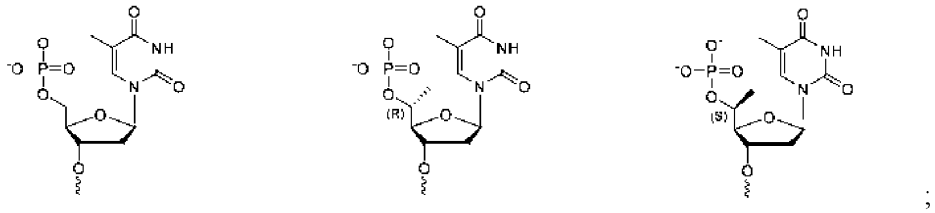
. In some embodiments, the 5' terminal modification, e.g. 5' phosphate modification, e.g. 5' triazole phosphate modification is 

:. In certain embodiments, the 5' terminal modification, e.g. 5' phosphate modification, e.g. 5' triazole phosphate

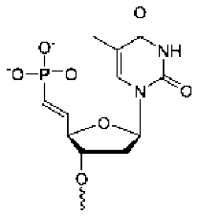
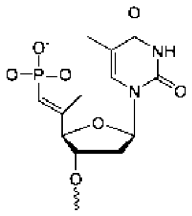
modification is  . In certain embodiments, the guide strand comprises the 5' MeP modification  , a backbone phosphorothioate chiral center in Sp configuration between the 5' terminal (+1) nucleotide and the immediately downstream, i.e., in the 3' direction, (+2) nucleotide, and a backbone phosphorothioate chiral center in the Rp configuration between the +2 nucleotide and the immediately downstream (+3) nucleotide.

In certain other embodiments, the present disclosure encompasses the recognition that stereochemistry, e.g., stereochemistry of chiral centers at the 5' terminal nucleotide of guide strands, can unexpectedly maintain or improve properties of ds oligonucleotides wherein the guide strand of the ds oligonucleotide also comprises a phosphorothioate chiral center in Rp or Sp configuration. For example, but not by way of limitation, the instant disclosure relates, in part, to ds oligonucleotides comprising a guide stranding comprising: (1) a phosphorothioate chiral center in Rp or Sp configuration; (2) an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage where the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage comprises a 2' modification, e.g., a 2' F; and (3) a 5' terminal modification, e.g. 5' phosphate modification, e.g. 5' triazole phosphate modification selected from:

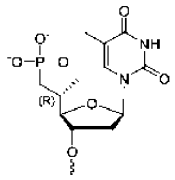
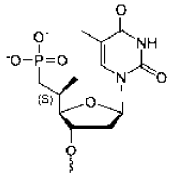
(a) 5' PO nucleotides, such as, but not limited to:

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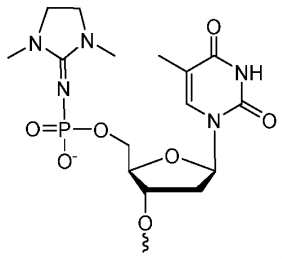
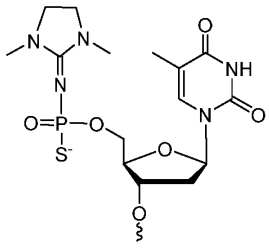
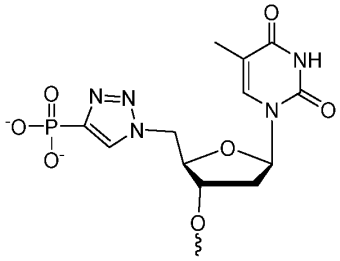
(b) 5' VP nucleotides, such as, but not limited to:



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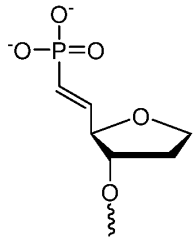
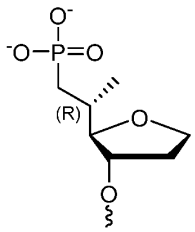
(c) 5' MeP nucleotides, such as, but not limited to:



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(d) 5' PN and 5' triazole-P nucleotides, such as, but not limited to:


, 
and 
;

(e) 5' abasic VP and 5' abasic MeP nucleotides, such as, but not limited to:


and 
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In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In certain embodiments, the present disclosure encompasses the recognition that non-

naturally occurring internucleotidic linkages, e.g., neutral internucleotidic linkages, can, in certain embodiments, be used to link one or more molecules to the double-stranded oligonucleotides described herein. In certain embodiments, such linked molecules can facilitate targeting and/or delivery of the double-stranded oligonucleotide. For example, but not limitation, such linked molecules an include lipophilic molecules. In certain embodiments, the linked molecule is a molecule comprising one or more GalNAc moieties. In certain embodiments, the linked molecule is a receptor. In certain embodiments, the linked molecule is a receptor ligand.

In certain embodiments, the present disclosure provides technologies for incorporating various additional chemical moieties into ds oligonucleotides. In certain embodiments, the present disclosure provides, for example, reagents and methods for introducing additional chemical moieties through nucleobases (*e.g.*, by covalent linkage, optionally via a linker, to a site on a nucleobase).

In certain embodiments, the present disclosure provides technologies, e.g., ds oligonucleotide compositions and methods thereof, that achieve allele-specific suppression, wherein transcripts from one allele of a particular target gene is selectively knocked down relative to at least one other allele of the same gene.

Among other things, the present disclosure provides structural elements, technologies and/or features that can be incorporated into ds oligonucleotides and can impart or tune one or more properties thereof (*e.g.*, relative to an otherwise identical ds oligonucleotide lacking the relevant technology or feature). In certain embodiments, the present disclosure documents that one or more provided technologies and/or features can usefully be incorporated into ds oligonucleotides of various sequences.

In certain embodiments, the present disclosure demonstrates that certain provided structural elements, technologies and/or features are particularly useful for ds oligonucleotides that participate in and/or direct RNAi mechanisms (*e.g.*, RNAi agents). Regardless, however, the teachings of the present disclosure are not limited to ds oligonucleotides that participate in or operate via any particular mechanism. In certain embodiments, the present disclosure pertains to any ds oligonucleotide, useful for any purpose, which operates through any mechanism, and which comprises any sequence, structure or format (or portion thereof) described herein. In certain embodiments, the present disclosure provides a ds oligonucleotide, useful for any purpose, which operates through any mechanism, and which comprises any sequence, structure or format (or portion thereof) described herein, comprising one or more of:

(1) a guide strand comprising backbone non-negatively charged internucleotidic linkage in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction;

(2) a guide strand comprising backbone non-negatively charged internucleotidic linkage in the Rp configuration between the +10 nucleotide and the immediately downstream (+11) nucleotide, i.e., in the 3' direction;

(3) a guide strand comprising backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream, i.e., in the 5' direction, (N-2) nucleotide;

(4) a guide strand comprising backbone phosphorothioate chiral centers in Rp, Sp, or alternating configurations between the 5' terminal (+1) nucleotide and the immediately downstream, i.e., in the 3' direction, (+2) nucleotide and between the +2 nucleotide and the immediately downstream (+3) nucleotide;

(5) a guide strand comprising one or more backbone phosphorothioate chiral centers upstream, i.e., in the 5' direction, relative to backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide, where the upstream backbone phosphorothioate chiral centers are in Rp or Sp configuration;

(6) a guide strand comprising one or more backbone phosphorothioate chiral centers in Rp or Sp configuration between the N-2 nucleotide and the immediately upstream (N-3) nucleotide, i.e., in the 5' direction;

(7) a guide strand comprising a 5' terminal modification, e.g. 5' phosphate modification, e.g. 5' triazole phosphate modification;

wherein the ds oligonucleotide further comprises one or more of:

(1) a guide strand where one or both of the 5' and 3' terminal dinucleotides are ***not*** linked by non-negatively charged internucleotidic linkages, i.e., the guide strand comprises one more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkages downstream, i.e., in the 3' direction, relative to the linkage between the 5'

terminal dinucleotide and/or upstream, i.e., in the 5' direction, relative to the linkage between the 3' terminal dinucleotide;

(2) a guide strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide;

(3) a guide strand where an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between the third (+3) and fourth (+4) nucleotides, relative to the 5' terminal nucleotide, of the guide strand and/or between the tenth (+10) and eleventh (+11) nucleotides, relative to the 5' terminal nucleotide;

(4) a passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs upstream, i.e., in the 5' direction, relative to the central nucleotide of the passenger strand; and

(5) a passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs downstream, i.e., in the 3' direction, relative to the central nucleotide of the passenger strand, and

wherein the ds oligonucleotide further comprises a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide or passenger strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In certain embodiments, the provided ds oligonucleotides may participate in (*e.g.*, direct) RNAi mechanisms.

In certain embodiments, the guide strand comprises backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide, and one or more of:

(1) a guide strand where one or both of the 5' and 3' terminal dinucleotides are ***not*** linked by non-negatively charged internucleotidic linkages, i.e., the guide strand comprises one more non-negatively charged internucleotidic linkages downstream, i.e., in the 3' direction, relative to the linkage between the 5' terminal dinucleotide and/or upstream, i.e., in the 5' direction, relative to the linkage between the 3' terminal dinucleotide;

(2) a guide strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide;

(3) a guide strand where an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between the third (+3) and fourth (+4) nucleotides, relative to the 5' terminal nucleotide, of the guide strand and/or between the tenth (+10) and eleventh (+11) nucleotides, relative to the 5' terminal nucleotide;

(4) a passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs upstream, i.e., in the 5' direction, relative to the central nucleotide of the passenger strand; and

(5) a passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs downstream, i.e., in the 3' direction, relative to the central nucleotide of the passenger strand, and

wherein the ds oligonucleotide further comprises a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises 0-n Rp, Sp, or stereorandom non-negatively charged internucleotidic linkages, where n is about 1 to 49,

In certain embodiments, the present disclosure demonstrates that compositions comprising ds oligonucleotides (e.g., dsRNAi oligonucleotides, also referred to as dsRNAi agents) with controlled structural elements provide unexpected properties and/or activities.

In certain embodiments, the guide strand comprises backbone phosphorothioate chiral centers in Rp, Sp, or alternating configurations between the 5' terminal (+1) nucleotide and the immediately downstream (+2) nucleotide and between the +2 nucleotide and the immediately downstream (+3) nucleotide, and one or more of:

(1) a guide strand where one or both of the 5' and 3' terminal dinucleotides are ***not*** linked by non-negatively charged internucleotidic linkages, i.e., the guide strand comprises one more non-negatively charged internucleotidic linkages downstream, i.e., in the 3' direction, relative to the linkage between the 5' terminal dinucleotide and/or upstream, i.e., in the 5' direction, relative to the linkage between the 3' terminal dinucleotide;

(2) a guide strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide;

(3) a guide strand where an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between the third (+3) and fourth (+4) nucleotides, relative to the 5' terminal nucleotide, of the guide strand and/or between the tenth (+10) and eleventh (+11) nucleotides, relative to the 5' terminal nucleotide;

(4) a passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs upstream, i.e., in the 5' direction, relative to the central nucleotide of the passenger strand; and

(5) a passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs downstream, i.e., in the 3' direction, relative to the central nucleotide of the passenger strand, and

wherein the ds oligonucleotide further comprises a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises 0-n Rp, Sp, or stereorandom non-negatively charged internucleotidic linkages, where n is about 1 to 49. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide or passenger strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In certain embodiments, the guide strand comprises one or more backbone phosphorothioate chiral centers in Rp or Sp configuration upstream of backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide, and one or more of:

(1) a guide strand where one or both of the 5' and 3' terminal dinucleotides are ***not*** linked by non-negatively charged internucleotidic linkages, i.e., the guide strand comprises one more non-negatively charged internucleotidic linkages downstream, i.e., in the 3' direction, relative to the linkage between the 5' terminal dinucleotide and/or upstream, i.e., in the 5' direction, relative to the linkage between the 3' terminal dinucleotide;

(2) a guide strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide;

(3) a guide strand where an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between the third (+3) and fourth (+4) nucleotides, relative to the 5' terminal nucleotide, of the guide strand and/or between the tenth (+10) and eleventh (+11) nucleotides, relative to the 5' terminal nucleotide;

(4) a passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs upstream, i.e., in the 5' direction, relative to the central nucleotide of the passenger strand; and

(5) Passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs downstream, i.e., in the 3' direction, relative to the central nucleotide of the passenger strand, and

wherein the ds oligonucleotide further comprises a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises 0-n Rp, Sp, or stereorandom non-negatively charged internucleotidic linkages, where n is about 1 to 49. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide or passenger strand is an Rp non-negatively

charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In certain embodiments, the guide strand comprises one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between the second (+2) and third (+3) nucleotides, relative to the 5' terminal nucleotide, of the guide strand and the internucleotidic linkage to the penultimate 3' (N-1) nucleotide, and one or more of:

(1) a guide strand where one or both of the 5' and 3' terminal dinucleotides are ***not*** linked by non-negatively charged internucleotidic linkages, i.e., the guide strand comprises one more non-negatively charged internucleotidic linkages downstream, i.e., in the 3' direction, relative to the linkage between the 5' terminal dinucleotide and/or upstream, i.e., in the 5' direction, relative to the linkage between the 3' terminal dinucleotide;

(2) a guide strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide;

(3) a guide strand where an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between the third (+3) and fourth (+4) nucleotides, relative to the 5' terminal nucleotide, of the guide strand and/or between the tenth (+10) and eleventh (+11) nucleotides, relative to the 5' terminal nucleotide;

(4) a passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs upstream, i.e., in the 5' direction, relative to the central nucleotide of the passenger strand; and

(5) Passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs downstream, i.e., in the 3' direction, relative to the central nucleotide of the passenger strand, and

wherein the ds oligonucleotide further comprises a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively

charged internucleotidic linkage, and the passenger strand comprises 0-n Rp, Sp, or stereorandom non-negatively charged internucleotidic linkages, where n is about 1 to 49. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide or passenger strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In certain embodiments, the guide strand comprises backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide, and one or more of:

(1) a guide strand where one or both of the 5' and 3' terminal dinucleotides are ***not*** linked by non-negatively charged internucleotidic linkages, i.e., the guide strand comprises one more non-negatively charged internucleotidic linkages downstream, i.e., in the 3' direction, relative to the linkage between the 5' terminal dinucleotide and/or upstream, i.e., in the 5' direction, relative to the linkage between the 3' terminal dinucleotide;

(2) a guide strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide;

(3) a guide strand where an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between the third (+3) and fourth (+4) nucleotides, relative to the 5' terminal nucleotide, of the guide strand and/or between the tenth (+10) and eleventh (+11) nucleotides, relative to the 5' terminal nucleotide;

(4) a passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs upstream, i.e., in the 5' direction, relative to the central nucleotide of the passenger strand; and

(5) Passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs downstream, i.e., in the 3' direction, relative to the central nucleotide of the passenger strand, and

wherein the ds oligonucleotide further comprises a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises one or more backbone phosphorothioate chiral centers in Rp or Sp configuration. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide or passenger strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In certain embodiments, the guide strand comprises backbone phosphorothioate chiral centers in Rp, Sp, or alternating configurations between the 5' terminal (+1) nucleotide and the immediately downstream (+2) nucleotide and between the +2 nucleotide and the immediately downstream (+3) nucleotide, and one or more of:

(1) a guide strand where one or both of the 5' and 3' terminal dinucleotides are ***not*** linked by non-negatively charged internucleotidic linkages, i.e., the guide strand comprises one more non-negatively charged internucleotidic linkages downstream, i.e., in the 3' direction, relative to the linkage between the 5' terminal dinucleotide and/or upstream, i.e., in the 5' direction, relative to the linkage between the 3' terminal dinucleotide;

(2) a guide strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide;

(3) a guide strand where an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between the third (+3) and fourth (+4) nucleotides, relative to the 5' terminal nucleotide, of the guide strand and/or between the tenth (+10) and eleventh (+11) nucleotides, relative to the 5' terminal nucleotide;

(4) a passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs upstream, i.e., in the 5' direction, relative to the central nucleotide of the passenger strand; and

(5) Passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs downstream, i.e., in the 3' direction, relative to the central nucleotide of the passenger strand, and

wherein the ds oligonucleotide further comprises a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises one or more backbone chiral centers in Rp or Sp configuration. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide or passenger strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In certain embodiments, the guide strand comprises one or more backbone phosphorothioate chiral centers in Rp or Sp configuration upstream of backbone chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide, and one or more of:

(1) a guide strand where one or both of the 5' and 3' terminal dinucleotides are ***not*** linked by non-negatively charged internucleotidic linkages, i.e., the guide strand comprises one more non-negatively charged internucleotidic linkages downstream, i.e., in the 3' direction, relative to the linkage between the 5' terminal dinucleotide and/or upstream, i.e., in the 5' direction, relative to the linkage between the 3' terminal dinucleotide;

(2) a guide strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide;

(3) a guide strand where an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between the third (+3) and fourth (+4) nucleotides, relative to the 5' terminal nucleotide, of the guide strand and/or between the tenth (+10) and eleventh (+11) nucleotides, relative to the 5' terminal nucleotide;

(4) a passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs upstream, i.e., in the 5' direction, relative to the central nucleotide of the passenger strand; and

(5) Passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs downstream, i.e., in the 3' direction, relative to the central nucleotide of the passenger strand, and

wherein the ds oligonucleotide further comprises a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises one or more backbone chiral centers in Rp or Sp configuration. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide or passenger strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In certain embodiments, the guide strand comprises one or more backbone phosphorothioate chiral centers in Rp or Sp configuration between the 5' terminal (+1) nucleotide and the immediately downstream (+2) nucleotide and between the (+2) nucleotide and the immediately downstream (+3) nucleotide, and one or more of:

(1) a guide strand where one or both of the 5' and 3' terminal dinucleotides are ***not*** linked by non-negatively charged internucleotidic linkages, i.e., the guide strand comprises one more non-negatively charged internucleotidic linkages downstream, i.e., in the 3' direction, relative to the linkage between the 5' terminal dinucleotide and/or upstream, i.e., in the 5' direction, relative to the linkage between the 3' terminal dinucleotide;

(2) a guide strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the

second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide;

(3) a guide strand where an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between the third (+3) and fourth (+4) nucleotides, relative to the 5' terminal nucleotide, of the guide strand and/or between the tenth (+10) and eleventh (+11) nucleotides, relative to the 5' terminal nucleotide;

(4) a passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs upstream, i.e., in the 5' direction, relative to the central nucleotide of the passenger strand; and

(5) Passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs downstream, i.e., in the 3' direction, relative to the central nucleotide of the passenger strand, and

wherein the ds oligonucleotide further comprises a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises one or more backbone chiral centers in Rp or Sp configuration. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide or passenger strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In certain embodiments, the guide strand comprises one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide, a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises one or more backbone chiral centers in Rp or Sp configuration. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide strand is an Rp non-

negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In certain embodiments, the guide strand comprises backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide, a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises 0-n Rp, Sp, or stereorandom non-negatively charged internucleotidic linkages, where n is about 1 to 49 and one or more backbone chiral centers in Rp or Sp configuration. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In certain embodiments, the guide strand comprises backbone phosphorothioate chiral centers in Rp, Sp, or alternating configurations between the 5' terminal (+1) nucleotide and the immediately downstream (+2) nucleotide and between the +2 nucleotide and the immediately downstream (+3) nucleotide, a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises 0-n Rp, Sp, or stereorandom non-negatively charged internucleotidic linkages, where n is about 1 to 49 and one or more backbone chiral centers in Rp or Sp configuration. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In certain embodiments, the guide strand comprises one or more backbone

phosphorothioate chiral centers in Rp or Sp configuration upstream of backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide, a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises 0-n Rp, Sp, or stereorandom non-negatively charged internucleotidic linkages, where n is about 1 to 49 and one or more backbone chiral centers in Rp or Sp configuration. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In certain embodiments, the guide strand comprises one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide, a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises 0-n Rp, Sp, or stereorandom non-negatively charged internucleotidic linkages, where n is about 1 to 49 and one or more backbone chiral centers in Rp or Sp configuration. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In certain embodiments, provided ds oligonucleotides may participate in exon skipping mechanisms. In certain embodiments, provided ds oligonucleotides may be aptamers. In certain embodiments, provided ds oligonucleotides may bind to and inhibit the function of a protein, small molecule, nucleic acid or cell. In certain embodiments, provided ds oligonucleotides may participate in forming a triplex helix with a double-stranded nucleic acid

in the cell. In certain embodiments, provided ds oligonucleotides may bind to genomic (*e.g.*, chromosomal) nucleic acid. In certain embodiments, provided ds oligonucleotides may bind to genomic (*e.g.*, chromosomal) nucleic acid, thus preventing or decreasing expression of the nucleic acid (*e.g.*, by preventing or decreasing transcription, transcriptional enhancement, modification, etc.). In certain embodiments, provided ds oligonucleotides may bind to DNA quadruplexes. In certain embodiments, provided ds oligonucleotides may be immunomodulatory. In certain embodiments, provided ds oligonucleotides may be immunostimulatory. In certain embodiments, provided oligonucleotides may be immunostimulatory and may comprise a CpG sequence. In certain embodiments, provided ds oligonucleotides may be immunostimulatory and may comprise a CpG sequence and may be useful as an adjuvant. In certain embodiments, provided ds oligonucleotides may be immunostimulatory and may comprise a CpG sequence and may be useful as an adjuvant in treating a disease (*e.g.*, an infectious disease or cancer). In certain embodiments, provided ds oligonucleotides may be therapeutic. In certain embodiments, provided ds oligonucleotides may be non-therapeutic. In certain embodiments, provided ds oligonucleotides may be therapeutic or non-therapeutic. In certain embodiments, provided ds oligonucleotides are useful in therapeutic, diagnostic, research and/or nanomaterials applications. In certain embodiments, provided ds oligonucleotides may be useful for experimental purposes. In certain embodiments, provided ds oligonucleotides may be useful for experimental purposes, *e.g.*, as a probe, in a microarray, etc. In certain embodiments, provided ds oligonucleotides may participate in more than one biological mechanism; in certain such embodiments, for example, provided ds oligonucleotides may participate in both RNAi and RNase H mechanisms.

In certain embodiments, provided ds oligonucleotides are directed to an INHBE target (*e.g.*, an INHBE target sequence, an INHBE target RNA, an INHBE target mRNA, an INHBE target pre-mRNA, an INHBE target gene, etc.). An INHBE target gene is a gene with respect to which expression and/or activity of one or more INHBE gene products (*e.g.*, INHBE RNA and/or protein products) are intended to be altered. In certain embodiments, an INHBE target gene is intended to be inhibited. Thus, when a ds oligonucleotide as described herein acts on an INHBE target gene, presence and/or activity of one or more INHBE gene products are altered when the ds oligonucleotide is present as compared with when it is absent.

In certain embodiments, an INHBE target is a specific INHBE allele with respect to which expression and/or activity of one or more products (*e.g.*, INHBE RNA and/or protein products) are intended to be altered. In certain embodiments, an INHBE target allele is one

whose presence and/or expression is associated (*e.g.*, correlated) with presence, incidence, and/or severity, of one or more INHBE associated diseases and/or conditions. Alternatively or additionally, in certain embodiments, an INHBE target allele is one for which alteration of level and/or activity of one or more INHBE gene products correlates with improvement (*e.g.*, delay of onset, reduction of severity, responsiveness to other therapy, etc.) in one or more aspects of an INHBE associated disease and/or condition.

In certain embodiments, e.g., where presence and/or activity of a particular INHBE allele (an INHBE disease-associated allele) is associated (*e.g.*, correlated) with presence, incidence and/or severity of one or more disorders, diseases and/or conditions, a different INHBE allele exists and is not so associated, or is associated to a lesser extent (*e.g.*, shows less significant, or statistically insignificant correlation), ds oligonucleotides and methods thereof as described herein may preferentially or specifically target the associated allele relative to the one or more less-associated/unassociated allele(s), thus mediating allele-specific suppression.

In certain embodiments, an INHBE target sequence is an INHBE sequence to which an oligonucleotide as described herein binds. In certain embodiments, an INHBE target sequence is identical to, or is an exact complement of, an INHBE sequence of a provided oligonucleotide, or of consecutive residues therein (*e.g.*, a provided oligonucleotide includes an INHBE target-binding sequence that is identical to, or an exact complement of, an INHBE target sequence). In certain embodiments, an INHBE target-binding sequence is an exact complement of an INHBE target sequence of an INHBE transcript (*e.g.*, pre-mRNA, mRNA, *etc.*). An INHBE target-binding sequence/target sequence can be of various lengths to provided oligonucleotides with desired activities and/or properties. In certain embodiments, an INHBE target binding sequence/target sequence comprises 5-50 (*e.g.*, 10-40, 15-30, 15-25, 16-25, 17-25, 18-25, 19-25, 20-25, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or more) bases. In certain embodiments, a small number of differences/mismatches is tolerated between (a relevant portion of) an oligonucleotide and its target sequence, including but not limited to the 5' and/or 3'-end regions of the INHBE target and/or oligonucleotide sequence. In certain embodiments, an INHBE target sequence is present within an INHBE target gene. In certain embodiments, an INHBE target sequence is present within an INHBE transcript (*e.g.*, an mRNA and/or a pre-mRNA) produced from an INHBE target gene.

In certain embodiments, an INHBE target sequence includes one or more allelic sites (*i.e.*, positions within an INHBE target gene at which allelic variation occurs). In certain embodiments, an allelic site is a mutation. In certain embodiments, an allelic site is a SNP. In some such embodiments, a provided oligonucleotide binds to one allele preferentially or

specifically relative to one or more other alleles. In certain embodiments, a provided oligonucleotide binds preferentially to a disease-associated allele. For example, in certain embodiments, an oligonucleotide (or a target-binding sequence portion thereof) provided herein has a sequence that is, fully or at least in part, identical to, or an exact complement of a particular allelic version of an INHBE target sequence.

In certain embodiments, an oligonucleotide (or a target-binding sequence portion thereof) provided herein has a sequence that is identical to, or an exact complement of an INHBE target sequence comprising an allelic site, or an allelic site, of a disease-associated allele. In certain embodiments, an oligonucleotide provided herein has an INHBE target binding sequence that is an exact complement of an INHBE target sequence comprising an allelic site of an INHBE transcript of an allele (in certain embodiments, a disease-associated allele), wherein the allelic site is a mutation. In certain embodiments, an oligonucleotide provided herein has an INHBE target binding sequence that is an exact complement of an INHBE target sequence comprising an allelic site of an INHBE transcript of an allele (in certain embodiments, a disease-associated allele), wherein the allelic site is a SNP. In certain embodiments, a sequence is any sequence disclosed herein.

Unless otherwise noted, all sequences (including, but not limited to base sequences and patterns of chemistry, modification, and/or stereochemistry) are presented in 5' to 3' order, with the 5' terminal nucleotide identified as the "+1" position and the 3' terminal nucleotide identified either by the number of nucleotides of the full sequence or by "N", with the penultimate nucleotide identified, e.g., as "N-1", and so on.

In certain embodiments, the present disclosure provides compositions and methods related to an oligonucleotide which is specific to an INHBE target and which has any format, structural element or base sequence of any oligonucleotide disclosed herein.

In certain embodiments, the present disclosure provides compositions and methods related to an oligonucleotide which is specific to an INHBE target and which has or comprises the base sequence of any oligonucleotide disclosed herein, or a region of at least 15 contiguous nucleotides of the base sequence of any oligonucleotide disclosed herein, wherein the first nucleotide of the base sequence or the first nucleotide of the at least 15 contiguous nucleotides can be optionally replaced by T or DNA T.

In certain embodiments, the present disclosure provides compositions and methods for RNA interference directed by a RNAi agent (also referred to as a RNAi oligonucleotides). In certain embodiments, oligonucleotides of such compositions can have a format, structural element or base sequence of an oligonucleotide disclosed herein.

In certain embodiments, the present disclosure provides compositions and methods for RNase H-mediated knockdown of an INHBE target gene RNA directed by an oligonucleotide (*e.g.*, an antisense oligonucleotide).

Provided oligonucleotides and oligonucleotide compositions can have any format, structural element or base sequence of any oligonucleotide disclosed herein. In certain embodiments, a structural element is a 5'-end structure, 5'-end region, 5'-nucleotide, seed region, post-seed region, 3'-end region, 3'-terminal dinucleotide, 3'-end cap, or any portion of any of these structures, GC content, long GC stretch, and/or any modification, chemistry, stereochemistry, pattern of modification, chemistry or stereochemistry, or a chemical moiety (*e.g.*, including but not limited to, a targeting moiety, a lipid moiety, a GalNAc moiety, a carbohydrate moiety, etc.), any component, or any combination of any of the above.

In certain embodiments, the present disclosure provides compositions and methods of use of an oligonucleotide.

In certain embodiments, the present disclosure provides compositions and methods of use of an oligonucleotide which can direct both RNA interference and RNase H-mediated knockdown of an INHBE target gene RNA. In certain embodiments, oligonucleotides of such compositions can have a format, structural element or base sequence of an oligonucleotide disclosed herein.

In certain embodiments, an oligonucleotide directing a particular event or activity participates in the particular event or activity, e.g., a decrease in the expression, level or activity of a target gene or a gene product thereof. In certain embodiments, an oligonucleotide is deemed to "direct" a particular event or activity when presence of the oligonucleotide in a system in which the event or activity can occur correlates with increased detectable incidence, frequency, intensity and/or level of the event or activity.

In certain embodiments, a provided oligonucleotide comprises any one or more structural elements of an oligonucleotide as described herein, *e.g.*, a base sequence (or a portion thereof of at least 15 contiguous bases); a pattern of internucleotidic linkages (or a portion thereof of at least 5 contiguous internucleotidic linkage); a pattern of stereochemistry of internucleotidic linkages (or a portion thereof of at least 5 contiguous internucleotidic linkages); a 5'-end structure; a 5'-end region; a first region; a second region; and a 3'-end region (which can be a 3'-terminal dinucleotide and/or a 3'-end cap); and an optional additional chemical moiety; and, in certain embodiments, at least one structural element comprises a chirally controlled chiral center. In certain embodiments, a 3'-terminal dinucleotide can comprise two total nucleotides. In certain embodiments, an oligonucleotide further comprises

a chemical moiety selected from, as non-limiting examples, a targeting moiety, a carbohydrate moiety, a GalNAc moiety, a lipid moiety, and any other chemical moiety described herein or known in the art. In certain embodiments, a moiety that binds APGR is a moiety of GalNAc, or a variant, derivative or modified version thereof, as described herein and/or known in the art. In certain embodiments, an oligonucleotide is a RNAi agent. In certain embodiments, a first region is a seed region. In certain embodiments, a second region is a post-seed region.

In certain embodiments, a provided oligonucleotide comprises any one or more structural elements of a RNAi agent as described herein, *e.g.*, a 5'-end structure; a 5'-end region; a seed region; a post-seed region (the region between the seed region and the 3'-end region); and a 3'-end region (which can be a 3'-terminal dinucleotide and/or a 3'-end cap); and an optional additional chemical moiety; and, in certain embodiments, at least one structural element comprises a chirally controlled chiral center. In certain embodiments, a 3'-terminal dinucleotide can comprise two total nucleotides. In certain embodiments, an oligonucleotide further comprises a chemical moiety selected from, as non-limiting examples, a targeting moiety, a carbohydrate moiety, a GalNAc moiety, and a lipid moiety. In certain embodiments, a moiety that binds APGR is any GalNAc, or variant, derivative or modification thereof, as described herein or known in the art.

In certain embodiments, a provided oligonucleotide comprises any one or more structural elements of an oligonucleotide as described herein, *e.g.*, a 5'-end structure, a 5'-end region, a first region, a second region, a 3'-end region, and an optional additional chemical moiety, wherein at least one structural element comprises a chirally controlled chiral center. In certain embodiments, the oligonucleotide comprises a span of at least 5 total nucleotides without 2'-modifications. In certain embodiments, the oligonucleotide further comprises an additional chemical moiety selected from, as non-limiting examples, a targeting moiety, a carbohydrate moiety, a GalNAc moiety, and a lipid moiety. In certain embodiments, a provided oligonucleotide is capable of directing RNA interference. In certain embodiments, a provided oligonucleotide is capable of directing RNase H-mediated knockdown. In certain embodiments, a provided oligonucleotide is capable of directing both RNA interference and RNase H-mediated knockdown. In certain embodiments, a first region is a seed region. In certain embodiments, a second region is a post-seed region.

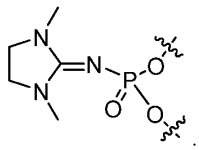
In certain embodiments, a provided oligonucleotide comprises any one or more structural elements of a RNAi agent, *e.g.*, a 5'-end structure, a 5'-end region, a seed region, a post-seed region, and a 3'-end region and an optional additional chemical moiety, wherein at least one structural element comprises a chirally controlled chiral center; and, in certain

embodiments, the oligonucleotide is also capable of directing RNase H-mediated knockdown of a target gene RNA. In certain embodiments, the oligonucleotide comprises a span of at least 5 total 2'-deoxy nucleotides. In certain embodiments, the oligonucleotide further comprises a chemical moiety selected from, as non-limiting examples, a targeting moiety, a carbohydrate moiety, a GalNAc moiety, and a lipid moiety, and any other additional chemical moiety described herein.

In certain embodiments, the present disclosure demonstrates that oligonucleotide properties can be modulated through chemical modifications. In certain embodiments, the present disclosure provides an oligonucleotide composition comprising a first plurality of oligonucleotides which have a common base sequence and comprise one or more internucleotidic linkage, sugar, and/or base modifications. In certain embodiments, the present disclosure provides an oligonucleotide composition capable of directing RNA interference and comprising a first plurality of oligonucleotides which have a common base sequence and comprise one or more internucleotidic linkage, and/or one or more sugar, and/or one or more base modifications. In certain embodiments, an oligonucleotide or oligonucleotide composition is also capable of directing RNase H-mediated knockdown of an INHBE target gene RNA. In certain embodiments, the present disclosure demonstrates that oligonucleotide properties, *e.g.*, activities, toxicities, *etc.*, can be modulated through chemical modifications of sugars, nucleobases, and/or internucleotidic linkages. In certain embodiments, the present disclosure provides an oligonucleotide composition comprising a plurality of oligonucleotides which have a common base sequence, and comprise one or more modified internucleotidic linkages (or "non-natural internucleotidic linkages", linkages that can be utilized in place of a natural phosphate internucleotidic linkage (−OP(O)(OH)O−, which may exist as a salt form (−OP(O)(O^-)O−) at a physiological pH) found in natural DNA and RNA), one or more modified sugar moieties, and/or one or more natural phosphate linkages. In certain embodiments, provided oligonucleotides may comprise two or more types of modified internucleotidic linkages. In certain embodiments, a provided oligonucleotide comprises a non-negatively charged internucleotidic linkage. In certain embodiments, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage. In certain embodiments, a neutral internucleotidic linkage comprises a cyclic guanidine moiety. Such moieties an optionally substituted. In certain embodiments, a provided oligonucleotide comprises a neutral internucleotidic linkage and another internucleotidic linkage which is not a neutral backbone. In certain embodiments, a provided oligonucleotide comprises a neutral internucleotidic linkage and a phosphorothioate internucleotidic linkage. In certain embodiments, provided

oligonucleotide compositions comprising a plurality of oligonucleotides are chirally controlled and level of the plurality of oligonucleotides in the composition is controlled or pre-determined, and oligonucleotides of the plurality share a common stereochemistry configuration at one or more chiral internucleotidic linkages. For example, in certain embodiments, oligonucleotides of a plurality share a common stereochemistry configuration at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50 or more chiral internucleotidic linkages, each of which is independently *R*p or *S*p; in certain embodiments, oligonucleotides of a plurality share a common stereochemistry configuration at each chiral internucleotidic linkages. In certain embodiments, a chiral internucleotidic linkage where a controlled level of oligonucleotides of a composition share a common stereochemistry configuration (independently in the *R*p or *S*p configuration) is referred to as a chirally controlled internucleotidic linkage. In certain embodiments, a modified internucleotidic linkage is a non-negatively charged (neutral or cationic) internucleotidic linkage in that at a pH, (e.g., human physiological pH (~ 7.4), pH of a delivery site (e.g., an organelle, cell, tissue, organ, organism, etc.), etc.), it largely (*e.g.*, at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, etc.; in certain embodiments, at least 30%; in certain embodiments, at least 40%; in certain embodiments, at least 50%; in certain embodiments, at least 60%; in certain embodiments, at least 70%; in certain embodiments, at least 80%; in certain embodiments, at least 90%; in certain embodiments, at least 99%; etc.;) exists as a neutral or cationic form (as compared to an anionic form (e.g., $-O-P(O)(O^-)-O-$ (the anionic form of natural phosphate linkage), $-O-P(O)(S^-)-O-$ (the anionic form of phosphorothioate linkage), etc.)), respectively. In certain embodiments, a modified internucleotidic linkage is a neutral internucleotidic linkage in that at a pH, it largely exists as a neutral form. In certain embodiments, a modified internucleotidic linkage is a cationic internucleotidic linkage in that at a pH, it largely exists as a cationic form. In certain embodiments, a pH is human physiological pH (~ 7.4). In certain embodiments, a modified internucleotidic linkage is a neutral internucleotidic linkage in that at pH 7.4 in a water solution, at least 90% of the internucleotidic linkage exists as its neutral form. In certain embodiments, a modified internucleotidic linkage is a neutral internucleotidic linkage in that in a water solution of the oligonucleotide, at least 50%, 60%, 70%, 80%, 90%, 95%, or 99% of the internucleotidic linkage exists in its neutral form. In certain embodiments, the percentage is at least 90%. In certain embodiments, the percentage is at least 95%. In certain embodiments, the percentage is at least 99%. In certain embodiments, a non-negatively charged internucleotidic linkage, e.g., a neutral internucleotidic linkage, when in its neutral form has no moiety with a pKa that is less than 8, 9, 10, 11. 12, 13, or 14. In certain

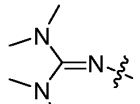
embodiments, pKa of an internucleotidic linkage in the present disclosure can be represented by pKa of CH_3–the internucleotidic linkage–CH_3 (i.e., replacing the two nucleoside units connected by the internucleotidic linkage with two $-CH_3$ groups). Without wishing to be bound by any particular theory, in at least some cases, a neutral internucleotidic linkage in an oligonucleotide can provide improved properties and/or activities, e.g., improved delivery, improved resistance to exonucleases and endonucleases, improved cellular uptake, improved endosomal escape and/or improved nuclear uptake, etc., compared to a comparable nucleic acid which does not comprises a neutral internucleotidic linkage.

In certain embodiments, a non-negatively charged internucleotidic linkage has the structure of e.g., of formula **I-n-1**, **I-n-2**, **I-n-3**, **II**, **II-a-1**, **II-a-2, II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, as described in US 9394333, US 9744183, US 9605019, US 9598458, US 9982257, US 10160969, US 10479995, US 2020/0056173, US 2018/0216107, US 2019/0127733, US 10450568, US 2019/0077817, US 2019/0249173, US 2019/0375774, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, and/or WO 2019/032612 etc. In certain embodiments, a non-negatively charged internucleotidic linkage comprises a cyclic guanidine moiety. In certain embodiments, a modified internucleotidic linkage comprising a cyclic guanidine moiety has the structure of:  . In certain embodiments, a neutral internucleotidic linkage comprising a cyclic guanidine moiety is chirally controlled. In certain embodiments, the present disclosure pertains to a composition comprising an oligonucleotide comprising at least one neutral internucleotidic linkage and at least one phosphorothioate internucleotidic linkage.

In certain embodiments, the present disclosure pertains to a composition comprising an oligonucleotide comprising at least one neutral internucleotidic linkage and at least one phosphorothioate internucleotidic linkage, wherein the phosphorothioate internucleotidic linkage is a chirally controlled internucleotidic linkage in the Sp configuration.

In certain embodiments, the present disclosure pertains to a composition comprising an oligonucleotide comprising at least one neutral internucleotidic linkage and at least one phosphorothioate internucleotidic linkage, wherein the phosphorothioate is a chirally controlled internucleotidic linkage in the Rp configuration.

In certain embodiments, the present disclosure pertains to a composition comprising an

oligonucleotide comprising at least one neutral internucleotidic linkage of a neutral internucleotidic linkage comprising a Tmg group (), and at least one phosphorothioate.

In certain embodiments, each internucleotidic linkage in an oligonucleotide is independently selected from a natural phosphate linkage, a phosphorothioate linkage, and a non-negatively charged internucleotidic linkage (e.g., n001, n003, n004, n006, n008, n009, n013, n020, n021, n025, n026, n029, n031, n037, n046, n047, n048, n054, or n055). In some embodiments, each internucleotidic linkage in an oligonucleotide is independently selected from a natural phosphate linkage, a phosphorothioate linkage, and a neutral internucleotidic linkage (e.g., n001, n003, n004, n006, n008, n009, n013 n020, n021, n025, n026, n029, n031, n037, n046, n047, n048, n054, or n055).

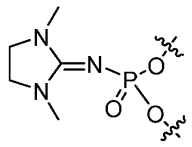
In certain embodiments, the present disclosure pertains to a composition comprising an oligonucleotide comprising at least one neutral internucleotidic linkage of a neutral internucleotidic linkage comprising a Tmg group, and at least one phosphorothioate, wherein the phosphorothioate is a chirally controlled internucleotidic linkage in the Sp configuration.

In certain embodiments, the present disclosure pertains to a composition comprising an oligonucleotide comprising at least one neutral internucleotidic linkage selected from a neutral internucleotidic linkage of a neutral internucleotidic linkage comprising a Tmg group, and at least one phosphorothioate, wherein the phosphorothioate is a chirally controlled internucleotidic linkage in the Rp configuration.

Various types of internucleotidic linkages differ in properties. Without wishing to be bound by any theory, the present disclosure notes that a natural phosphate linkage (phosphodiester internucleotidic linkage) is anionic and may be unstable when used by itself without other chemical modifications in vivo; a phosphorothioate internucleotidic linkage is anionic, generally more stable in vivo than a natural phosphate linkage, and generally more hydrophobic; a neutral internucleotidic linkage such as one exemplified in the present disclosure comprising a cyclic guanidine moiety is neutral at physiological pH, can be more stable in vivo than a natural phosphate linkage, and more hydrophobic.

In certain embodiments, a chirally controlled neutral internucleotidic linkage sis neutral at physiological pH, chirally controlled, stable in vivo, hydrophobic, and may increase endosomal escape.

In certain embodiments, provided oligonucleotides comprise one or more regions, e.g.,

a block, wing, core, 5'-end, 3'-end, middle, seed, post-seed region, etc. In certain embodiments, a region (e.g., a block, wing, core, 5'-end, 3'-end, middle region, etc.) comprises a non-negatively charged internucleotidic linkage, e.g., of formula **I-n-1**, **I-n-2**, **I-n-3**, **II**, **II-a-1**, **II-a-2, II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc. as described in US 9394333, US 9744183, US 9605019, US 9598458, US 9982257, US 10160969, US 10479995, US 2020/0056173, US 2018/0216107, US 2019/0127733, US 10450568, US 2019/0077817, US 2019/0249173, US 2019/0375774, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, and/or WO 2019/032612. In certain embodiments, a region comprises a neutral internucleotidic linkage. In certain embodiments, a region comprises an internucleotidic linkage which comprises a cyclic guanidine. In certain embodiments, a region comprises an internucleotidic linkage which comprises a cyclic guanidine moiety. In certain embodiments, a region comprises an internucleotidic linkage having the structure of  . In certain embodiments, such internucleotidic linkages are chirally controlled.

In certain embodiments, a nucleotide is a natural nucleotide. In certain embodiments, a nucleotide is a modified nucleotide. In certain embodiments, a nucleotide is a nucleotide analog. In certain embodiments, a base is a modified base. In certain embodiments, a base is protected nucleobase, such as a protected nucleobase used in oligonucleotide synthesis. In certain embodiments, a base is a base analog. In certain embodiments, a sugar is a modified sugar. In certain embodiments, a sugar is a sugar analog. In certain embodiments, an internucleotidic linkage is a modified internucleotidic linkage. In certain embodiments, a nucleotide comprises a base, a sugar, and an internucleotidic linkage, wherein each of the base, the sugar, and the internucleotidic linkage is independently and optionally naturally-occurring or non-naturally occurring. In certain embodiments, a nucleoside comprises a base and a sugar, wherein each of the base and the sugar is independently and optionally naturally-occurring or non-naturally occurring. Non-limiting examples of nucleotides include DNA (2'-deoxy) and RNA (2'-OH) nucleotides; and those which comprise one or more modifications at the base, sugar and/or internucleotidic linkage. Non-limiting examples of sugars include ribose and deoxyribose; and ribose and deoxyribose with 2'-modifications, including but not limited to 2'-F, LNA, 2'-OMe, and 2'-MOE modifications. In certain embodiments, an internucleotidic

linkage is a moiety which does not a comprise a phosphorus but serves to link two natural or non-natural sugars.

In certain embodiments, a composition comprises a multimer of two or more of any: oligonucleotides of a first plurality and/or oligonucleotides of a second plurality, wherein the oligonucleotides of the first and second plurality can independently direct knockdown of the same or different targets independently via RNA interference and/or RNase H-mediated knockdown.

In certain embodiments, the present disclosure provides an oligonucleotide composition comprising a first plurality of oligonucleotides which share:

1) a common base sequence;

2) a common pattern of backbone linkages;

3) common stereochemistry independently at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, or 50 chiral internucleotidic linkages ("chirally controlled internucleotidic linkages"); which composition is chirally controlled in that level of the first plurality of oligonucleotides in the composition is predetermined.

In certain embodiments, an oligonucleotide composition comprising a plurality of oligonucleotides (e.g., a first plurality of oligonucleotides) is chirally controlled in that oligonucleotides of the plurality share a common stereochemistry independently at one or more chiral internucleotidic linkages. In certain embodiments, oligonucleotides of the plurality share a common stereochemistry configuration at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50 or more chiral internucleotidic linkages, each of which is independently *R*p or *S*p In certain embodiments, oligonucleotides of the plurality share a common stereochemistry configuration at each chiral internucleotidic linkages. In certain embodiments, a chiral internucleotidic linkage where a predetermined level of oligonucleotides of a composition share a common stereochemistry configuration (independently *R*p or *S*p) is referred to as a chirally controlled internucleotidic linkage.

In certain embodiments, a predetermined level of oligonucleotides of a provided composition, *e.g.*, a first plurality of oligonucleotides of certain example compositions, comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50 or more chirally controlled internucleotidic linkages.

In certain embodiments, at least 5 internucleotidic linkages are chirally controlled; in certain embodiments, at least 10 internucleotidic linkages are chirally controlled; in certain

embodiments, at least 15 internucleotidic linkages are chirally controlled; in certain embodiments, each chiral internucleotidic linkage is chirally controlled.

In certain embodiments, 1%-100% of chiral internucleotidic linkages are chirally controlled. In certain embodiments, at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of chiral internucleotidic linkages are chirally controlled.

In certain embodiments, the present disclosure provides an oligonucleotide composition comprising a first plurality of oligonucleotides which share:

1) a common base sequence;

2) a common pattern of backbone linkages; and

3) a common pattern of backbone chiral centers, which composition is a substantially pure preparation of oligonucleotide in that a predetermined level of the oligonucleotides in the composition have the common base sequence and length, the common pattern of backbone linkages, and the common pattern of backbone chiral centers. In certain embodiments, the common pattern of backbone chiral centers comprises at least one internucleotidic linkage comprising a chirally controlled chiral center. In certain embodiments, a predetermined level of oligonucleotides is at least 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of all oligonucleotides in a provided composition. In certain embodiments, a predetermined level of oligonucleotides is at least 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of all oligonucleotides in a provided composition that are of or comprise a common base sequence. In certain embodiments, all oligonucleotides in a provided composition that are of or comprise a common base sequence are at least 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of all oligonucleotides in the composition. In certain embodiments, a predetermined level of oligonucleotides is at least 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of all oligonucleotides in a provided composition that are of or comprise a common base sequence, base modification, sugar modification and/or modified internucleotidic linkage. In certain embodiments, all oligonucleotides in a provided composition that are of or comprise a common base sequence, base modification, sugar modification and/or modified internucleotidic linkage are at least 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%,

85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of all oligonucleotides in the composition. In certain embodiments, a predetermined level of oligonucleotides is at least 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of all oligonucleotides in a provided composition that are of or comprise a common base sequence, pattern of base modification, pattern of sugar modification, and/or pattern of modified internucleotidic linkage. In certain embodiments, all oligonucleotides in a provided composition that are of or comprise a common base sequence, pattern of base modification, pattern of sugar modification, and/or pattern of modified internucleotidic linkage are at least 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of all oligonucleotides in the composition. In certain embodiments, a predetermined level of oligonucleotides is at least 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of all oligonucleotides in a provided composition that share a common base sequence, a common pattern of base modification, a common pattern of sugar modification, and/or a common pattern of modified internucleotidic linkages. In certain embodiments, all oligonucleotides in a provided composition that share a common base sequence, a common pattern of base modification, a common pattern of sugar modification, and/or a common pattern of modified internucleotidic linkages are at least 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of all oligonucleotides in the composition. In certain embodiments, a predetermined level is 1-100%. In certain embodiments, a predetermined level is at least 1%. In certain embodiments, a predetermined level is at least 5%. In certain embodiments, a predetermined level is at least 10%. In certain embodiments, a predetermined level is at least 20%. In certain embodiments, a predetermined level is at least 30%. In certain embodiments, a predetermined level is at least 40%. In certain embodiments, a predetermined level is at least 50%. In certain embodiments, a predetermined level is at least 60%. In certain embodiments, a predetermined level is at least 10%. In certain embodiments, a predetermined level is at least 70%. In certain embodiments, a predetermined level is at least 80%. In certain embodiments, a predetermined level is at least 90%. In certain embodiments, a predetermined level is at least 5*(1/2g), wherein g is the number of chirally controlled internucleotidic linkages. In certain embodiments, a predetermined level is at least 10*(1/2g), wherein g is the number of chirally controlled internucleotidic linkages. In certain embodiments, a predetermined level is at least 100*(1/2g), wherein g is the number of chirally

controlled internucleotidic linkages. In certain embodiments, a predetermined level is at least (0.80)g, wherein g is the number of chirally controlled internucleotidic linkages. In certain embodiments, a predetermined level is at least (0.80)g, wherein g is the number of chirally controlled internucleotidic linkages. In certain embodiments, a predetermined level is at least (0.80)g, wherein g is the number of chirally controlled internucleotidic linkages. In certain embodiments, a predetermined level is at least (0.85)g, wherein g is the number of chirally controlled internucleotidic linkages. In certain embodiments, a predetermined level is at least (0.90)g, wherein g is the number of chirally controlled internucleotidic linkages. In certain embodiments, a predetermined level is at least (0.95)g, wherein g is the number of chirally controlled internucleotidic linkages. In certain embodiments, a predetermined level is at least (0.96)g, wherein g is the number of chirally controlled internucleotidic linkages. In certain embodiments, a predetermined level is at least (0.97)g, wherein g is the number of chirally controlled internucleotidic linkages. In certain embodiments, a predetermined level is at least (0.98)g, wherein g is the number of chirally controlled internucleotidic linkages. In certain embodiments, a predetermined level is at least (0.99)g, wherein g is the number of chirally controlled internucleotidic linkages. In certain embodiments, to determine level of oligonucleotides having g chirally controlled internucleotidic linkages in a composition, product of diastereopurity of each of the g chirally controlled internucleotidic linkages: (diastereopurity of chirally controlled internucleotidic linkage 1) * (diastereopurity of chirally controlled internucleotidic linkage 2) * … * (diastereopurity of chirally controlled internucleotidic linkage g) is utilized as the level, wherein diastereopurity of each chirally controlled internucleotidic linkage is independently represented by diastereopurity of a dimer comprising the same internucleotidic linkage and nucleosides flanking the internucleotidic linkage and prepared under comparable methods as the oligonucleotides (e.g., comparable or preferably identical oligonucleotide preparation cycles, including comparable or preferably identical reagents and reaction conditions). In certain embodiments, levels of oligonucleotides and/or diastereopurity can be determined by analytical methods, e.g., chromatographic, spectrometric, spectroscopic methods or any combinations thereof. Among other things, the present disclosure encompasses the recognition that stereorandom oligonucleotide preparations contain a plurality of distinct chemical entities that differ from one another, e.g., in the stereochemical structure (or stereochemistry) of individual backbone chiral centers within the oligonucleotide chain. Without control of stereochemistry of backbone chiral centers, stereorandom oligonucleotide preparations provide uncontrolled compositions comprising undetermined levels of oligonucleotide stereoisomers. Even though these stereoisomers may

have the same base sequence and/or chemical modifications, they are different chemical entities at least due to their different backbone stereochemistry, and they can have, as demonstrated herein, different properties, e.g., sensitivity to nucleases, activities, distribution, etc. In certain embodiments, a particular stereoisomer may be defined, for example, by its base sequence, its length, its pattern of backbone linkages, and its pattern of backbone chiral centers. In certain embodiments, the present disclosure demonstrates that improvements in properties and activities achieved through control of stereochemistry within an oligonucleotide can be comparable to, or even better than those achieved through use of chemical modification.

Among other things, the present disclosure encompasses the recognition that stereorandom oligonucleotide preparations contain a plurality of distinct chemical entities that differ from one another, *e.g.*, in the stereochemical structure (or stereochemistry) of individual backbone chiral centers within the oligonucleotide chain. Without control of stereochemistry of backbone chiral centers, stereorandom oligonucleotide preparations provide uncontrolled compositions comprising undetermined levels of oligonucleotide stereoisomers. Even though these stereoisomers may have the same base sequence and/or chemical modifications, they are different chemical entities at least due to their different backbone stereochemistry, and they can have, as demonstrated herein, different properties, *e.g.*, sensitivity to nucleases, activities, distribution, etc. In certain embodiments, a particular stereoisomer may be defined, for example, by its base sequence, its length, its pattern of backbone linkages, and its pattern of backbone chiral centers. In certain embodiments, the present disclosure demonstrates that improvements in properties and activities achieved through control of stereochemistry within an oligonucleotide can be comparable to, or even better than those achieved through use of chemical modification

In some embodiments, a ds oligonucleotide targeting INHBE or ds oligonucleotide targeting INHBE composition is useful for prevention or treatment of a INHBE-associated condition, disorder, or disease, in a subject in need thereof. In some embodiments, the present disclosure provides a method for preventing or treating a INHBE-associated condition, disorder, or disease, comprising administering to a subject suffering therefrom or subject thereto a therapeutically effective amount of a provided ds oligonucleotide or a pharmaceutical composition that can deliver or comprise a therapeutically effective amount of a provided ds oligonucleotide. In some embodiments, the present disclosure provides pharmaceutical compositions which comprise a provided ds oligonucleotide targeting INHBE and a pharmaceutically acceptable carrier. In some embodiments, oligonucleotides in a pharmaceutical composition are in one or more pharmaceutically acceptable salt forms, e.g., a

sodium salt form, an ammonium salt form, etc.

In some embodiments, an oligonucleotide or oligonucleotide composition is useful for the manufacture of a medicament for prevention or treatment of a INHBE-associated condition, disorder, or disease, such as metabolic disorders, e.g., metabolic syndrome, and related diseases, e.g., obesity, cardiovascular disease, diabetes, and hypertension, in a subject in need thereof.

Various INHBE-associated conditions, disorders, or diseases may be prevented and/or treated utilizing provided technologies (e.g., oligonucleotide, compositions, methods, etc.). In some embodiments, a condition, disorder, or disease is a metabolic disorder, e.g., metabolic syndrome, or related disease, e.g., obesity, cardiovascular disease, diabetes, or hypertension.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

Technologies of the present disclosure may be understood more readily by reference to the following detailed description of certain embodiments.

Definitions

As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001.

As used herein in the present disclosure, unless otherwise clear from context, (i) the term “a” or “an” may be understood to mean “at least one”; (ii) the term “or” may be understood to mean “and/or”; (iii) the terms “comprising”, “comprise”, “including” (whether used with “not limited to” or not), and “include” (whether used with “not limited to” or not) may be understood to encompass itemized components or steps whether presented by themselves or together with one or more additional components or steps; (iv) the term “another” may be understood to mean at least an additional/second one or more; (v) the terms “about” and “approximately” may be understood to permit standard variation as would be understood by those of ordinary skill in the art; and (vi) where ranges are provided, endpoints are included.

Unless otherwise specified, description of oligonucleotides and elements thereof (e.g., base sequence, sugar modifications, internucleotidic linkages, linkage phosphorus stereochemistry, patterns thereof, etc.) is from 5’ to 3’. As those skilled in the art will

appreciate, in some embodiments, oligonucleotides may be provided and/or utilized as salt forms, particularly pharmaceutically acceptable salt forms, e.g., sodium salts. Unless otherwise indicated, oligonucleotides include various forms of the oligonucleotides. As those skilled in the art will also appreciate, in some embodiments, individual oligonucleotides within a composition may be considered to be of the same constitution and/or structure even though, within such composition (e.g., a liquid composition), particular such oligonucleotides might be in different salt form(s) (and may be dissolved and the oligonucleotide chain may exist as an anion form when, e.g., in a liquid composition) at a particular moment in time. For example, those skilled in the art will appreciate that, at a given pH, individual internucleotidic linkages along an oligonucleotide chain may be in an acid (H) form, or in one of a plurality of possible salt forms (e.g., a sodium salt, or a salt of a different cation, depending on which ions might be present in the preparation or composition), and will understand that, so long as their acid forms (e.g., replacing all cations, if any, with H^+) are of the same constitution and/or structure, such individual oligonucleotides may properly be considered to be of the same constitution and/or structure.

Analog: The term "analog" includes any chemical moiety which differs structurally from a reference chemical moiety or class of moieties, but which is capable of performing at least one function of such a reference chemical moiety or class of moieties. As non-limiting examples, a nucleotide analog differs structurally from a nucleotide but performs at least one function of a nucleotide; a nucleobase analog differs structurally from a nucleobase but performs at least one function of a nucleobase; etc.

Antisense: The term "antisense", as used herein, refers to a characteristic of an oligonucleotide or other nucleic acid having a base sequence complementary or substantially complementary to a target nucleic acid to which it is capable of hybridizing. In some embodiments, a target nucleic acid is a target gene mRNA. In some embodiments, hybridization is required for or results in at one activity, e.g., a decrease in the level, expression or activity of the target nucleic acid or a gene product thereof. The term "antisense oligonucleotide", as used herein, refers to an oligonucleotide complementary to a target nucleic acid. In some embodiments, an antisense oligonucleotide is capable of directing a decrease in the level, expression or activity of a target nucleic acid or a product thereof. In some embodiments, an antisense oligonucleotide is capable of directing a decrease in the level, expression or activity of the target nucleic acid or a product thereof, via a mechanism that involves RNA interference.

Chiral control: As used herein, "chiral control" refers to control of the stereochemical designation of the chiral linkage phosphorus in a chiral internucleotidic linkage within an oligonucleotide. As used herein, a chiral internucleotidic linkage is an internucleotidic linkage whose linkage phosphorus is chiral. In some embodiments, a control is achieved through a chiral element that is absent from the sugar and base moieties of an oligonucleotide, for example, in some embodiments, a control is achieved through use of one or more chiral auxiliaries during oligonucleotide preparation as described in the present disclosure, which chiral auxiliaries often are part of chiral phosphoramidites used during oligonucleotide preparation. In contrast to chiral control, a person having ordinary skill in the art appreciates that conventional oligonucleotide synthesis which does not use chiral auxiliaries cannot control stereochemistry at a chiral internucleotidic linkage if such conventional oligonucleotide synthesis is used to form the chiral internucleotidic linkage. In some embodiments, the stereochemical designation of each chiral linkage phosphorus in each chiral internucleotidic linkage within an oligonucleotide is controlled.

Chirally controlled oligonucleotide composition: The terms "chirally controlled oligonucleotide composition", "chirally controlled nucleic acid composition", and the like, as used herein, refers to a composition that comprises a plurality of oligonucleotides (or nucleic acids) which share 1) a common base sequence, 2) a common pattern of backbone linkages, and 3) a common pattern of backbone phosphorus modifications, wherein the plurality of oligonucleotides (or nucleic acids) share the same linkage phosphorus stereochemistry at one or more chiral internucleotidic linkages (chirally controlled or stereodefined internucleotidic linkages, whose chiral linkage phosphorus is *R*p or *S*p in the composition ("stereodefined"), not a random *R*p and *S*p mixture as non-chirally controlled internucleotidic linkages). Level of the plurality of oligonucleotides (or nucleic acids) in a chirally controlled oligonucleotide composition is pre-determined/controlled (e.g., through chirally controlled oligonucleotide preparation to stereoselectively form one or more chiral internucleotidic linkages). In some embodiments, about 1%-100%, (e.g., about 5%-100%, 10%-100%, 20%-100%, 30%-100%, 40%-100%, 50%-100%, 60%-100%, 70%-100%, 80-100%, 90-100%, 95-100%, 50%-90%, or about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, or at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) of all oligonucleotides in a chirally controlled oligonucleotide composition are oligonucleotides of the plurality. In some embodiments, about 1%-100%, (e.g., about 5%-100%, 10%-100%, 20%-100%, 30%-100%, 40%-100%, 50%-100%, 60%-100%, 70%-100%, 80-100%, 90-100%, 95-100%, 50%-

90%, or about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, or at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) of all oligonucleotides in a chirally controlled oligonucleotide composition that share the common base sequence, the common pattern of backbone linkages, and the common pattern of backbone phosphorus modifications are oligonucleotides of the plurality. In some embodiments, a level is about 1%-100%, (e.g., about 5%-100%, 10%-100%, 20%-100%, 30%-100%, 40%-100%, 50%-100%, 60%-100%, 70%-100%, 80-100%, 90-100%, 95-100%, 50%-90%, or about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, or at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) of all oligonucleotides in a composition, or of all oligonucleotides in a composition that share a common base sequence (e.g., of a plurality of oligonucleotide or an oligonucleotide type), or of all oligonucleotides in a composition that share a common base sequence, a common pattern of backbone linkages, and a common pattern of backbone phosphorus modifications, or of all oligonucleotides in a composition that share a common base sequence, a common patter of base modifications, a common pattern of sugar modifications, a common pattern of internucleotidic linkage types, and/or a common pattern of internucleotidic linkage modifications. In some embodiments, the plurality of oligonucleotides share the same stereochemistry at about 1-50 chiral internucleotidic linkages. In some embodiments, the plurality of oligonucleotides share the same stereochemistry at about 1%-100% of chiral internucleotidic linkages. In some embodiments, oligonucleotides (or nucleic acids) of a plurality are of the same constitution (as appreciated by those skilled in the art, in some embodiments may exist in one or more forms, e.g., acid forms, salt forms, etc.). In some embodiments, level of the oligonucleotides (or nucleic acids) of the plurality is about 1%-100% of all oligonucleotides (or nucleic acids) in a composition that share the same constitution as the oligonucleotides (or nucleic acids) of the plurality. In some embodiments, each chiral internucleotidic linkage is a chiral controlled internucleotidic linkage, and the composition is a completely chirally controlled oligonucleotide composition. In some embodiments, oligonucleotides (or nucleic acids) of a plurality are structurally identical. In some embodiments, a chirally controlled internucleotidic linkage has a diastereopurity of at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5%, typically at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5%. In some embodiments, a chirally controlled internucleotidic linkage has a diastereopurity of at least 95%. In some embodiments, a chirally controlled internucleotidic

linkage has a diastereopurity of at least 96%. In some embodiments, a chirally controlled internucleotidic linkage has a diastereopurity of at least 97%. In some embodiments, a chirally controlled internucleotidic linkage has a diastereopurity of at least 98%. In some embodiments, a chirally controlled internucleotidic linkage has a diastereopurity of at least 99%. In some embodiments, a percentage (e.g., a level as described herein) is or is at least $(DS)^{nc}$, wherein DS is a diastereopurity as described in the present disclosure (e.g., 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5% or more) and nc is the number of chirally controlled internucleotidic linkages as described in the present disclosure (e.g., 1-50, 1-40, 1-30, 1-25, 1-20, 5-50, 5-40, 5-30, 5-25, 5-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 or more). In some embodiments, a percentage (e.g., a level as described herein) is or is at least $(DS)^{nc}$, wherein DS is 95%-100%. For example, when DS is 99% and nc is 10, the percentage is or is at least 90% ($(99\%)^{10} \approx 0.90 = 90\%$). In some embodiments, level of a plurality of oligonucleotides in a composition is represented as the product of the diastereopurity of each chirally controlled internucleotidic linkage in the oligonucleotides. In some embodiments, diastereopurity of an internucleotidic linkage connecting two nucleosides in an oligonucleotide (or nucleic acid) is represented by the diastereopurity of an internucleotidic linkage of a dimer connecting the same two nucleosides, wherein the dimer is prepared using comparable conditions, in some instances, identical synthetic cycle conditions (e.g., for the linkage between Nx and Ny in an oligonucleotide ….NxNy….., the dimer is NxNy). In some embodiments, not all chiral internucleotidic linkages are chiral controlled internucleotidic linkages, and the composition is a partially chirally controlled oligonucleotide composition. In some embodiments, a non-chirally controlled internucleotidic linkage has a diastereopurity of less than about 80%, 75%, 70%, 65%, 60%, 55%, or of about 50%, as typically observed in stereorandom oligonucleotide compositions (e.g., as appreciated by those skilled in the art, from traditional oligonucleotide synthesis, e.g., the phosphoramidite method). In some embodiments, oligonucleotides (or nucleic acids) of a plurality are of the same type. In some embodiments, a chirally controlled oligonucleotide composition comprises non-random or controlled levels of individual oligonucleotide or nucleic acids types. For instance, in some embodiments a chirally controlled oligonucleotide composition comprises one and no more than one oligonucleotide type. In some embodiments, a chirally controlled oligonucleotide composition comprises more than one oligonucleotide type. In some embodiments, a chirally controlled oligonucleotide composition comprises multiple oligonucleotide types. In some embodiments, a chirally controlled oligonucleotide composition is a composition of oligonucleotides of an oligonucleotide type, which

composition comprises a non-random or controlled level of a plurality of oligonucleotides of the oligonucleotide type.

Internucleotidic linkage: As used herein, the phrase "internucleotidic linkage" refers generally to a linkage linking nucleoside units of an oligonucleotide or a nucleic acid. In some embodiments, an internucleotidic linkage is a phosphodiester linkage, as extensively found in naturally occurring DNA and RNA molecules (natural phosphate linkage (−OP(=O)(OH)O−), which as appreciated by those skilled in the art may exist as a salt form). In some embodiments, an internucleotidic linkage is a modified internucleotidic linkage (not a natural phosphate linkage). In some embodiments, an internucleotidic linkage is a "modified internucleotidic linkage" wherein at least one oxygen atom or −OH of a phosphodiester linkage is replaced by a different organic or inorganic moiety. In some embodiments, such an organic or inorganic moiety is selected from =S, =Se, =NR', –SR', –SeR', –$N(R')_2$, $B(R')_3$, –S–, –Se–, and –N(R')–, wherein each R' is independently as defined and described in the present disclosure. In some embodiments, an internucleotidic linkage is a phosphotriester linkage, phosphorothioate linkage (or phosphorothioate diester linkage, −OP(=O)(SH)O−, which as appreciated by those skilled in the art may exist as a salt form), or phosphorothioate triester linkage. In some embodiments, a modified internucleotidic linkage is a phosphorothioate linkage. In some embodiments, an internucleotidic linkage is one of, e.g., PNA (peptide nucleic acid) or PMO (phosphorodiamidate Morpholino oligomer) linkage. In some embodiments, a modified internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a neutral internucleotidic linkage (e.g., n001 in certain provided oligonucleotides). It is understood by a person of ordinary skill in the art that an internucleotidic linkage may exist as an anion or cation at a given pH due to the existence of acid or base moieties in the linkage. In some embodiments, a modified internucleotidic linkages is a modified internucleotidic linkages designated as s, s1, s2, s3, s4, s5, s6, s7, s8, s9, s10, s11, s12, s13, s14, s15, s16, s17 and s18 as described in WO 2017/210647.

In vitro: As *used* herein, the term "*in vitro*" refers to events that occur in an artificial environment, *e.g.*, in a test tube or reaction vessel, in cell culture, etc., rather than within an organism (*e.g.*, animal, plant and/or microbe).

In vivo: As used herein, the term "*in vivo*" refers to events that occur within an organism (*e.g.*, animal, plant and/or microbe).

Linkage phosphorus: as defined herein, the phrase "linkage phosphorus" is used to indicate that the particular phosphorus atom being referred to is the phosphorus atom present

in the internucleotidic linkage, which phosphorus atom corresponds to the phosphorus atom of a phosphodiester internucleotidic linkage as occurs in naturally occurring DNA and RNA. In some embodiments, a linkage phosphorus atom is in a modified internucleotidic linkage, wherein each oxygen atom of a phosphodiester linkage is optionally and independently replaced by an organic or inorganic moiety. In some embodiments, a linkage phosphorus atom is the P of Formula I as described herein. In some embodiments, a linkage phosphorus atom is chiral. In some embodiments, a linkage phosphorus atom is achiral (e.g., as in natural phosphate linkages).

Linker: The terms “linker”, “linking moiety” and the like refer to any chemical moiety which connects one chemical moiety to another. As appreciated by those skilled in the art, a linker can be bivalent or trivalent or more, depending on the number of chemical moieties the linker connects. In some embodiments, a linker is a moiety which connects one oligonucleotide to another oligonucleotide in a multimer. In some embodiments, a linker is a moiety optionally positioned between the terminal nucleoside and the solid support or between the terminal nucleoside and another nucleoside, nucleotide, or nucleic acid. In some embodiments, in an oligonucleotide a linker connects a chemical moiety (e.g., a targeting moiety, a lipid moiety, a carbohydrate moiety, etc.) with an oligonucleotide chain (e.g., through its 5’-end, 3’-end, nucleobase, sugar, internucleotidic linkage, etc.)

Modified nucleobase: The terms "modified nucleobase", "modified base" and the like refer to a chemical moiety which is chemically distinct from a nucleobase, but which is capable of performing at least one function of a nucleobase. In some embodiments, a modified nucleobase is a nucleobase which comprises a modification. In some embodiments, a modified nucleobase is capable of at least one function of a nucleobase, e.g., forming a moiety in a polymer capable of base-pairing to a nucleic acid comprising an at least complementary sequence of bases. In some embodiments, a modified nucleobase is substituted A, T, C, G, or U, or a substituted tautomer of A, T, C, G, or U. In some embodiments, a modified nucleobase in the context of oligonucleotides refer to a nucleobase that is not A, T, C, G or U.

Modified nucleoside: The term "modified nucleoside" refers to a moiety derived from or chemically similar to a natural nucleoside, but which comprises a chemical modification which differentiates it from a natural nucleoside. Non-limiting examples of modified nucleosides include those which comprise a modification at the base and/or the sugar. Non-limiting examples of modified nucleosides include those with a 2’ modification at a sugar. Non-limiting examples of modified nucleosides also include abasic nucleosides (which lack a

nucleobase). In some embodiments, a modified nucleoside is capable of at least one function of a nucleoside, e.g., forming a moiety in a polymer capable of base-pairing to a nucleic acid comprising an at least complementary sequence of bases.

Modified nucleotide: The term "modified nucleotide" includes any chemical moiety which differs structurally from a natural nucleotide but is capable of performing at least one function of a natural nucleotide. In some embodiments, a modified nucleotide comprises a modification at a sugar, base and/or internucleotidic linkage. In some embodiments, a modified nucleotide comprises a modified sugar, modified nucleobase and/or modified internucleotidic linkage. In some embodiments, a modified nucleotide is capable of at least one function of a nucleotide, e.g., forming a subunit in a polymer capable of base-pairing to a nucleic acid comprising an at least complementary sequence of bases.

Modified sugar: The term "modified sugar" refers to a moiety that can replace a sugar. A modified sugar mimics the spatial arrangement, electronic properties, or some other physicochemical property of a sugar. In some embodiments, as described in the present disclosure, a modified sugar is substituted ribose or deoxyribose. In some embodiments, a modified sugar comprises a 2'-modification. Examples of useful 2'-modification are widely utilized in the art and described herein. In some embodiments, a 2'-modification is 2'-OR, wherein R is optionally substituted C_{1-10} aliphatic. In some embodiments, a 2'-modification is 2'-OMe. In some embodiments, a 2'-modification is 2'-MOE. In some embodiments, a modified sugar is a bicyclic sugar (e.g., a sugar used in LNA, BNA, etc.). In some embodiments, in the context of oligonucleotides, a modified sugar is a sugar that is not ribose or deoxyribose as typically found in natural RNA or DNA.

Nucleic acid: The term "nucleic acid", as used herein, includes any nucleotides and polymers thereof. The term "polynucleotide", as used herein, refers to a polymeric form of nucleotides of any length, either ribonucleotides (RNA) or deoxyribonucleotides (DNA) or a combination thereof. These terms refer to the primary structure of the molecules and, thus, include double- and single-stranded DNA, and double- and single-stranded RNA. These terms include, as equivalents, analogs of either RNA or DNA comprising modified nucleotides and/or modified polynucleotides, such as, though not limited to, methylated, protected and/or capped nucleotides or polynucleotides. The terms encompass poly- or oligo-ribonucleotides (RNA) and poly- or oligo-deoxyribonucleotides (DNA); RNA or DNA derived from N-glycosides or C-glycosides of nucleobases and/or modified nucleobases; nucleic acids derived from sugars and/or modified sugars; and nucleic acids derived from phosphate bridges and/or modified

internucleotidic linkages. The term encompasses nucleic acids containing any combinations of nucleobases, modified nucleobases, sugars, modified sugars, phosphate bridges or modified internucleotidic linkages. Examples include, and are not limited to, nucleic acids containing ribose moieties, nucleic acids containing deoxy-ribose moieties, nucleic acids containing both ribose and deoxyribose moieties, nucleic acids containing ribose and modified ribose moieties. Unless otherwise specified, the prefix poly- refers to a nucleic acid containing 2 to about 10,000 nucleotide monomer units and wherein the prefix oligo- refers to a nucleic acid containing 2 to about 200 nucleotide monomer units.

Nucleobase: The term "nucleobase" refers to the parts of nucleic acids that are involved in the hydrogen-bonding that binds one nucleic acid strand to another complementary strand in a sequence specific manner. The most common naturally-occurring nucleobases are adenine (A), guanine (G), uracil (U), cytosine (C), and thymine (T). In some embodiments, a naturally-occurring nucleobases are modified adenine, guanine, uracil, cytosine, or thymine. In some embodiments, a naturally-occurring nucleobases are methylated adenine, guanine, uracil, cytosine, or thymine. In some embodiments, a nucleobase comprises a heteroaryl ring wherein a ring atom is nitrogen, and when in a nucleoside, the nitrogen is bonded to a sugar moiety. In some embodiments, a nucleobase comprises a heterocyclic ring wherein a ring atom is nitrogen, and when in a nucleoside, the nitrogen is bonded to a sugar moiety. In some embodiments, a nucleobase is a "modified nucleobase," a nucleobase other than adenine (A), guanine (G), uracil (U), cytosine (C), and thymine (T). In some embodiments, a modified nucleobase is substituted A, T, C, G or U. In some embodiments, a modified nucleobase is a substituted tautomer of A, T, C, G, or U. In some embodiments, a modified nucleobases is methylated adenine, guanine, uracil, cytosine, or thymine. In some embodiments, a modified nucleobase mimics the spatial arrangement, electronic properties, or some other physicochemical property of the nucleobase and retains the property of hydrogen-bonding that binds one nucleic acid strand to another in a sequence specific manner. In some embodiments, a modified nucleobase can pair with all of the five naturally occurring bases (uracil, thymine, adenine, cytosine, or guanine) without substantially affecting the melting behavior, recognition by intracellular enzymes or activity of the oligonucleotide duplex. As used herein, the term "nucleobase" also encompasses structural analogs used in lieu of natural or naturally-occurring nucleotides, such as modified nucleobases and nucleobase analogs. In some embodiments, a nucleobase is optionally substituted A, T, C, G, or U, or an optionally substituted tautomer of A, T, C, G, or U. In some embodiments, a "nucleobase" refers to a nucleobase unit in an oligonucleotide or

a nucleic acid (e.g., A, T, C, G or U as in an oligonucleotide or a nucleic acid).

Nucleoside: The term "nucleoside" refers to a moiety wherein a nucleobase or a modified nucleobase is covalently bound to a sugar or a modified sugar. In some embodiments, a nucleoside is a natural nucleoside, e.g., adenosine, deoxyadenosine, guanosine, deoxyguanosine, thymidine, uridine, cytidine, or deoxycytidine. In some embodiments, a nucleoside is a modified nucleoside, e.g., a substituted natural nucleoside selected from adenosine, deoxyadenosine, guanosine, deoxyguanosine, thymidine, uridine, cytidine, and deoxycytidine. In some embodiments, a nucleoside is a modified nucleoside, e.g., a substituted tautomer of a natural nucleoside selected from adenosine, deoxyadenosine, guanosine, deoxyguanosine, thymidine, uridine, cytidine, and deoxycytidine. In some embodiments, a "nucleoside" refers to a nucleoside unit in an oligonucleotide or a nucleic acid.

Nucleotide: The term "nucleotide" as used herein refers to a monomeric unit of a polynucleotide that consists of a nucleobase, a sugar, and one or more internucleotidic linkages (e.g., phosphate linkages in natural DNA and RNA). The naturally occurring bases [guanine, (G), adenine, (A), cytosine, (C), thymine, (T), and uracil (U)] are derivatives of purine or pyrimidine, though it should be understood that naturally and non-naturally occurring base analogs are also included. The naturally occurring sugar is the pentose (five-carbon sugar) deoxyribose (which forms DNA) or ribose (which forms RNA), though it should be understood that naturally and non-naturally occurring sugar analogs are also included. Nucleotides are linked via internucleotidic linkages to form nucleic acids, or polynucleotides. Many internucleotidic linkages are known in the art (such as, though not limited to, phosphate, phosphorothioates, boranophosphates and the like). Artificial nucleic acids include PNAs (peptide nucleic acids), phosphotriesters, phosphorothionates, H-phosphonates, phosphoramidates, boranophosphates, methylphosphonates, phosphonoacetates, thiophosphonoacetates and other variants of the phosphate backbone of native nucleic acids, such as those described herein. In some embodiments, a natural nucleotide comprises a naturally occurring base, sugar and internucleotidic linkage. As used herein, the term "nucleotide" also encompasses structural analogs used in lieu of natural or naturally-occurring nucleotides, such as modified nucleotides and nucleotide analogs. In some embodiments, a "nucleotide" refers to a nucleotide unit in an oligonucleotide or a nucleic acid.

Oligonucleotide: The term "oligonucleotide" refers to a polymer or oligomer of nucleotides, and may contain any combination of natural and non-natural nucleobases, sugars, and internucleotidic linkages.

Oligonucleotides can be single-stranded or double-stranded. A single-stranded

oligonucleotide can have double-stranded regions (formed by two portions of the single-stranded oligonucleotide) and a double-stranded oligonucleotide, which comprises two oligonucleotide chains, can have single-stranded regions for example, at regions where the two oligonucleotide chains are not complementary to each other. Example oligonucleotides include, but are not limited to structural genes, genes including control and termination regions, self-replicating systems such as viral or plasmid DNA, single-stranded and double-stranded RNAi agents and other RNA interference reagents (RNAi agents or iRNA agents), shRNA, antisense oligonucleotides, ribozymes, microRNAs, microRNA mimics, supermirs, aptamers, antimirs, antagomirs, Ul adaptors, triplex-forming oligonucleotides, G-quadruplex oligonucleotides, RNA activators, immuno-stimulatory oligonucleotides, and decoy oligonucleotides.

Oligonucleotides of the present disclosure can be of various lengths. In particular embodiments, oligonucleotides can range from about 2 to about 200 nucleosides in length. In various related embodiments, oligonucleotides, single-stranded, double-stranded, or triple-stranded, can range in length from about 4 to about 10 nucleosides, from about 10 to about 50 nucleosides, from about 20 to about 50 nucleosides, from about 15 to about 30 nucleosides, from about 20 to about 30 nucleosides in length. In some embodiments, the oligonucleotide is from about 9 to about 39 nucleosides in length. In some embodiments, the oligonucleotide is at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleosides in length. In some embodiments, the oligonucleotide is at least 19 nucleosides in length. In some embodiments, the oligonucleotide is at least 20 nucleosides in length. In some embodiments, the oligonucleotide is at least 25 nucleosides in length. In some embodiments, the oligonucleotide is at least 30 nucleosides in length. In some embodiments, the oligonucleotide is a duplex of complementary strands of at least 18 nucleosides in length. In some embodiments, the oligonucleotide is a duplex of complementary strands of at least 21 nucleosides in length. In some embodiments, each nucleoside counted in an oligonucleotide length independently comprises A, T, C, G, or U, or optionally substituted A, T, C, G, or U, or an optionally substituted tautomer of A, T, C, G or U.

Oligonucleotide type: As used herein, the phrase "oligonucleotide type" is used to define an oligonucleotide that has a particular base sequence, pattern of backbone linkages (i.e., pattern of internucleotidic linkage types, for example, phosphate, phosphorothioate, phosphorothioate triester, etc.), pattern of backbone chiral centers [i.e., pattern of linkage phosphorus stereochemistry (*R*p/*S*p)], and pattern of backbone phosphorus modifications (e.g., pattern of "$-XLR^1$" groups in Formula I as described herein). In some embodiments,

oligonucleotides of a common designated "type" are structurally identical to one another.

One of skill in the art will appreciate that synthetic methods of the present disclosure provide for a degree of control during the synthesis of an oligonucleotide strand such that each nucleotide unit of the oligonucleotide strand can be designed and/or selected in advance to have a particular stereochemistry at the linkage phosphorus and/or a particular modification at the linkage phosphorus, and/or a particular base, and/or a particular sugar. In some embodiments, an oligonucleotide strand is designed and/or selected in advance to have a particular combination of stereocenters at the linkage phosphorus. In some embodiments, an oligonucleotide strand is designed and/or determined to have a particular combination of modifications at the linkage phosphorus. In some embodiments, an oligonucleotide strand is designed and/or selected to have a particular combination of bases. In some embodiments, an oligonucleotide strand is designed and/or selected to have a particular combination of one or more of the above structural characteristics. In some embodiments, the present disclosure provides compositions comprising or consisting of a plurality of oligonucleotide molecules (e.g., chirally controlled oligonucleotide compositions). In some embodiments, all such molecules are of the same type (i.e., are structurally identical to one another). In some embodiments, however, provided compositions comprise a plurality of oligonucleotides of different types, typically in pre-determined relative amounts.

Optionally Substituted: As described herein, compounds, *e.g.*, oligonucleotides, of the disclosure may contain optionally substituted and/or substituted moieties. In general, the term "substituted," whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. In some embodiments, an optionally substituted group is unsubstituted. Combinations of substituents envisioned by this disclosure are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein. Certain substituents are described below.

Suitable monovalent substituents on a substitutable atom, *e.g.*, a suitable carbon atom, are independently halogen; $–(CH_2)_{0–4}R°$; $–(CH_2)_{0–4}OR°$; $–O(CH_2)_{0-4}R°$, $–O–(CH_2)_{0–4}C(O)OR°$; $–(CH_2)_{0–4}CH(OR°)_2$; $–(CH_2)_{0–4}Ph$, which may be substituted with R°; $–(CH_2)_{0–4}O(CH_2)_{0–1}Ph$ which may be substituted with R°; –CH=CHPh, which may be substituted with R°; $–(CH_2)_{0–4}O(CH_2)_{0–1}$-pyridyl which may be substituted with R°; $–NO_2$; –CN; $–N_3$; $-(CH_2)_{0–4}N(R°)_2$; $–(CH_2)_{0–4}N(R°)C(O)R°$; $–N(R°)C(S)R°$; $–(CH_2)_{0–4}N(R°)C(O)NR°_2$; $–N(R°)C(S)NR°_2$; $–(CH_2)_{0–4}N(R°)C(O)OR°$; $–N(R°)N(R°)C(O)R°$; $–N(R°)N(R°)C(O)NR°_2$; $–N(R°)N(R°)C(O)OR°$; $–(CH_2)_{0–4}C(O)R°$; $–C(S)R°$; $–(CH_2)_{0–4}C(O)OR°$; $–(CH_2)_{0–4}C(O)SR°$; $-(CH_2)_{0–4}C(O)OSiR°_3$; $–(CH_2)_{0–4}OC(O)R°$; $–OC(O)(CH_2)_{0–4}SR°$, $–SC(S)SR°$; $–(CH_2)_{0–4}SC(O)R°$; $–(CH_2)_{0–4}C(O)NR°_2$; $–C(S)NR°_2$; $–C(S)SR°$; $-(CH_2)_{0–4}OC(O)NR°_2$; $-C(O)N(OR°)R°$; $–C(O)C(O)R°$; $–C(O)CH_2C(O)R°$; $–C(NOR°)R°$; $-(CH_2)_{0–4}SSR°$; $–(CH_2)_{0–4}S(O)_2R°$; $–(CH_2)_{0–4}S(O)_2OR°$; $–(CH_2)_{0–4}OS(O)_2R°$; $–S(O)_2NR°_2$; $-(CH_2)_{0–4}S(O)R°$; $–N(R°)S(O)_2NR°_2$; $–N(R°)S(O)_2R°$; $–N(OR°)R°$; $–C(NH)NR°_2$; $–Si(R°)_3$; $–OSi(R°)_3$; $–B(R°)_2$; $–OB(R°)_2$; $–OB(OR°)_2$; $–P(R°)_2$; $–P(OR°)_2$; $–P(R°)(OR°)$; $–OP(R°)_2$; $–OP(OR°)_2$; $–OP(R°)(OR°)$; $–P(O)(R°)_2$; $–P(O)(OR°)_2$; $–OP(O)(R°)_2$; $–OP(O)(OR°)_2$; $–OP(O)(OR°)(SR°)$; $–SP(O)(R°)_2$; $–SP(O)(OR°)_2$; $–N(R°)P(O)(R°)_2$; $–N(R°)P(O)(OR°)_2$; $–P(R°)_2[B(R°)_3]$; $–P(OR°)_2[B(R°)_3]$; $–OP(R°)_2[B(R°)_3]$; $–OP(OR°)_2[B(R°)_3]$; $–(C_{1–4}$ straight or branched alkylene$)O–N(R°)_2$; or $–(C_{1–4}$ straight or branched alkylene$)C(O)O–N(R°)_2$, wherein each R° may be substituted as defined herein and is independently hydrogen, $C_{1–20}$ aliphatic, $C_{1–20}$ heteroaliphatic having 1–5 heteroatoms independently selected from nitrogen, oxygen, sulfur, silicon and phosphorus, $–CH_2–(C_{6-14}$ aryl$)$, $–O(CH_2)_{0–1}(C_{6-14}$ aryl$)$, $–CH_2$-(5-14 membered heteroaryl ring), a 5–20 membered, monocyclic, bicyclic, or polycyclic, saturated, partially unsaturated or aryl ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, sulfur, silicon and phosphorus, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 5–20 membered, monocyclic, bicyclic, or polycyclic, saturated, partially unsaturated or aryl ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, sulfur, silicon and phosphorus, which may be substituted as defined below.

Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $–(CH_2)_{0–2}R^•$, –(halo$R^•$), $–(CH_2)_{0–2}OH$, $–(CH_2)_{0–2}OR^•$, $–(CH_2)_{0–2}CH(OR^•)_2$; $–O($halo$R^•)$, –CN, $–N_3$, $–(CH_2)_{0–2}C(O)R^•$, $–(CH_2)_{0–2}C(O)OH$, $–(CH_2)_{0–2}C(O)OR^•$, $–(CH_2)_{0–2}SR^•$, $–(CH_2)_{0–2}SH$, –

$(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^{\bullet}$, $-(CH_2)_{0-2}NR^{\bullet}_2$, $-NO_2$, $-SiR^{\bullet}_3$, $-OSiR^{\bullet}_3$, -C(O)$SR^{\bullet}$, $-(C_{1-4}$ straight or branched alkylene)C(O)$OR^{\bullet}$, or $-SSR^{\bullet}$ wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, and a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

Suitable divalent substituents, *e.g.*, on a suitable carbon atom, are independently the following: =O, =S, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, and an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, and an unsubstituted 5–6–membered saturated, partially unsaturated, and aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

Suitable substituents on the aliphatic group of R^* are independently halogen, $-R^{\bullet}$, -(halo$R^{\bullet}$), –OH, $-OR^{\bullet}$, -O(halo$R^{\bullet}$), –CN, –C(O)OH, $-C(O)OR^{\bullet}$, $-NH_2$, $-NHR^{\bullet}$, $-NR^{\bullet}_2$, or $-NO_2$, wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

In some embodiments, suitable substituents on a substitutable nitrogen are independently $-R^{\dagger}$, $-NR^{\dagger}_2$, $-C(O)R^{\dagger}$, $-C(O)OR^{\dagger}$, $-C(O)C(O)R^{\dagger}$, $-C(O)CH_2C(O)R^{\dagger}$, $-S(O)_2R^{\dagger}$, $-S(O)_2NR^{\dagger}_2$, $-C(S)NR^{\dagger}_2$, $-C(NH)NR^{\dagger}_2$, or $-N(R^{\dagger})S(O)_2R^{\dagger}$; wherein each $R^{\dagger}$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted –OPh, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or, notwithstanding the definition above, two independent occurrences of $R^{\dagger}$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and

sulfur.

Suitable substituents on the aliphatic group of $R^{\dagger}$ are independently halogen, $-R^{\bullet}$, -(halo$R^{\bullet}$), –OH, $-OR^{\bullet}$, –O(halo$R^{\bullet}$), –CN, –C(O)OH, $-C(O)OR^{\bullet}$, $-NH_2$, $-NHR^{\bullet}$, $-NR^{\bullet}_2$, or $-NO_2$, wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

Oral: The phrases "oral administration" and "administered orally" as used herein have their art-understood meaning referring to administration by mouth of a compound or composition.

Parenteral: The phrases "parenteral administration" and "administered parenterally" as used herein have their art-understood meaning referring to modes of administration other than enteral and topical administration, usually by injection, and include, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticulare, subcapsular, subarachnoid, intraspinal, and intrasternal injection and infusion.

Partially unsaturated: As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

Pharmaceutical composition: As used herein, the term "pharmaceutical composition" refers to an active agent, formulated together with one or more pharmaceutically acceptable carriers. In some embodiments, an active agent is present in unit dose amount appropriate for administration in a therapeutic regimen that shows a statistically significant probability of achieving a predetermined therapeutic effect when administered to a relevant population. In some embodiments, pharmaceutical compositions may be specially formulated for administration in solid or liquid form, including those adapted for the following: oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, *e.g.*, those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; topical application, for example, as a

cream, ointment, or a controlled-release patch or spray applied to the skin, lungs, or oral cavity; intravaginally or intrarectally, for example, as a pessary, cream, or foam; sublingually; ocularly; transdermally; or nasally, pulmonary, and to other mucosal surfaces.

Pharmaceutically acceptable: As used herein, the phrase "pharmaceutically acceptable" refers to those compounds, materials, compositions and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

Pharmaceutically acceptable carrier: As used herein, the term "pharmaceutically acceptable carrier" means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; pH buffered solutions; polyesters, polycarbonates and/or polyanhydrides; and other non-toxic compatible substances employed in pharmaceutical formulations.

Pharmaceutically acceptable salt: The term "pharmaceutically acceptable salt", as used herein, refers to salts of such compounds that are appropriate for use in pharmaceutical contexts, *i.e.*, salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977). In some embodiments, pharmaceutically acceptable salt include, but are not limited to,

nontoxic acid addition salts, which are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. In some embodiments, pharmaceutically acceptable salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. In some embodiments, a provided compound comprises one or more acidic groups, e.g., an oligonucleotide, and a pharmaceutically acceptable salt is an alkali, alkaline earth metal, or ammonium (e.g., an ammonium salt of $N(R)_3$, wherein each R is independently defined and described in the present disclosure) salt. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. In some embodiments, a pharmaceutically acceptable salt is a sodium salt. In some embodiments, a pharmaceutically acceptable salt is a potassium salt. In some embodiments, a pharmaceutically acceptable salt is a calcium salt. In some embodiments, pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate. In some embodiments, a provided compound comprises more than one acid groups, for example, an oligonucleotide may comprise two or more acidic groups (e.g., in natural phosphate linkages and/or modified internucleotidic linkages). In some embodiments, a pharmaceutically acceptable salt, or generally a salt, of such a compound comprises two or more cations, which can be the same or different. In some embodiments, in a pharmaceutically acceptable salt (or generally, a salt), all ionizable hydrogen (e.g., in an aqueous solution with a pKa no more than about 11, 10, 9, 8, 7, 6, 5, 4, 3, or 2; in some embodiments, no more than about 7; in some embodiments, no more than about 6; in some embodiments, no more than about 5; in some embodiments, no more than about 4; in some embodiments, no more than about 3) in the acidic groups are replaced with cations. In some embodiments, each phosphorothioate and phosphate group

independently exists in its salt form (e.g., if sodium salt, −O−P(O)(SNa)−O− and −O−P(O)(ONa)−O−, respectively). In some embodiments, each phosphorothioate and phosphate internucleotidic linkage independently exists in its salt form (e.g., if sodium salt, −O−P(O)(SNa)−O− and −O−P(O)(ONa)−O−, respectively). In some embodiments, a pharmaceutically acceptable salt is a sodium salt of an oligonucleotide. In some embodiments, a pharmaceutically acceptable salt is a sodium salt of an oligonucleotide, wherein each acidic phosphate and modified phosphate group (e.g., phosphorothioate, phosphate, etc.), if any, exists as a salt form (all sodium salt).

Protecting group: The term "protecting group," as used herein, is well known in the art and includes those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entirety of which is incorporated herein by reference. Also included are those protecting groups specially adapted for nucleoside and nucleotide chemistry described in *Current Protocols in Nucleic Acid Chemistry*, edited by Serge L. Beaucage *et al.* 06/2012, the entirety of Chapter 2 is incorporated herein by reference. Suitable amino–protecting groups include but are not limited to described herein and/or in: WO 2018/022473, WO 2018/098264, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, and/or WO 2019/075357, or US Provisional patent applications 62/825766 and 62/911339, the description of the protecting groups of each of which is independently incorporated herein by reference.

Sample: As used herein, the term "sample" typically refers to an aliquot of material obtained or derived from a source of interest. In some embodiments, a source of interest is a biological or environmental source. In some embodiments, a source of interest may be or comprise a cell or an organism, such as a microbe, a plant, or an animal (e.g., a human). In some embodiments, a source of interest is or comprises biological tissue or fluid. In some embodiments, a biological tissue or fluid may be or comprise amniotic fluid, aqueous humor, ascites, bile, bone marrow, blood, breast milk, cerebrospinal fluid, cerumen, chyle, chime, ejaculate, endolymph, exudate, feces, gastric acid, gastric juice, lymph, mucus, pericardial fluid, perilymph, peritoneal fluid, pleural fluid, pus, rheum, saliva, sebum, semen, serum, smegma, sputum, synovial fluid, sweat, tears, urine, vaginal secreations, vitreous humour, vomit, and/or combinations or component(s) thereof. In some embodiments, a biological fluid may be or comprise an intracellular fluid, an extracellular fluid, an intravascular fluid (blood plasma), an interstitial fluid, a lymphatic fluid, and/or a transcellular fluid. In some embodiments, a biological fluid may be or comprise a plant exudate. In some embodiments, a

biological tissue or sample may be obtained, for example, by aspirate, biopsy (e.g., fine needle or tissue biopsy), swab (e.g., oral, nasal, skin, or vaginal swab), scraping, surgery, washing or lavage (e.g., brocheoalvealar, ductal, nasal, ocular, oral, uterine, vaginal, or other washing or lavage). In some embodiments, a biological sample is or comprises cells obtained from an individual. In some embodiments, a sample is a "primary sample" obtained directly from a source of interest by any appropriate means. In some embodiments, as will be clear from context, the term "sample" refers to a preparation that is obtained by processing (e.g., by removing one or more components of and/or by adding one or more agents to) a primary sample. For example, filtering using a semi-permeable membrane. Such a "processed sample" may comprise, for example nucleic acids or proteins extracted from a sample or obtained by subjecting a primary sample to one or more techniques such as amplification or reverse transcription of nucleic acid, isolation and/or purification of certain components, *etc.*

Subject: As used herein, the term "subject" or "test subject" refers to any organism to which a provided compound (e.g., a provided oligonucleotide) or composition is administered in accordance with the present disclosure *e.g.*, for experimental, diagnostic, prophylactic and/or therapeutic purposes. Typical subjects include animals (*e.g.*, mammals such as mice, rats, rabbits, non-human primates, and humans; insects; worms; etc.) and plants. In some embodiments, a subject is a human. In some embodiments, a subject may be suffering from and/or susceptible to a disease, disorder and/or condition.

Substantially: As used herein, the term "substantially" refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. A base sequence which is substantially complementary to a second sequence is not identical to the second sequence, but is mostly or nearly identical to the second sequence. In addition, one of ordinary skill in the biological and/or chemical arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term "substantially" is therefore used herein to capture the potential lack of completeness inherent in many biological and/or chemical phenomena.

Sugar: The term "sugar" refers to a monosaccharide or polysaccharide in closed and/or open form. In some embodiments, sugars are monosaccharides. In some embodiments, sugars are polysaccharides. Sugars include, but are not limited to, ribose, deoxyribose, pentofuranose, pentopyranose, and hexopyranose moieties. As used herein, the term "sugar" also encompasses structural analogs used in lieu of conventional sugar molecules, such as glycol, polymer of

which forms the backbone of the nucleic acid analog, glycol nucleic acid ("GNA"), etc. As used herein, the term "sugar" also encompasses structural analogs used in lieu of natural or naturally-occurring nucleotides, such as modified sugars and nucleotide sugars. In some embodiments, a sugar is a RNA or DNA sugar (ribose or deoxyribose). In some embodiments, a sugar is a modified ribose or deoxyribose sugar, e.g., 2'-modified, 5'-modified, etc. As described herein, in some embodiments, when used in oligonucleotides and/or nucleic acids, modified sugars may provide one or more desired properties, activities, etc. In some embodiments, a sugar is optionally substituted ribose or deoxyribose. In some embodiments, a "sugar" refers to a sugar unit in an oligonucleotide or a nucleic acid.

Susceptible to: An individual who is "susceptible to" a disease, disorder and/or condition is one who has a higher risk of developing the disease, disorder and/or condition than does a member of the general public. In some embodiments, an individual who is susceptible to a disease, disorder and/or condition is predisposed to have that disease, disorder and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder and/or condition may not have been diagnosed with the disease, disorder and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder and/or condition may exhibit symptoms of the disease, disorder and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder and/or condition may not exhibit symptoms of the disease, disorder and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will develop the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will not develop the disease, disorder, and/or condition.

Therapeutic agent: As used herein, the term "therapeutic agent" in general refers to any agent that elicits a desired effect (e.g., a desired biological, clinical, or pharmacological effect) when administered to a subject. In some embodiments, an agent is considered to be a therapeutic agent if it demonstrates a statistically significant effect across an appropriate population. In some embodiments, an appropriate population is a population of subjects suffering from and/or susceptible to a disease, disorder or condition. In some embodiments, an appropriate population is a population of model organisms. In some embodiments, an appropriate population may be defined by one or more criterion such as age group, gender, genetic background, preexisting clinical conditions, prior exposure to therapy. In some embodiments, a therapeutic agent is a substance that alleviates, ameliorates, relieves, inhibits, prevents, delays onset of, reduces severity of, and/or reduces incidence of one or more

symptoms or features of a disease, disorder, and/or condition in a subject when administered to the subject in an effective amount. In some embodiments, a "therapeutic agent" is an agent that has been or is required to be approved by a government agency before it can be marketed for administration to humans. In some embodiments, a "therapeutic agent" is an agent for which a medical prescription is required for administration to humans. In some embodiments, a therapeutic agent is a provided compound, e.g., a provided oligonucleotide.

Therapeutically effective amount: As used herein, the term "therapeutically effective amount" means an amount of a substance (*e.g.*, a therapeutic agent, composition, and/or formulation) that elicits a desired biological response when administered as part of a therapeutic regimen. In some embodiments, a therapeutically effective amount of a substance is an amount that is sufficient, when administered to a subject suffering from or susceptible to a disease, disorder, and/or condition, to treat, diagnose, prevent, and/or delay the onset of the disease, disorder, and/or condition. As will be appreciated by those of ordinary skill in this art, the effective amount of a substance may vary depending on such factors as the desired biological endpoint, the substance to be delivered, the target cell or tissue, etc. For example, the effective amount of compound in a formulation to treat a disease, disorder, and/or condition is the amount that alleviates, ameliorates, relieves, inhibits, prevents, delays onset of, reduces severity of and/or reduces incidence of one or more symptoms or features of the disease, disorder, and/or condition. In some embodiments, a therapeutically effective amount is administered in a single dose; in some embodiments, multiple unit doses are required to deliver a therapeutically effective amount.

Treat: As used herein, the term "treat," "treatment," or "treating" refers to any method used to partially or completely alleviate, ameliorate, relieve, inhibit, prevent, delay onset of, reduce severity of, and/or reduce incidence of one or more symptoms or features of a disease, disorder, and/or condition. Treatment may be administered to a subject who does not exhibit signs of a disease, disorder, and/or condition. In some embodiments, treatment may be administered to a subject who exhibits only early signs of the disease, disorder, and/or condition, for example for the purpose of decreasing the risk of developing pathology associated with the disease, disorder, and/or condition.

Unsaturated: The term "unsaturated," as used herein, means that a moiety has one or more units of unsaturation.

Wild-type: As used herein, the term "wild-type" has its art-understood meaning that refers to an entity having a structure and/or activity as found in nature in a "normal" (as contrasted with mutant, diseased, altered, etc.) state or context. Those of ordinary skill in the art will appreciate that wild type genes and polypeptides often exist in multiple different forms (*e.g.*, alleles).

As those skilled in the art will appreciate, methods and compositions described herein relating to provided compounds (e.g., ds oligonucleotides) generally also apply to pharmaceutically acceptable salts of such compounds.

Description of Certain Embodiments

Double stranded oligonucleotides are useful tools for a wide variety of applications. For example, ds oligonucleotides targeting INHBE (e.g., NCBI Gene ID: 345275 for human INHBE and related sequences from other organisms) from are useful in therapeutic, diagnostic, and research applications, including the treatment of a variety of INHBE-associated conditions, disorders, and diseases, including but not limited to metabolic disorders, e.g., metabolic syndrome, and related diseases, e.g., obesity, cardiovascular disease, diabetes, and hypertension. The use of naturally occurring nucleic acids (*e.g.*, unmodified DNA or RNA) is limited, for example, by their susceptibility to endo- and exo-nucleases. As such, various synthetic counterparts have been developed to circumvent these shortcomings and/or to further improve various properties and activities. These include synthetic oligonucleotides that contain chemical modifications, e.g., base modifications, sugar modifications, backbone modifications, etc., which, among other things, render these molecules less susceptible to degradation and improve other properties and/or activities. From a structural point of view, modifications to internucleotidic linkages can introduce chirality and/or alter charge, and certain properties may be affected by configurations of linkage phosphorus atoms of oligonucleotides. For example, binding affinity, sequence specific binding to complementary RNA, stability against nucleases, cleavage of target nucleic acids, delivery, pharmacokinetics, etc., can be affected by, inter alia, chirality and/or charge of backbone linkage atoms.

In certain embodiments, a dsRNAi agent capable of directing INHBE (Inhibin subunit βE)-specific RNA interference to induce lipolysis while preserving muscle mass, the dsRNAi agent comprises a guide strand and a passenger strand, wherein:

c) the guide strand is complementary or substantially complementary to an INHBE target RNA sequence;

d) the guide strand comprises:

i. a non-negatively charged internucleotidic linkage in the *S*p configuration between the +3 nucleotide relative to the 5' terminal nucleotide and the immediately downstream (+4) nucleotide;

ii. a non-negatively charged internucleotidic linkage in the *R*p configuration between the +10 nucleotide and the immediately downstream (+11) nucleotide;

iii. phosphorothioate internucleotidic linkages in *S*p configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide; and/or

iv. phosphorothioate internucleotidic linkages in *R*p, *S*p, or alternating configurations between the 5' terminal (+1) nucleotide and the immediately downstream (+2) nucleotide and between the +2 nucleotide and the immediately downstream (+3) nucleotide;

c) the guide strand further comprises a 5' phosphate modification;

d) the passenger strand comprises one or more chiral internucleotidic linkages in *R*p or *S*p configuration; and

e) the guide strand and the passenger strand each independently has a length of 15-49 nucleotides.

In alternative embodiments, a ds oligonucleotide, *e.g.* a dsRNAi agent, targeting INHBE comprises one or more of:

(1) a guide strand comprising backbone non-negatively charged internucleotidic linkage in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction;

(2) a guide strand comprising backbone non-negatively charged internucleotidic linkage in the Rp configuration between the +10 nucleotide and the immediately downstream (+11) nucleotide, i.e., in the 3' direction;

(3) a guide strand comprising backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream, i.e., in the 5' direction, (N-2) nucleotide;

(4) a guide strand comprising backbone phosphorothioate chiral centers in Rp, Sp, or alternating configurations between the 5' terminal (+1) nucleotide and the immediately downstream, i.e., in the 3' direction, (+2) nucleotide and between the +2 nucleotide and the immediately downstream (+3) nucleotide;

(5) a guide strand comprising one or more backbone phosphorothioate chiral centers upstream, i.e., in the 5' direction, relative to backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide, where the upstream backbone phosphorothioate chiral centers are in Rp or Sp configuration;

(6) a guide strand comprising one or more backbone phosphorothioate chiral centers in Rp or Sp configuration between the N-2 nucleotide and the immediately upstream (N-3) nucleotide, i.e., in the 5' direction;

(7) a guide strand comprising a 5' terminal modification, e.g. 5' phosphate modification, e.g. 5' triazole phosphate modification;

wherein the ds oligonucleotide further comprises one or more of:

(1) a guide strand where one or both of the 5' and 3' terminal dinucleotides are ***not*** linked by non-negatively charged internucleotidic linkages, i.e., the guide strand comprises one more non-negatively charged internucleotidic linkages downstream, i.e., in the 3' direction, relative to the linkage between the 5' terminal dinucleotide and/or upstream, i.e., in the 5' direction, relative to the linkage between the 3' terminal dinucleotide;

(2) a guide strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide;

(3) a guide strand where an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between the third (+3) and fourth (+4) nucleotides, relative to the 5' terminal nucleotide, of the guide strand and/or between the tenth (+10) and eleventh (+11) nucleotides, relative to the 5' terminal nucleotide;

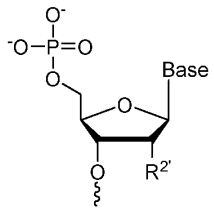
(4) a passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs upstream, i.e., in the 5' direction, relative to the central nucleotide of the passenger strand; and

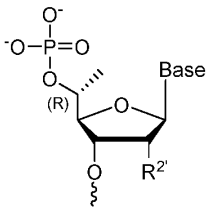
(5) Passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs downstream, i.e., in the 3' direction, relative to the central nucleotide of the passenger strand, and

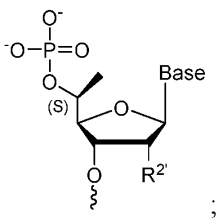
wherein the ds oligonucleotide further comprises a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide or passenger strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In some embodiments, a ds oligonucleotide targeting INHBE comprises: (1) a phosphorothioate chiral center in Rp or Sp configuration; (2) an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage where the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage comprises a 2' modification, e.g., a 2' F; and (3) a 5' terminal modification, e.g. 5' phosphate modification, e.g. 5' triazole phosphate modification selected from:

(a) 5' PO modifications, such as, but not limited to:

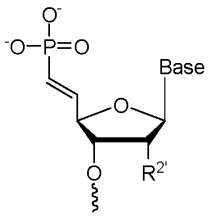
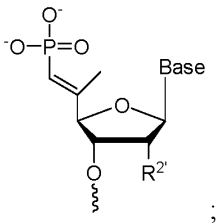




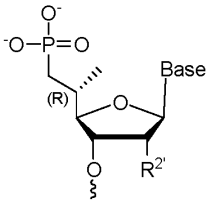
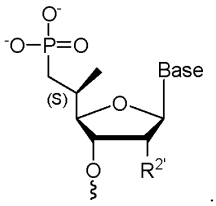


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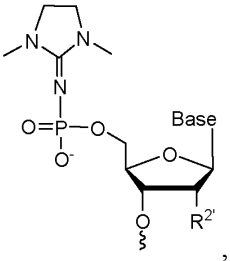
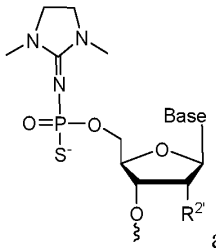
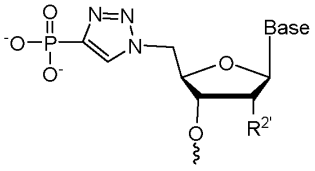
(b) 5' VP modifications, such as, but not limited to:



;

(c) 5' MeP modifications, such as, but not limited to:

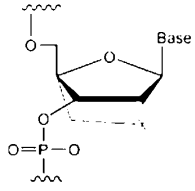
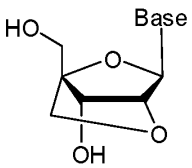


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(d) 5' PN and 5' triazole-P modifications, such as, but not limited to:

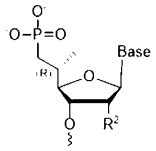


and

;

wherein Base is selected from A, C, G, T, U, abasic and modified nucleobases;

$R^{2'}$ is selected from H, OH, O-alkyl, F, MOE, locked nucleic acid (LNA) bridges and bridged nucleic acid (BNA) bridges to the 4' C, such as, but not limited to:

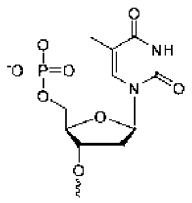
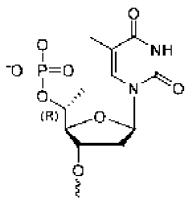
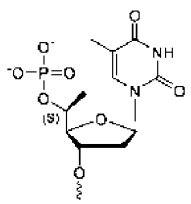

, and

. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom

non-negatively charged internucleotidic linkage. In certain embodiments, the guide strand comprises, a backbone phosphorothioate chiral center in Sp configuration between the 5' terminal (+1) nucleotide and the immediately downstream, i.e., in the 3' direction, (+2) nucleotide, and a backbone phosphorothioate chiral center in the Rp configuration between the +2 nucleotide and the immediately downstream (+3) nucleotide.

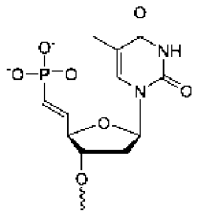
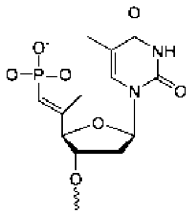
In certain embodiments, the guide strand comprises a 5' terminal modification, e.g. 5' phosphate modification, e.g. 5' triazole phosphate modification selected from, but not limited to, 5' MeP modifications and 5' triazole-P modifications. In certain embodiments, the guide strand comprises the 5' MeP modification  , a backbone phosphorothioate chiral center in Sp configuration between the 5' terminal (+1) nucleotide and the immediately downstream, i.e., in the 3' direction, (+2) nucleotide, and a backbone phosphorothioate chiral center in the Rp configuration between the +2 nucleotide and the immediately downstream (+3) nucleotide.

In some embodiments, a ds oligonucleotide targeting INHBE comprises: (1) a phosphorothioate chiral center in Rp or Sp configuration; (2) an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage where the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage comprises a 2' modification, e.g., a 2' F; and (3) a 5' terminal modification, e.g. 5' phosphate modification, e.g. 5' triazole phosphate modification selected from:

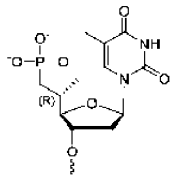
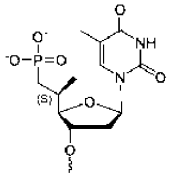
(a) 5' PO nucleotides, such as, but not limited to:




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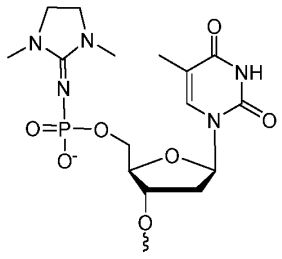
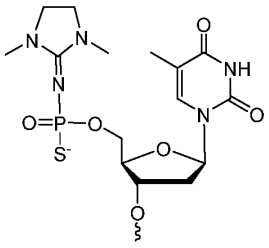
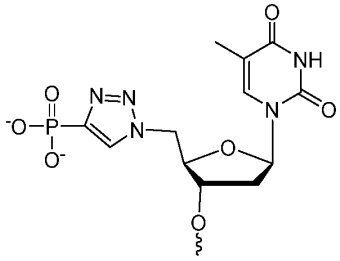
(b) 5' VP nucleotides, such as, but not limited to:



;

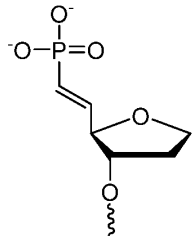
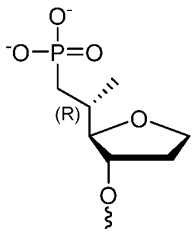
(c) 5' MeP nucleotides, such as, but not limited to:



;

(d) 5' PN and 5' triazole-P nucleotides, such as, but not limited to:




;

(e) 5' abasic VP and 5' abasic MeP nucleotides, such as, but not limited to:



. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In some embodiments, a ds oligonucleotide targeting INHBE comprises one or more of:

(1) a guide strand comprising backbone non-negatively charged internucleotidic linkage in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction;

(2) a guide strand comprising backbone non-negatively charged internucleotidic linkage in the Rp configuration between the +10 nucleotide and the immediately downstream (+11) nucleotide, i.e., in the 3' direction;

(3) a guide strand comprising backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream, i.e., in the 5' direction, (N-2) nucleotide;

(4) a guide strand comprising backbone phosphorothioate chiral centers in Rp, Sp, or alternating configurations between the 5' terminal (+1) nucleotide and the immediately downstream, i.e., in the 3' direction, (+2) nucleotide and between the +2 nucleotide and the immediately downstream (+3) nucleotide;

(5) a guide strand comprising one or more backbone phosphorothioate chiral centers upstream, i.e., in the 5' direction, relative to backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide, where the upstream backbone phosphorothioate chiral centers are in Rp or Sp configuration;

(6) a guide strand comprising one or more backbone phosphorothioate chiral centers in Rp or Sp configuration between the N-2 nucleotide and the immediately upstream (N-3) nucleotide, i.e., in the 5' direction;

(7) a guide strand comprising a 5' terminal modification, e.g. 5' phosphate modification, e.g. 5' triazole phosphate modification;

wherein the ds oligonucleotide further comprises one or more of:

(1) a guide strand where one or both of the 5' and 3' terminal dinucleotides are ***not*** linked by non-negatively charged internucleotidic linkages, i.e., the guide strand comprises one more non-negatively charged internucleotidic linkages downstream, i.e., in the 3' direction, relative to the linkage between the 5' terminal dinucleotide and/or

upstream, i.e., in the 5' direction, relative to the linkage between the 3' terminal dinucleotide;

(2) a guide strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide;

(3) a guide strand where an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between the third (+3) and fourth (+4) nucleotides, relative to the 5' terminal nucleotide, of the guide strand and/or between the tenth (+10) and eleventh (+11) nucleotides, relative to the 5' terminal nucleotide;

(4) a passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs upstream, i.e., in the 5' direction, relative to the central nucleotide of the passenger strand;

(5) Passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs downstream, i.e., in the 3' direction, relative to the central nucleotide of the passenger strand, and

wherein the ds oligonucleotide further comprises a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide or passenger strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In some embodiments, a ds oligonucleotide targeting INHBE comprises non-naturally occurring internucleotidic linkages, e.g., neutral internucleotidic linkages, which can, in certain embodiments, be used to link one or more molecules to the double-stranded oligonucleotides described herein. In certain embodiments, such linked molecules can facilitate targeting and/or delivery of the double-stranded oligonucleotide. For example, but not limitation, such linked molecules an include lipophilic molecules. In certain embodiments, the linked molecule is a

molecule comprising one or more GalNac moieties. In certain embodiments, the linked molecule is a receptor. In certain embodiments, the linked molecule is a receptor ligand.

In certain embodiments, the present disclosure provides technologies (*e.g.*, compounds, methods, etc.) for improving oligonucleotide stability while maintaining or increasing activity, including compositions of improved-stability oligonucleotides.

In certain embodiments, the present disclosure provides technologies for incorporating various additional chemical moieties into ds oligonucleotides. In certain embodiments, the present disclosure provides, for example, reagents and methods for introducing additional chemical moieties through nucleobases (*e.g.*, by covalent linkage, optionally via a linker, to a site on a nucleobase).

In certain embodiments, the present disclosure provides technologies, e.g., ds oligonucleotide compositions and methods thereof, that achieve allele-specific suppression, wherein transcripts from one allele of a particular target gene is selectively knocked down relative to at least one other allele of the same gene.

Among other things, the present disclosure provides structural elements, technologies and/or features that can be incorporated into ds oligonucleotides and can impart or tune one or more properties thereof (*e.g.*, relative to an otherwise identical ds oligonucleotide lacking the relevant technology or feature). In certain embodiments, the present disclosure documents that one or more provided technologies and/or features can usefully be incorporated into ds oligonucleotides of various sequences.

In certain embodiments, the present disclosure demonstrates that certain provided structural elements, technologies and/or features are particularly useful for ds oligonucleotides that participate in and/or direct RNAi mechanisms (*e.g.*, RNAi agents). Regardless, however, the teachings of the present disclosure are not limited to ds oligonucleotides that participate in or operate via any particular mechanism.

In certain embodiments, the present disclosure pertains to any ds oligonucleotide, useful for any purpose, which operates through any mechanism, and which comprises any sequence, structure or format (or portion thereof) described herein.

In some embodiments, a ds oligonucleotide targeting INHBE comprises a guide strand comprising backbone non-negatively charged internucleotidic linkage in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction; and one or more of:

(1) a guide strand comprising backbone non-negatively charged internucleotidic linkage in the Rp configuration between the +10 nucleotide and the immediately downstream (+11) nucleotide, i.e., in the 3' direction;

(2) a guide strand comprising backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream, i.e., in the 5' direction, (N-2) nucleotide;

(3) a guide strand comprising backbone phosphorothioate chiral centers in Rp, Sp, or alternating configurations between the 5' terminal (+1) nucleotide and the immediately downstream, i.e., in the 3' direction, (+2) nucleotide and between the +2 nucleotide and the immediately downstream (+3) nucleotide;

(4) a guide strand comprising one or more backbone phosphorothioate chiral centers upstream, i.e., in the 5' direction, relative to backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide, where the upstream backbone phosphorothioate chiral centers are in Rp or Sp configuration;

(5) a guide strand comprising one or more backbone phosphorothioate chiral centers in Rp or Sp configuration between the N-2 nucleotide and the immediately upstream (N-3) nucleotide, i.e. in the 5' direction; (1) a guide strand comprising backbone non-negatively charged internucleotidic linkage in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction;

(6) a guide strand comprising a 5' terminal modification, e.g. 5' phosphate modification, e.g. 5' triazole phosphate modification.

In some embodiments, a ds oligonucleotide targeting INHBE comprises a guide strand comprising backbone non-negatively charged internucleotidic linkage in the Rp configuration between the +10 nucleotide and the immediately downstream (+11) nucleotide, i.e., in the 3' direction; and one or more of:

(1) a guide strand comprising backbone non-negatively charged internucleotidic linkage in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction;

(2) a guide strand comprising backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream, i.e., in the 5' direction, (N-2) nucleotide;

(3) a guide strand comprising backbone phosphorothioate chiral centers in Rp, Sp, or alternating configurations between the 5' terminal (+1) nucleotide and the immediately downstream, i.e., in the 3' direction, (+2) nucleotide and between the +2 nucleotide and the immediately downstream (+3) nucleotide;

(4) a guide strand comprising one or more backbone phosphorothioate chiral centers upstream, i.e., in the 5' direction, relative to backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide, where the upstream backbone phosphorothioate chiral centers are in Rp or Sp configuration;

(5) a guide strand comprising one or more backbone phosphorothioate chiral centers in Rp or Sp configuration between the N-2 nucleotide and the immediately upstream (N-3) nucleotide, i.e., in the 5' direction;

(6) a guide strand comprising a 5' terminal modification, e.g. 5' phosphate modification, e.g. 5' triazole phosphate modification.

In some embodiments, a ds oligonucleotide targeting INHBE comprises backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide, and one or more of:

(1) a guide strand comprising backbone non-negatively charged internucleotidic linkage in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction;

(2) a guide strand comprising backbone non-negatively charged internucleotidic linkage in the Rp configuration between the +10 nucleotide and the immediately downstream (+11) nucleotide, i.e., in the 3' direction;

(3) a guide strand comprising backbone phosphorothioate chiral centers in Rp, Sp, or alternating configurations between the 5' terminal (+1) nucleotide and the immediately

downstream, i.e., in the 3' direction, (+2) nucleotide and between the +2 nucleotide and the immediately downstream (+3) nucleotide;

(4) a guide strand comprising one or more backbone phosphorothioate chiral centers upstream, i.e., in the 5' direction, relative to backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide, where the upstream backbone phosphorothioate chiral centers are in Rp or Sp configuration;

(5) a guide strand comprising one or more backbone phosphorothioate chiral centers in Rp or Sp configuration between the N-2 nucleotide and the immediately upstream (N-3) nucleotide, i.e., in the 5' direction;

(6) a guide strand comprising a 5' terminal modification, e.g. 5' phosphate modification, e.g. 5' triazole phosphate modification;

wherein the ds oligonucleotide further comprises a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises 0-n Rp, Sp, or stereorandom non-negatively charged internucleotidic linkages, where n is about 1 to 49. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide or passenger strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In some embodiments, a ds oligonucleotide targeting INHBE comprises backbone phosphorothioate chiral centers in Rp, Sp, or alternating configurations between the 5' terminal (+1) nucleotide and the immediately downstream (+2) nucleotide and between the +2 nucleotide and the immediately downstream (+3) nucleotide, and one or more of:

(1) a guide strand comprising backbone non-negatively charged internucleotidic linkage in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction;

(2) a guide strand comprising backbone non-negatively charged internucleotidic linkage in the Rp configuration between the +10 nucleotide and the immediately downstream (+11) nucleotide, i.e., in the 3' direction;

(3) a guide strand comprising backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream, i.e., in the 5' direction, (N-2) nucleotide;

(4) a guide strand comprising one or more backbone phosphorothioate chiral centers upstream, i.e., in the 5' direction, relative to backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide, where the upstream backbone phosphorothioate chiral centers are in Rp or Sp configuration;

(5) a guide strand comprising one or more backbone phosphorothioate chiral centers in Rp or Sp configuration between the N-2 nucleotide and the immediately upstream (N-3) nucleotide, i.e., in the 5' direction, and

wherein the ds oligonucleotide further comprises a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises 0-n Rp, Sp, or stereorandom non-negatively charged internucleotidic linkages, where n is about 1 to 49. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide or passenger strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In some embodiments, the present disclosure provides a ds oligonucleotide targeting INHBE comprising one or more backbone phosphorothioate chiral centers in Rp or Sp configuration upstream of backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the

penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide, and one or more of:

(1) a guide strand comprising backbone non-negatively charged internucleotidic linkage in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction;

(2) a guide strand comprising backbone non-negatively charged internucleotidic linkage in the Rp configuration between the +10 nucleotide and the immediately downstream (+11) nucleotide, i.e., in the 3' direction;

(3) a guide strand comprising backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream, i.e., in the 5' direction, (N-2) nucleotide;

(4) a guide strand comprising backbone phosphorothioate chiral centers in Rp, Sp, or alternating configurations between the 5' terminal (+1) nucleotide and the immediately downstream, i.e., in the 3' direction, (+2) nucleotide and between the +2 nucleotide and the immediately downstream (+3) nucleotide;

(5) a guide strand comprising one or more backbone phosphorothioate chiral centers in Rp or Sp configuration between the N-2 nucleotide and the immediately upstream (N-3) nucleotide, i.e., in the 5' direction; and

wherein the ds oligonucleotide further comprises a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises 0-n Rp, Sp, or stereorandom non-negatively charged internucleotidic linkages, where n is about 1 to 49. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide or passenger strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In some embodiments, the guide strand comprises one or more Sp non-negatively charged internucleotidic linkage occurs between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction, and one or more of:

(1) a guide strand where one or both of the 5' and 3' terminal dinucleotides are ***not*** linked by non-negatively charged internucleotidic linkages, i.e., the guide strand comprises one more non-negatively charged internucleotidic linkages downstream, i.e., in the 3' direction, relative to the linkage between the 5' terminal dinucleotide and/or upstream, i.e., in the 5' direction, relative to the linkage between the 3' terminal dinucleotide;

(2) a guide strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide;

(3) a guide strand where an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between the third (+3) and fourth (+4) nucleotides, relative to the 5' terminal nucleotide, of the guide strand and/or between the tenth (+10) and eleventh (+11) nucleotides, relative to the 5' terminal nucleotide;

(4) a passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs upstream, i.e., in the 5' direction, relative to the central nucleotide of the passenger strand; and

(5) Passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs downstream, i.e., in the 3' direction, relative to the central nucleotide of the passenger strand.

In some embodiments, the guide strand comprises one or more Rp non-negatively charged internucleotidic linkage occurs between the +10 nucleotide and the immediately downstream (+11) nucleotide, i.e., in the 3' direction, and one or more of:

(1) a guide strand where one or both of the 5' and 3' terminal dinucleotides are ***not*** linked by non-negatively charged internucleotidic linkages, i.e., the guide strand comprises one more non-negatively charged internucleotidic linkages downstream, i.e., in the 3' direction, relative to the linkage between the 5' terminal dinucleotide and/or

upstream, i.e., in the 5' direction, relative to the linkage between the 3' terminal dinucleotide;

(2) a guide strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide;

(3) a guide strand where an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between the third (+3) and fourth (+4) nucleotides, relative to the 5' terminal nucleotide, of the guide strand and/or between the tenth (+10) and eleventh (+11) nucleotides, relative to the 5' terminal nucleotide;

(4) a passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs upstream, i.e., in the 5' direction, relative to the central nucleotide of the passenger strand; and

(5) Passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs downstream, i.e., in the 3' direction, relative to the central nucleotide of the passenger strand.

In some embodiments, the guide strand comprises one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between the second (+2) and third (+3) nucleotides, relative to the 5' terminal nucleotide, of the guide strand and the internucleotidic linkage to the penultimate 3' (N-1) nucleotide, and one or more of:

(1) a guide strand where one or both of the 5' and 3' terminal dinucleotides are ***not*** linked by non-negatively charged internucleotidic linkages, i.e., the guide strand comprises one more non-negatively charged internucleotidic linkages downstream, i.e., in the 3' direction, relative to the linkage between the 5' terminal dinucleotide and/or upstream, i.e., in the 5' direction, relative to the linkage between the 3' terminal dinucleotide;

(2) a guide strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide;

(3) a guide strand where an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between the third (+3) and fourth (+4) nucleotides, relative to the 5' terminal nucleotide, of the guide strand and/or between the tenth (+10) and eleventh (+11) nucleotides, relative to the 5' terminal nucleotide;

(4) a passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs upstream, i.e., in the 5' direction, relative to the central nucleotide of the passenger strand; and

(5) Passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs downstream, i.e., in the 3' direction, relative to the central nucleotide of the passenger strand, and

wherein the ds oligonucleotide further comprises a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises 0-n Rp, Sp, or stereorandom non-negatively charged internucleotidic linkages, where n is about 1 to 49. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide or passenger strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In some embodiments, the guide strand comprises backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide, and one or more of:

(1) a guide strand where one or both of the 5' and 3' terminal dinucleotides are ***not*** linked by non-negatively charged internucleotidic linkages, i.e., the guide strand comprises one more non-negatively charged internucleotidic linkages downstream, i.e., in the 3' direction, relative to the linkage between the 5' terminal dinucleotide and/or upstream, i.e., in the 5' direction, relative to the linkage between the 3' terminal dinucleotide;

(2) a guide strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide;

(3) a guide strand where an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between the third (+3) and fourth (+4) nucleotides, relative to the 5' terminal nucleotide, of the guide strand and/or between the tenth (+10) and eleventh (+11) nucleotides, relative to the 5' terminal nucleotide;

(4) a passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs upstream, i.e., in the 5' direction, relative to the central nucleotide of the passenger strand; and

(5) Passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs downstream, i.e., in the 3' direction, relative to the central nucleotide of the passenger strand, and

wherein the ds oligonucleotide further comprises a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises one or more backbone phosphorothioate chiral centers in Rp or Sp configuration. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide or passenger strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In some embodiments, the guide strand comprises backbone phosphorothioate chiral centers in Rp, Sp, or alternating configurations between the 5' terminal (+1) nucleotide and the immediately downstream (+2) nucleotide and between the +2 nucleotide and the immediately downstream (+3) nucleotide, and one or more of:

(1) a guide strand where one or both of the 5' and 3' terminal dinucleotides are ***not*** linked by non-negatively charged internucleotidic linkages, i.e., the guide strand comprises one more non-negatively charged internucleotidic linkages downstream, i.e.,

in the 3' direction, relative to the linkage between the 5' terminal dinucleotide and/or upstream, i.e., in the 5' direction, relative to the linkage between the 3' terminal dinucleotide;

(2) a guide strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide;

(3) a guide strand where an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between the third (+3) and fourth (+4) nucleotides, relative to the 5' terminal nucleotide, of the guide strand and/or between the tenth (+10) and eleventh (+11) nucleotides, relative to the 5' terminal nucleotide;

(4) a passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs upstream, i.e., in the 5' direction, relative to the central nucleotide of the passenger strand; and

(5) Passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs downstream, i.e., in the 3' direction, relative to the central nucleotide of the passenger strand, and

wherein the ds oligonucleotide further comprises a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises one or more backbone chiral centers in Rp or Sp configuration. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide or passenger strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage. In certain of the embodiments disclosed herein, the backbone phosphorothioate chiral centers are in Rp configurations between the 5' terminal (+1) nucleotide and the immediately downstream (+2) nucleotide and between the +2 nucleotide and the immediately downstream (+3) nucleotide. In certain embodiments described herein, the backbone phosphorothioate chiral

centers are in Sp configurations between the 5' terminal (+1) nucleotide and the immediately downstream (+2) nucleotide and between the +2 nucleotide and the immediately downstream (+3) nucleotide. In certain embodiments, backbone phosphorothioate chiral centers in Rp and Sp configurations, respectively, between the 5' terminal (+1) nucleotide and the immediately downstream (+2) nucleotide and between the +2 nucleotide and the immediately downstream (+3) nucleotide. In certain embodiments described herein, the backbone phosphorothioate chiral centers are in Sp, Rp configurations, respectively, between the 5' terminal (+1) nucleotide and the immediately downstream (+2) nucleotide and between the +2 nucleotide and the immediately downstream (+3) nucleotide.

In some embodiments, the guide strand comprises one or more backbone phosphorothioate chiral centers in Rp or Sp configuration upstream of backbone chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide, and one or more of:

(1) a guide strand where one or both of the 5' and 3' terminal dinucleotides are ***not*** linked by non-negatively charged internucleotidic linkages, i.e., the guide strand comprises one more non-negatively charged internucleotidic linkages downstream, i.e., in the 3' direction, relative to the linkage between the 5' terminal dinucleotide and/or upstream, i.e., in the 5' direction, relative to the linkage between the 3' terminal dinucleotide;

(2) a guide strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide;

(3) a guide strand where an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between the third (+3) and fourth (+4) nucleotides, relative to the 5' terminal nucleotide, of the guide strand and/or between the tenth (+10) and eleventh (+11) nucleotides, relative to the 5' terminal nucleotide;

(4) a passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs upstream, i.e., in the 5' direction, relative to the central nucleotide of the passenger strand; and

(5) Passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs downstream, i.e., in the 3' direction, relative to the central nucleotide of the passenger strand, and

wherein the ds oligonucleotide further comprises a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises one or more backbone chiral centers in Rp or Sp configuration. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide or passenger strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In some embodiments, the guide strand comprises one or more backbone phosphorothioate chiral centers in Rp or Sp configuration between the 5' terminal (+1) nucleotide and the immediately downstream (+2) nucleotide and between the (+2) nucleotide and the immediately downstream (+3) nucleotide, as well as between one or both of: (a) the (+3) nucleotide and the (+4) nucleotide; and (b) the (+5) nucleotide and the (+6) nucleotide, and one or more of:

(1) a guide strand where one or both of the 5' and 3' terminal dinucleotides are ***not*** linked by non-negatively charged internucleotidic linkages, i.e., the guide strand comprises one more non-negatively charged internucleotidic linkages downstream, i.e., in the 3' direction, relative to the linkage between the 5' terminal dinucleotide and/or upstream, i.e., in the 5' direction, relative to the linkage between the 3' terminal dinucleotide;

(2) a guide strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide;

(3) a guide strand where an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between the third (+3) and fourth (+4) nucleotides,

relative to the 5' terminal nucleotide, of the guide strand and/or between the tenth (+10) and eleventh (+11) nucleotides, relative to the 5' terminal nucleotide;

(4) a passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs upstream, i.e., in the 5' direction, relative to the central nucleotide of the passenger strand; and

(5) Passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs downstream, i.e., in the 3' direction, relative to the central nucleotide of the passenger strand, and

wherein the ds oligonucleotide further comprises a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises one or more backbone chiral centers in Rp or Sp configuration. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide or passenger strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In some embodiments, the guide strand comprises one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide, a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises one or more backbone chiral centers in Rp or Sp configuration.

In certain embodiments, the guide strand comprises backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide, a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises 0-n Rp, Sp, or stereorandom non-negatively charged

internucleotidic linkages, where n is about 1 to 49 and one or more backbone chiral centers in Rp or Sp configuration.

In certain embodiments, the guide strand comprises backbone phosphorothioate chiral centers in Rp, Sp, or alternating configurations between the 5' terminal (+1) nucleotide and the immediately downstream (+2) nucleotide and between the +2 nucleotide and the immediately downstream (+3) nucleotide, a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises 0-n Rp, Sp, or stereorandom non-negatively charged internucleotidic linkages, where n is about 1 to 49 and one or more backbone chiral centers in Rp or Sp configuration. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide or passenger strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In certain embodiments, the guide strand comprises one or more backbone phosphorothioate chiral centers in Rp or Sp configuration upstream of backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide, a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises 0-n Rp, Sp, or stereorandom non-negatively charged internucleotidic linkages, where n is about 1 to 49 and one or more backbone chiral centers in Rp or Sp configuration. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In certain embodiments, the guide strand comprises one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two

adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide, a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage, and the passenger strand comprises 0-n Rp, Sp, or stereorandom non-negatively charged internucleotidic linkages, where n is about 1 to 49 and one or more backbone chiral centers in Rp or Sp configuration. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In certain embodiments, internucleotidic linkages of an oligonucleotide comprise or consist of 1-5, 1-10, 1-15, 1-20, 1-25, 1-30, 1-40, 1-50, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more chirally controlled internucleotidic linkages. In certain embodiments, the present disclosure provides a dsRNAi oligonucleotide composition wherein the dsRNAi oligonucleotides comprise at least one chirally controlled internucleotidic linkage. In certain embodiments, the present disclosure provides a dsRNAi oligonucleotide composition wherein the dsRNAi oligonucleotides are stereorandom or not chirally controlled. In certain embodiments, in a dsRNAi oligonucleotide, at least one internucleotidic linkage is stereorandom and at least one internucleotidic linkage is chirally controlled.

In certain embodiments, internucleotidic linkages of an oligonucleotide comprise or consist of one or more neutrally charged internucleotidic linkages.

INHBE

In some embodiments, INHBE refers to a gene or a gene product thereof (including but not limited to, a nucleic acid, including but not limited to a DNA or RNA, a transcript, a protein encoded thereby; can be from any form of INHBE, e.g., wide-type or mutant alleles) from any species. In some embodiments, it refers to the gene and product thereof in human. In some embodiments, it refers to the gene and product thereof in a non-human primate. Various INHBE sequences, including variants thereof, from human, mouse, rat, monkey, etc., are readily available to those of skill in the art. In some embodiments, INHBE is a human or mouse INHBE, which is wild-type or mutant. It has been reported that INHBE can have a number of

functions. Various technologies, e.g., assays, cells, animal models, etc., have also been reported and can be utilized for characterization and/or assessment of provided technologies (e.g., oligonucleotides, compositions, methods, etc.) in accordance with the present disclosure.

In some embodiments, a INHBE gene, transcript (e.g., mRNA before or after splicing), or protein variant or isoform comprises a mutation. In some embodiments, a INHBE gene, transcript or protein is or a transcription or translation product of an alternatively spliced variant or isoform.

INHBE-Associated Conditions, disorders, or diseases

Various conditions, disorders, or diseases are reported to be associated with INHBE. Generally, a disease, disorder, or condition is associated with INHBE if the presence, level, activity, and/or form of INHBE and/or products (e.g., transcripts, encoded proteins, etc.) thereof correlates with incidence of and/or susceptibility to the disease, disorder, or condition (e.g., across a relevant population). In some embodiments, a condition, disorder, or disease associated with INHBE may be treated and/or prevented by reducing expression, level and/or activity of INHBE transcripts and/or proteins.

Various INHBE-associated conditions, disorders, or diseases are reported. In some embodiments, an INHBE-associated condition, disorder, or disease is metabolic syndromes such as heart diseases, type 2 and type 1 diabetes, kidney diseases, and obesity. In some embodiments, an INHBE-associated condition, disorder, or disease is type 2 diabetes. In some embodiments, an INHBE-associated condition, disorder, or disease is obesity.

Among other things, provided technologies are useful for treating or preventing a condition, disorder, or disease associated with INHBE, including, but not limited to, metabolic disorders, e.g., metabolic syndrome, and related diseases, e.g., obesity, cardiovascular disease, diabetes, and hypertension. In some embodiments, the present disclosure pertains to the use of a ds oligonucleotide targeting INHBE or a composition thereof in the treatment of a INHBE-associated disorder, disease or condition, including, but not limited to, metabolic disorders, e.g., metabolic syndrome, and related diseases, e.g., obesity, cardiovascular disease, diabetes, and hypertension.

In some embodiments, treatment or prevention with provided technologies reduces rate of INHBE production and reduces or halts or reverses accumulation of INHBE. In some embodiments, treatment or prevention with provided technologies increases the rate of weight loss or otherwise allows for control of body weight.

As appreciated by those skilled in the art, mechanisms, genotypes, symptoms,

biomarkers, etc. of such conditions, disorders, or diseases may be utilized in accordance with the present disclosure to characterize/assess provided technologies.

Double Stranded Oligonucleotides

Among other things, the present disclosure provides ds oligonucleotides of various designs, which may comprise various nucleobases and patterns thereof, sugars and patterns thereof, internucleotidic linkages and patterns thereof, and/or additional chemical moieties and patterns thereof as described in the present disclosure. In some embodiments, provided ds oligonucleotides targeting INHBE can direct a decrease in the expression, level and/or activity of a INHBE gene and/or one or more of its products (e.g., transcripts, mRNA, proteins, etc.). In some embodiments, provided ds oligonucleotides targeting INHBE can direct a decrease in the expression, level and/or activity of a INHBE gene and/or one or more of its products in a cell of a subject or patient. In some embodiments, a cell normally expresses INHBE or produces INHBE protein. In some embodiments, provided ds oligonucleotides targeting INHBE can direct a decrease in the expression, level and/or activity of a INHBE target gene or a gene product and has a base sequence which consists of, comprises, or comprises a portion (e.g., a span of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more contiguous bases) of the base sequence of a ds oligonucleotide targeting INHBE disclosed herein, wherein each T can be independently substituted with U and *vice versa*, and the ds oligonucleotide comprises at least one non-naturally-occurring modification of a base, sugar and/or internucleotidic linkage.

In some embodiments, ds oligonucleotides targeting INHBE can direct a decrease in the expression, level and/or activity of a target gene, e.g., a INHBE target gene, or a product thereof. In some embodiments, ds oligonucleotides targeting INHBE can direct a decrease in the expression, level and/or activity of a INHBE target gene or a product thereof via RNase H-mediated knockdown. In some embodiments, ds oligonucleotides targeting INHBE can direct a decrease in the expression, level and/or activity of a INHBE target gene or a product thereof by sterically blocking translation after binding to a INHBE target gene mRNA, and/or by altering or interfering with mRNA splicing. Regardless, however, the present disclosure is not limited to any particular mechanism. In some embodiments, the present disclosure provides oligonucleotides, compositions, methods, etc., capable of operating via double-stranded RNA interference.

In some embodiments, a ds oligonucleotide targeting INHBE is capable of mediating a decrease in the expression, level and/or activity of INHBE. In some embodiments, a ds oligonucleotide targeting INHBE is capable of mediating a decrease in the level of INHBE

proteins. In some embodiments, a ds oligonucleotide targeting INHBE is capable of mediating a decrease in the level of INHBE proteins.

In some embodiments, a ds oligonucleotide targeting INHBE is capable of mediating a decrease in the expression, level and/or activity of INHBE via a mechanism involving mRNA degradation.

In some embodiments, a ds oligonucleotide targeting INHBE is capable of mediating a decrease in the expression, level and/or activity of more than one INHBE allele.

In some embodiments, the present disclosure pertains to a method of treatment of a INHBE-associated disease, disorder or condition, wherein INHBE is expressed, comprising the step of administering a therapeutically effective amount of a ds oligonucleotide targeting INHBE capable of mediating a decrease in the expression, level and/or activity of INHBE. In some embodiments, multiple forms, e.g., alleles, of INHBE may exist, and provided technologies can reduce expression, level and/or activity of two or more or all of the forms and products thereof.

In some embodiments, the present disclosure pertains to a method of treatment of a INHBE-associated disease, disorder or condition, comprising the step of administering a therapeutic amount of a ds oligonucleotide targeting INHBE capable of mediating a decrease in the expression, level and/or activity of INHBE.

In some embodiments, a ds oligonucleotide targeting INHBE is capable of mediating a decrease in the expression, level and/or activity of INHBE via a mechanism involving splicing modulation, e.g., exon skipping.

In some embodiments, a ds oligonucleotide targeting INHBE comprises a structural element or a portion thereof described herein, e.g., in Table 1. In some embodiments, a ds oligonucleotide targeting INHBE comprises a base sequence (or a portion thereof) described herein, wherein each T can be independently substituted with U and *vice versa*, a chemical modification or a pattern of chemical modifications (or a portion thereof), and/or a format or a portion thereof described herein. In some embodiments, a ds oligonucleotide targeting INHBE has a base sequence which comprises the base sequence (or a portion thereof) wherein each T can be independently substituted with U, pattern of chemical modifications (or a portion thereof), and/or a format of an oligonucleotide disclosed herein, e.g., in Table 1, or otherwise disclosed herein. In some embodiments, such oligonucleotides, e.g., ds oligonucleotides targeting INHBE, reduce expression, level and/or activity of a gene, e.g., a INHBE gene, or a gene product thereof.

Among other things, ds oligonucleotides targeting INHBE can hybridize to their target

nucleic acids (e.g., pre-mRNA, mature mRNA, etc.). For example, in some embodiments, a ds oligonucleotide targeting INHBE can hybridize to a INHBE nucleic acid derived from a DNA strand (either strand of the INHBE gene). In some embodiments, a ds oligonucleotide targeting INHBE can hybridize to a INHBE transcript. In some embodiments, a ds oligonucleotide targeting INHBE can hybridize to a INHBE nucleic acid in any stage of RNA processing, including but not limited to a pre-mRNA or a mature mRNA. In some embodiments, a ds oligonucleotide targeting INHBE can hybridize to any element of a INHBE nucleic acid or its complement, including but not limited to: a promoter region, an enhancer region, a transcriptional stop region, a translational start signal, a translation stop signal, a coding region, a non-coding region, an exon, an intron, an intron/exon or exon/intron junction, the 5' UTR, or the 3' UTR. In some embodiments, ds oligonucleotides targeting INHBE can hybridize to their targets with no more than 2 mismatches. In some embodiments, ds oligonucleotides targeting INHBE can hybridize to their targets with no more than one mismatch. In some embodiments, ds oligonucleotides targeting INHBE can hybridize to their targets with no mismatches (e.g., when all C-G and/or A-T/U base paring).

In some embodiments, an oligonucleotide can hybridize to two or more variants of transcripts. In some embodiments, a ds oligonucleotide targeting INHBE can hybridize to two or more or all variants of INHBE transcripts. In some embodiments, a ds oligonucleotide targeting INHBE can hybridize to two or more or all variants of INHBE transcripts derived from the sense strand.

In some embodiments, a INHBE target of a ds oligonucleotide targeting INHBE is a INHBE RNA which is not a mRNA.

In some embodiments, oligonucleotides, e.g., ds oligonucleotides targeting INHBE, contain increased levels of one or more isotopes. In some embodiments, oligonucleotides, e.g., ds oligonucleotides targeting INHBE, are labeled, e.g., by one or more isotopes of one or more elements, e.g., hydrogen, carbon, nitrogen, etc. In some embodiments, oligonucleotides, e.g., ds oligonucleotides targeting INHBE, in provided compositions, e.g., oligonucleotides of a plurality of a composition, comprise base modifications, sugar modifications, and/or internucleotidic linkage modifications, wherein the oligonucleotides contain an enriched level of deuterium. In some embodiments, oligonucleotides, e.g., ds oligonucleotides targeting INHBE, are labeled with deuterium (replacing $^{-1}$H with $^{-2}$H) at one or more positions. In some embodiments, one or more ^{1}H of an oligonucleotide chain or any moiety conjugated to the oligonucleotide chain (e.g., a targeting moiety, etc.) is substituted with ^{2}H. Such oligonucleotides can be used in compositions and methods described herein.

In some embodiments, the present disclosure provides an oligonucleotide composition comprising a plurality of oligonucleotides which:

1) have a common base sequence complementary to a target sequence (e.g., a INHBE target sequence) in a transcript; and

2) comprise one or more modified sugar moieties and/or modified internucleotidic linkages.

In some embodiments, ds oligonucleotides targeting INHBE having a common base sequence may have the same pattern of nucleoside modifications, e.g., sugar modifications, base modifications, etc. In some embodiments, a pattern of nucleoside modifications may be represented by a combination of locations and modifications. In some embodiments, a pattern of backbone linkages comprises locations and types (e.g., phosphate, phosphorothioate, substituted phosphorothioate, etc.) of each internucleotidic linkage.

In some embodiments, oligonucleotides of a plurality, e.g., in provided compositions, are of the same oligonucleotide type. In some embodiments, oligonucleotides of an oligonucleotide type have a common pattern of sugar modifications. In some embodiments, oligonucleotides of an oligonucleotide type have a common pattern of base modifications. In some embodiments, oligonucleotides of an oligonucleotide type have a common pattern of nucleoside modifications. In some embodiments, oligonucleotides of an oligonucleotide type have the same constitution. In some embodiments, oligonucleotides of an oligonucleotide type are identical. In some embodiments, oligonucleotides of a plurality are identical. In some embodiments, oligonucleotides of a plurality share the same constitution.

In some embodiments, as exemplified herein, ds oligonucleotides targeting INHBE are chiral controlled, comprising one or more chirally controlled internucleotidic linkages. In some embodiments, ds oligonucleotides targeting INHBE are stereochemically pure. In some embodiments, ds oligonucleotides targeting INHBE are substantially separated from other stereoisomers.

In some embodiments, ds oligonucleotides targeting INHBE comprise one or more modified nucleobases, one or more modified sugars, and/or one or more modified internucleotidic linkages.

In some embodiments, ds oligonucleotides targeting INHBE comprise one or more modified sugars. In some embodiments, oligonucleotides of the present disclosure comprise one or more modified nucleobases. Various modifications can be introduced to a sugar and/or nucleobase in accordance with the present disclosure. For example, in some embodiments, a modification is a modification described in US 9006198. In some embodiments, a modification

is a modification described in US 9394333, US 9744183, US 9605019, US 9598458, US 9982257, US 10160969, US 10479995, US 2020/0056173, US 2018/0216107, US 2019/0127733, US 10450568, US 2019/0077817, US 2019/0249173, US 2019/0375774, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, and/or WO 2020/191252, the sugar, base, and internucleotidic linkage modifications of each of which are independently incorporated herein by reference.

As used in the present disclosure, in some embodiments, "one or more" is 1-200, 1-150, 1-100, 1-90, 1-80, 1-70, 1-60, 1-50, 1-40, 1-30, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25. In some embodiments, "one or more" is one. In some embodiments, "one or more" is two. In some embodiments, "one or more" is three. In some embodiments, "one or more" is four. In some embodiments, "one or more" is five. In some embodiments, "one or more" is six. In some embodiments, "one or more" is seven. In some embodiments, "one or more" is eight. In some embodiments, "one or more" is nine. In some embodiments, "one or more" is ten. In some embodiments, "one or more" is at least one. In some embodiments, "one or more" is at least two. In some embodiments, "one or more" is at least three. In some embodiments, "one or more" is at least four. In some embodiments, "one or more" is at least five. In some embodiments, "one or more" is at least six. In some embodiments, "one or more" is at least seven. In some embodiments, "one or more" is at least eight. In some embodiments, "one or more" is at least nine. In some embodiments, "one or more" is at least ten.

As used in the present disclosure, in some embodiments, "at least one" is 1-200, 1-150, 1-100, 1-90, 1-80, 1-70, 1-60, 1-50, 1-40, 1-30, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25. In some embodiments, "at least one" is one. In some embodiments, "at least one" is two. In some embodiments, "at least one" is three. In some embodiments, "at least one" is four. In some embodiments, "at least one" is five. In some embodiments, "at least one" is six. In some embodiments, "at least one" is seven. In some embodiments, "at least one" is eight. In some embodiments, "at least one" is nine. In some embodiments, "at least one" is ten.

In some embodiments, a ds oligonucleotide targeting INHBE is or comprises a ds oligonucleotide targeting INHBE described in Table 1.

As demonstrated in the present disclosure, in some embodiments, a provided oligonucleotide (e.g., a ds oligonucleotide targeting INHBE) is characterized in that, when it is contacted with the transcript in a knockdown system, knockdown of its target (e.g., a INHBE

transcript for a ds oligonucleotide targeting INHBE) is achieved.

In some embodiments, ds oligonucleotides are provided as salt forms. In some embodiments, ds oligonucleotides are provided as salts comprising negatively-charged internucleotidic linkages (e.g., phosphorothioate internucleotidic linkages, natural phosphate linkages, etc.) existing as their salt forms. In some embodiments, ds oligonucleotides are provided as pharmaceutically acceptable salts. In some embodiments, ds oligonucleotides are provided as metal salts. In some embodiments, oligonucleotides are provided as sodium salts. In some embodiments, ds oligonucleotides are provided as metal salts, e.g., sodium salts, wherein each negatively-charged internucleotidic linkage is independently in a salt form (e.g., for sodium salts, −O−P(O)(SNa)−O− for a phosphorothioate internucleotidic linkage, −O−P(O)(ONa)−O− for a natural phosphate linkage, etc.).

Double Stranded Oligonucleotide Base Sequences

In some embodiments, a ds oligonucleotide targeting INHBE comprises a base sequence described herein or a portion (e.g., a span of 5-50, 5-40, 5-30, 5-20, or 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 30 or at least 10, at least 15, contiguous nucleobases) thereof with 0-5 (e.g., 0, 1, 2, 3, 4 or 5) mismatches, wherein each T can be independently substituted with U and *vice versa*. In some embodiments, a ds oligonucleotide targeting INHBE comprises a base sequence described herein, or a portion thereof, wherein a portion is a span of at least 10 contiguous nucleobases, or a span of at least 15 contiguous nucleobases with 1-5 mismatches. In some embodiments, ds oligonucleotides targeting INHBE comprise a base sequence described herein, or a portion thereof, wherein a portion is a span of at least 10 contiguous nucleobases, or a span of at least 10 contiguous nucleobases with 1-5 mismatches, wherein each T can be independently substituted with U and *vice versa*. In some embodiments, base sequences of oligonucleotides comprise or consists of 10-50 (e.g., about or at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45; in some embodiments, at least 15; in some embodiments, at least 16; in some embodiments, at least 17; in some embodiments, at least 18; in some embodiments, at least 19; in some embodiments, at least 20; in some embodiments, at least 21; in some embodiments, at least 22; in some embodiments, at least 23; in some embodiments, at least 24; in some embodiments, at least 25) contiguous bases of a base sequence that is identical to or complementary to a base sequence of a INHBE gene or a transcript (e.g., mRNA) thereof (e.g., in an intron).

Base sequences of ds oligonucleotides targeting INHBE, as appreciated by those skilled

in the art, typically have sufficient length and complementarity to their targets, e.g., RNA transcripts (e.g., pre-mRNA, mature mRNA, etc.) to mediate target-specific knockdown. In some embodiments, the base sequence of a ds oligonucleotide targeting INHBE has a sufficient length and identity to a INHBE transcript target to mediate target-specific knockdown. In some embodiments, the ds oligonucleotide targeting INHBE is complementary to a portion of a INHBE transcript (a INHBE transcript target sequence). In some embodiments, the base sequence of a ds oligonucleotide targeting INHBE has 90% or more identity with the base sequence of an oligonucleotide disclosed in Table 1, wherein each T can be independently substituted with U and *vice versa*. In some embodiments, the base sequence of a ds oligonucleotide targeting INHBE has 95% or more identity with the base sequence of an oligonucleotide disclosed in Table 1, wherein each T can be independently substituted with U and *vice versa*. In some embodiments, the base sequence of a ds oligonucleotide targeting INHBE comprises a continuous span of 15 or more bases of an oligonucleotide disclosed in Table 1, wherein each T can be independently substituted with U and *vice versa*, except that one or more bases within the span are abasic (e.g., a nucleobase is absent from a nucleotide). In some embodiments, the base sequence of a ds oligonucleotide targeting INHBE comprises a continuous span of 19 or more bases of a ds oligonucleotide targeting INHBE disclosed herein, except that one or more bases within the span are abasic (e.g., a nucleobase is absent from a nucleotide). In some embodiments, the base sequence of a ds oligonucleotide targeting INHBE comprises a continuous span of 19 or more bases of an oligonucleotide disclosed herein, wherein each T can be independently substituted with U and *vice versa*, except for a difference in the 1 or 2 bases at the 5' end and/or 3' end of the base sequences.

In some embodiments, the present disclosure pertains to an oligonucleotide having a base sequence which comprises the base sequence of any oligonucleotide disclosed herein, wherein each T may be independently replaced with U and *vice versa*.

In some embodiments, the present disclosure pertains to an oligonucleotide having a base sequence which comprises at least 15 contiguous bases of the base sequence of any oligonucleotide disclosed herein, wherein each T may be independently replaced with U and *vice versa*.

In some embodiments, the present disclosure pertains to an oligonucleotide having a base sequence which is at least 90% identical to the base sequence of any oligonucleotide disclosed herein, wherein each T may be independently replaced with U and *vice versa*.

In some embodiments, the present disclosure pertains to an oligonucleotide having a base sequence which is at least 95% identical to the base sequence of any oligonucleotide

disclosed herein, wherein each T may be independently replaced with U and *vice versa*.

In some embodiments, a ds oligonucleotide targeting INHBE is selected from Table 1.

In some embodiments, the base sequence of a ds oligonucleotide targeting INHBE is complementary to that of a INHBE transcript or a portion thereof.

In some embodiments, the base sequence of a ds oligonucleotide targeting INHBE is complementary to a portion of a INHBE nucleic acid sequence, e.g., a INHBE gene sequence, a INHBE transcript, a INHBE mRNA sequence, etc. In some embodiments, a ds oligonucleotide targeting INHBE is identical to a portion of a INHBE nucleic acid sequence, e.g., a INHBE gene sequence, a INHBE transcript, a INHBE mRNA sequence, etc. In some embodiments, the base sequence of such a portion is characteristic of INHBE in that no other genomic or transcript sequences in a system contain the same sequence as the portion. In some embodiments, no other genomic or transcript sequences in a system contain a sequence that differs from such a portion at no more than 1 nucleobase. In some embodiments, no other genomic or transcript sequences in a system contain a sequence that differs from such a portion at no more than 2 nucleobases. In some embodiments, a portion of a gene that is complementary to an oligonucleotide is referred to as a target sequence of the oligonucleotide. In some embodiments, a system is or comprises a cell, sample, tissue, organ, or a species. For example, for oligonucleotides targeting human INHBE, a relevant species in many embodiments is human. In some embodiments, a system can be or comprises multiple species, e.g., when cross-species activities and/or properties are characterized and/or assessed. In some embodiments, such a portion is in an exon. In some embodiments, such a portion is in an intron. In some embodiments, such a portion spans an intron and an exon. In some embodiments, such a portion spans two exons. In some embodiments, such a portion is in a 5'-UTR region. In some embodiments, such a portion is in a 3'-UTR region.

In some embodiments, a ds oligonucleotide targeting INHBE targets two or more or all alleles (if multiple alleles exist in a relevant system) of INHBE. In some embodiments, an oligonucleotide reduces expressions, levels and/or activities of both wild-type INHBE and mutant INHBE, and/or transcripts and/or products thereof.

In some embodiments, base sequences of provided oligonucleotides are fully complementary to both human and a non-human primate (NHP) INHBE target sequences. In some embodiments, such sequences can be particularly useful as they can be readily assessed in both human and non-human primates.

In some embodiments, a ds oligonucleotide targeting INHBE comprises a base sequence or portion thereof described in the Tables, wherein each T may be independently

replaced with U and *vice versa*, and/or a sugar, nucleobase, and/or internucleotidic linkage modification and/or a pattern thereof described in Table 1, and/or an additional chemical moiety (in addition to an oligonucleotide chain, e.g., a target moiety, a lipid moiety, a carbohydrate moiety, etc.) described in Table 1.

In some embodiments, the terms "complementary," "fully complementary" and "substantially complementary" may be used with respect to the base matching between n oligonucleotide (e.g., a ds oligonucleotide targeting INHBE) base sequence and a target sequence (e.g., a INHBE target sequence), as will be understood by those skilled in the art from the context of their use. It is noted that substitution of T for U, or *vice versa*, generally does not alter the amount of complementarity. As used herein, an oligonucleotide that is "substantially complementary" to a target sequence is largely or mostly complementary but not 100% complementary. In some embodiments, a sequence (e.g., a ds oligonucleotide targeting INHBE) which is substantially complementary has 1, 2, 3, 4 or 5 mismatches when aligned to its target sequence. In some embodiments, a ds oligonucleotide targeting INHBE has a base sequence which is substantially complementary to a INHBE target sequence. In some embodiments, a ds oligonucleotide targeting INHBE has a base sequence which is substantially complementary to the complement of the sequence of a ds oligonucleotide targeting INHBE disclosed herein. As appreciated by those skilled in the art, in some embodiments, sequences of oligonucleotides need not be 100% complementary to their targets for the oligonucleotides to perform their functions (e.g., knockdown of target nucleic acids. Typically, when determining complementarity, A and T (or U) are complementary nucleobases and C and G are complementary nucleobases.

In some embodiments, the present disclosure provides a ds oligonucleotide targeting INHBE comprising a sequence found in an oligonucleotide described in a Table. In some embodiments, the present disclosure provides a ds oligonucleotide targeting INHBE comprising a sequence found in an oligonucleotide described in Table 1, wherein one or more U is independently and optionally replaced with T or vice versa. In some embodiments, a ds oligonucleotide targeting INHBE can comprise at least one T and/or at least one U. In some embodiments, the present disclosure provides a ds oligonucleotide targeting INHBE comprising a sequence found in an oligonucleotide described in a Table, wherein the said sequence has over 50% identity with the sequence of the oligonucleotide described in the Table. In some embodiments, the present disclosure provides a ds oligonucleotide targeting INHBE comprising the sequence of an oligonucleotide disclosed in Table 1. In some embodiments, the present disclosure provides a ds oligonucleotide targeting INHBE whose base sequence is

the sequence of an oligonucleotide disclosed in Table 1, wherein each T may be independently replaced with U and vice versa. In some embodiments, the present disclosure provides a ds oligonucleotide targeting INHBE comprising a sequence found in an oligonucleotide in Table 1, wherein the oligonucleotides have a pattern of backbone linkages, pattern of backbone chiral centers, and/or pattern of backbone phosphorus modifications of the same oligonucleotide or another oligonucleotide in Table 1.

Among other things, the present disclosure presents, in Table 1 and elsewhere, various ds oligonucleotides, each of which has a defined base sequence. In some embodiments, the present disclosure, the present disclosure provides an oligonucleotide whose base sequence which is, comprises, or comprises a portion of the base sequence of an oligonucleotide disclosed herein, e.g., in Table 1 herein, wherein each T may be independently replaced with U and vice versa. In some embodiments, the disclosure provides an oligonucleotide having a base sequence which is, comprises, or comprises a portion of the base sequence of an oligonucleotide disclosed herein, e.g., in Table 1, wherein each T may be independently replaced with U and vice versa, wherein the oligonucleotide further comprises a chemical modification, stereochemistry, format, an additional chemical moiety described herein (e.g., a targeting moiety, lipid moiety, carbohydrate moiety, etc.), and/or another structural feature.

In some embodiments, a "portion" (e.g., of a base sequence or a pattern of modifications) is at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 monomeric units long (e.g., for a base sequence, at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 bases long). In some embodiments, a "portion" of a base sequence is at least 5 bases long. In some embodiments, a "portion" of a base sequence is at least 10 bases long. In some embodiments, a "portion" of a base sequence is at least 15 bases long. In some embodiments, a "portion" of a base sequence is at least 16, 17, 18, 19 or 20 bases long. In some embodiments, a "portion" of a base sequence is at least 20 bases long. In some embodiments, a portion of a base sequence is 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or more contiguous (consecutive) bases. In some embodiments, a portion of a base sequence is 15 or more contiguous (consecutive) bases. In some embodiments, a portion of a base sequence is 16, 17, 18, 19 or 20 or more contiguous (consecutive) bases. In some embodiments, a portion of a base sequence is 20 or more contiguous (consecutive) bases.

In some embodiments, the present disclosure provides an oligonucleotide (e.g., a ds oligonucleotide targeting INHBE) whose base sequence is a base sequence of an oligonucleotide in Table 1 or a portion thereof, wherein each T may be independently replaced with U and vice versa. In some embodiments, the present disclosure provides a ds

oligonucleotide targeting INHBE of a sequence of an oligonucleotide in Table 1, wherein the oligonucleotide is capable of directing a decrease in the expression, level and/or activity of a INHBE gene or a gene product thereof. As appreciated by those skilled in the art, in provided base sequence, each U may be optionally and independently replaced by T or vice versa, and a sequence can comprise a mixture of U and T. In some embodiments, C may be optionally and independently replaced with 5mC.

In some embodiments, a portion is a span of at least 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 total nucleotides. In some embodiments, a portion is a span of at least 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 total nucleotides with 0-3 mismatches. In some embodiments, a portion is a span of at least 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 total nucleotides with 0-3 mismatches, wherein a span with 0 mismatches is complementary and a span with 1 or more mismatches is a non-limiting example of substantial complementarity. In some embodiments, a base comprises a portion characteristic of a nucleic acid (e.g., a gene) in that the portion is identical or complementary to a portion of the nucleic acid or a transcript thereof, and is not identical or complementary to a portion of any other nucleic acid (e.g., a gene) or a transcript thereof in the same genome. In some embodiments, a portion is characteristic of human INHBE.

In some embodiments, a provided oligonucleotide, e.g., a ds oligonucleotide targeting INHBE, has a length of no more than about 49, 45, 40, 30, 35, 25, or 23 total nucleotides as described herein. In some embodiments, wherein the sequence recited herein starts with a U or T at the 5'-end, the U can be deleted and/or replaced by another base. In some embodiments, an oligonucleotide has a base sequence which is or comprises or comprises a portion of the base sequence of an oligonucleotide in a Table, wherein each T may be independently replaced with U and vice versa, which has a format or a portion of a format disclosed herein.

In some embodiments, oligonucleotides, e.g., ds oligonucleotides targeting INHBE are stereorandom. In some embodiments, ds oligonucleotides targeting INHBE are chirally controlled. In some embodiments, a ds oligonucleotide targeting INHBE is chirally pure (or "stereopure", "stereochemically pure"), wherein the oligonucleotide exists as a single stereoisomeric form (in many cases a single diastereoisomeric (or "diastereomeric") form as multiple chiral centers may exist in an oligonucleotide, e.g., at linkage phosphorus, sugar carbon, etc.). As appreciated by those skilled in the art, a chirally pure oligonucleotide is separated from its other stereoisomeric forms (to the extent that some impurities may exist as chemical and biological processes, selectivities and/or purifications etc. rarely, if ever, go to absolute completeness). In a chirally pure oligonucleotide, each chiral center is independently

defined with respect to its configuration (for a chirally pure oligonucleotide, each internucleotidic linkage is independently stereodefined or chirally controlled). In contrast to chirally controlled and chirally pure oligonucleotides which comprise stereodefined linkage phosphorus, racemic (or "stereorandom", "non-chirally controlled") oligonucleotides comprising chiral linkage phosphorus, e.g., from traditional phosphoramidite oligonucleotide synthesis without stereochemical control during coupling steps in combination with traditional sulfurization (creating stereorandom phosphorothioate internucleotidic linkages), refer to a random mixture of various stereoisomers (typically diastereoisomers (or "diastereomers") as there are multiple chiral centers in an oligonucleotide; *e.g.*, from traditional oligonucleotide preparation using reagents containing no chiral elements other than those in nucleosides and linkage phosphorus). For example, for A*A*A wherein * is a phosphorothioate internucleotidic linkage (which comprises a chiral linkage phosphorus), a racemic oligonucleotide preparation includes four diastereomers [$2^2 = 4$, considering the two chiral linkage phosphorus, each of which can exist in either of two configurations (*S*p or *R*p)]: A *S A *S A, A *S A *R A, A *R A *S A, and A *R A *R A, wherein *S represents a *S*p phosphorothioate internucleotidic linkage and *R represents a *R*p phosphorothioate internucleotidic linkage. For a chirally pure oligonucleotide, e.g., A *S A *S A, it exists in a single stereoisomeric form and it is separated from the other stereoisomers (e.g., the diastereomers A *S A *R A, A *R A *S A, and A *R A *R A).

In some embodiments, ds oligonucleotides targeting INHBE comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more stereorandom internucleotidic linkages (mixture of *R*p and *S*p linkage phosphorus at the internucleotidic linkage, e.g., from traditional non-chirally controlled oligonucleotide synthesis). In some embodiments, ds oligonucleotides targeting INHBE comprise one or more (e.g., 1-50, 1-40, 1-30, 1-25, 1-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 or more) chirally controlled internucleotidic linkages (*R*p or *S*p linkage phosphorus at the internucleotidic linkage, e.g., from chirally controlled oligonucleotide synthesis). In some embodiments, an internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage is a stereorandom phosphorothioate internucleotidic linkage. In some embodiments, an internucleotidic linkage is a chirally controlled phosphorothioate internucleotidic linkage.

Among other things, the present disclosure provides technologies for preparing chirally controlled (in some embodiments, stereochemically pure) oligonucleotides. In some embodiments, oligonucleotides are stereochemically pure. In some embodiments, oligonucleotides of the present disclosure are about 5%-100%, 10%-100%, 20%-100%, 30%-

100%, 40%-100%, 50%-100%, 60%-100%, 70%-100%, 80-100%, 90-100%, 95-100%, 50%-90%, or about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99%, pure. In some embodiments, internucleotidic linkages of oligonucleotides comprise or consist of one or more (e.g., 1-50, 1-40, 1-30, 1-25, 1-20, 5-50, 5-40, 5-30, 5-25, 5-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 or more) chiral internucleotidic linkages, each of which independently has a diastereopurity of at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5%, typically at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5%. In some embodiments, oligonucleotides of the present disclosure, e.g., Ds oligonucleotides targeting INHBE, have a diastereopurity of $(DS)^{CIL}$, wherein DS is a diastereopurity as described in the present disclosure (e.g., 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5% or more) and CIL is the number of chirally controlled internucleotidic linkages (e.g., 1-50, 1-40, 1-30, 1-25, 1-20, 5-50, 5-40, 5-30, 5-25, 5-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 or more). In some embodiments, DS is 95%-100%. In some embodiments, each internucleotidic linkage is independently chirally controlled, and CIL is the number of chirally controlled internucleotidic linkages.

As examples, certain ds oligonucleotides targeting INHBE comprising certain example base sequences, nucleobase modifications and patterns thereof, sugar modifications and patterns thereof, internucleotidic linkages and patterns thereof, linkage phosphorus stereochemistry and patterns thereof, linkers, and/or additional chemical moieties are presented in Table 1, below. Among other things, oligonucleotides, e.g., those in Table 1, may be utilized to target a INHBE transcript, e.g., to reduce the level of a INHBE transcript and/or a product thereof.

In certain exemplary embodiments, the ds oligonucleotide targeting INHBE of the present disclosure comprises the base sequence, nucleobase modifications and patterns thereof, sugar modifications and patterns thereof, internucleotidic linkages and patterns thereof, linkage phosphorus stereochemistry and patterns thereof, linkers, and/or additional chemical moieties of: DSR-0104068, DSR-0104099, DSR-0104072, DSR-0104075, DSR-0104083, DSR-0104091, and DSR-0104071. In certain exemplary embodiments, a ds oligonucleotide targeting INHBE of the present disclosure comprising the base sequence, nucleobase modifications and patterns thereof, sugar modifications and patterns thereof, internucleotidic linkages and patterns thereof, linkage phosphorus stereochemistry and patterns thereof, linkers, and/or

additional chemical moieties of: DSR-0104068, DSR-0104099, DSR-0104072, DSR-0104075, DSR-0104083, DSR-0104091, and DSR-0104071. In certain exemplary embodiments, a ds oligonucleotide targeting INHBE of the present disclosure comprises a passenger strand comprising the base sequence, nucleobase modifications and patterns thereof, sugar modifications and patterns thereof, internucleotidic linkages and patterns thereof, linkage phosphorus stereochemistry and patterns thereof, linkers, and/or additional chemical moieties of DSR-0104068. In certain exemplary embodiments, a ds oligonucleotide targeting INHBE of the present disclosure comprises a guide strand comprising the base sequence, nucleobase modifications and patterns thereof, sugar modifications and patterns thereof, internucleotidic linkages and patterns thereof, linkage phosphorus stereochemistry and patterns thereof, linkers, and/or additional chemical moieties DSR-0104068, DSR-0104099, DSR-0104072, DSR-0104075, DSR-0104083, DSR-0104091, and DSR-0104071comprising the base sequence, nucleobase modifications and patterns thereof, sugar modifications and patterns thereof, internucleotidic linkages and patterns thereof, linkage phosphorus stereochemistry and patterns thereof, linkers, and/or additional chemical moieties of DSR-0104068.

In certain exemplary embodiments, a ds oligonucleotide targeting INHBE of the present disclosure comprising the base sequence, nucleobase modifications and patterns thereof, sugar modifications and patterns thereof, internucleotidic linkages and patterns thereof, linkage phosphorus stereochemistry and patterns thereof, linkers, and/or additional chemical moieties of DSR-0104068 comprising the base sequence, nucleobase modifications and patterns thereof, sugar modifications and patterns thereof.

In certain exemplary embodiments, a ds oligonucleotide targeting INHBE of the present disclosure comprising the base sequence, nucleobase modifications and patterns thereof, sugar modifications and patterns thereof, internucleotidic linkages and patterns thereof, linkage phosphorus stereochemistry and patterns thereof, linkers, and/or additional chemical moieties of DSR-0104099.

In certain exemplary embodiments, a ds oligonucleotide targeting INHBE of the present disclosure comprising the base sequence, nucleobase modifications and patterns thereof, sugar modifications and patterns thereof, internucleotidic linkages and patterns thereof, linkage phosphorus stereochemistry and patterns thereof, linkers, and/or additional chemical moieties of DSR-0104072.

In certain exemplary embodiments, a ds oligonucleotide targeting INHBE of the present disclosure comprising the base sequence, nucleobase modifications and patterns thereof, sugar modifications and patterns thereof, internucleotidic linkages and patterns thereof, linkage

phosphorus stereochemistry and patterns thereof, linkers, and/or additional chemical moieties of DSR-0104075.

In certain exemplary embodiments, a ds oligonucleotide targeting INHBE of the present disclosure comprising the base sequence, nucleobase modifications and patterns thereof, sugar modifications and patterns thereof, internucleotidic linkages and patterns thereof, linkage phosphorus stereochemistry and patterns thereof, linkers, and/or additional chemical moieties of DSR-0104083.

In certain exemplary embodiments, a ds oligonucleotide targeting INHBE of the present disclosure comprising the base sequence, nucleobase modifications and patterns thereof, sugar modifications and patterns thereof, internucleotidic linkages and patterns thereof, linkage phosphorus stereochemistry and patterns thereof, linkers, and/or additional chemical moieties of DSR-0104091.

In certain exemplary embodiments, a ds oligonucleotide targeting INHBE of the present disclosure comprising the base sequence, nucleobase modifications and patterns thereof, sugar modifications and patterns thereof, internucleotidic linkages and patterns thereof, linkage phosphorus stereochemistry and patterns thereof, linkers, and/or additional chemical moieties of DSR-0104071.

Table 1. Example Double Stranded Oligonucleotides Targeting INHBE.

ID	GUIDE SEQUENCE	PASSENGER SEQUENCE
DSR-0103433	SSR-0106685	SSR-0106964
DSR-0103434	SSR-0106686	SSR-0106965
DSR-0103435	SSR-0106687	SSR-0106966
DSR-0103436	SSR-0106688	SSR-0106967
DSR-0103437	SSR-0106689	SSR-0106968
DSR-0103438	SSR-0106690	SSR-0106969
DSR-0103439	SSR-0106691	SSR-0106970
DSR-0103440	SSR-0106692	SSR-0106971
DSR-0103441	SSR-0106693	SSR-0106972
DSR-0103442	SSR-0106694	SSR-0106973
DSR-0103443	SSR-0106695	SSR-0106974
DSR-0103444	SSR-0106696	SSR-0106975
DSR-0103445	SSR-0106697	SSR-0106976
DSR-0103446	SSR-0106698	SSR-0106977
DSR-0103447	SSR-0106699	SSR-0106978
DSR-0103448	SSR-0106700	SSR-0106979
DSR-0103449	SSR-0106701	SSR-0106980
DSR-0103450	SSR-0106702	SSR-0106981
DSR-0103451	SSR-0106703	SSR-0106982
DSR-0103452	SSR-0106704	SSR-0106983
DSR-0103453	SSR-0106705	SSR-0106984
DSR-0103454	SSR-0106706	SSR-0106985
DSR-0103455	SSR-0106707	SSR-0106986
DSR-0103456	SSR-0106708	SSR-0106987
DSR-0103457	SSR-0106709	SSR-0106988
DSR-0103458	SSR-0106710	SSR-0106989
DSR-0103459	SSR-0106711	SSR-0106990
DSR-0103460	SSR-0106712	SSR-0106991
DSR-0103461	SSR-0106713	SSR-0106992
DSR-0103462	SSR-0106714	SSR-0106993
DSR-0103463	SSR-0106715	SSR-0106994
DSR-0103464	SSR-0106716	SSR-0106995
DSR-0103465	SSR-0106717	SSR-0106996
DSR-0103466	SSR-0106718	SSR-0106997
DSR-0103467	SSR-0106719	SSR-0106998
DSR-0103468	SSR-0106720	SSR-0106999
DSR-0103469	SSR-0106721	SSR-0107000
DSR-0103470	SSR-0106722	SSR-0107001
DSR-0103471	SSR-0106723	SSR-0107002
DSR-0103472	SSR-0106724	SSR-0107003
DSR-0103473	SSR-0106725	SSR-0107004
DSR-0103474	SSR-0106726	SSR-0107005

DSR-0103475	SSR-0106727	SSR-0107006
DSR-0103476	SSR-0106728	SSR-0107007
DSR-0103477	SSR-0106729	SSR-0107008
DSR-0103478	SSR-0106730	SSR-0107009
DSR-0103479	SSR-0106731	SSR-0107010
DSR-0103480	SSR-0106732	SSR-0107011
DSR-0103481	SSR-0106733	SSR-0107012
DSR-0103482	SSR-0106734	SSR-0107013
DSR-0103483	SSR-0106735	SSR-0107014
DSR-0103484	SSR-0106736	SSR-0107015
DSR-0103485	SSR-0106737	SSR-0107016
DSR-0103486	SSR-0106738	SSR-0107017
DSR-0103487	SSR-0106739	SSR-0107018
DSR-0103488	SSR-0106740	SSR-0107019
DSR-0103489	SSR-0106741	SSR-0107020
DSR-0103490	SSR-0106742	SSR-0107021
DSR-0103491	SSR-0106743	SSR-0107022
DSR-0103492	SSR-0106744	SSR-0107023
DSR-0103493	SSR-0106745	SSR-0107024
DSR-0103494	SSR-0106746	SSR-0107025
DSR-0103495	SSR-0106747	SSR-0107026
DSR-0103496	SSR-0106748	SSR-0107027
DSR-0103497	SSR-0106749	SSR-0107028
DSR-0103498	SSR-0106750	SSR-0107029
DSR-0103499	SSR-0106751	SSR-0107030
DSR-0103500	SSR-0106752	SSR-0107031
DSR-0103501	SSR-0106753	SSR-0107032
DSR-0103502	SSR-0106754	SSR-0107033
DSR-0103503	SSR-0106755	SSR-0107034
DSR-0103504	SSR-0106756	SSR-0107035
DSR-0103505	SSR-0106757	SSR-0107036
DSR-0103506	SSR-0106758	SSR-0107037
DSR-0103507	SSR-0106759	SSR-0107038
DSR-0103508	SSR-0106760	SSR-0107039
DSR-0103509	SSR-0106761	SSR-0107040
DSR-0103510	SSR-0106762	SSR-0107041
DSR-0103511	SSR-0106763	SSR-0107042
DSR-0103512	SSR-0106764	SSR-0107043
DSR-0103513	SSR-0106765	SSR-0107044
DSR-0103514	SSR-0106766	SSR-0107045
DSR-0103515	SSR-0106767	SSR-0107046
DSR-0103516	SSR-0106768	SSR-0107047
DSR-0103517	SSR-0106769	SSR-0107048
DSR-0103518	SSR-0106770	SSR-0107049

DSR-0103519	SSR-0106771	SSR-0107050
DSR-0103520	SSR-0106772	SSR-0107051
DSR-0103521	SSR-0106773	SSR-0107052
DSR-0103522	SSR-0106774	SSR-0107053
DSR-0103523	SSR-0106775	SSR-0107054
DSR-0103524	SSR-0106776	SSR-0107055
DSR-0103525	SSR-0106777	SSR-0107056
DSR-0103526	SSR-0106778	SSR-0107057
DSR-0103527	SSR-0106779	SSR-0107058
DSR-0103528	SSR-0106780	SSR-0107059
DSR-0103529	SSR-0106781	SSR-0107060
DSR-0103530	SSR-0106782	SSR-0107061
DSR-0103531	SSR-0106783	SSR-0107062
DSR-0103532	SSR-0106784	SSR-0107063
DSR-0103533	SSR-0106785	SSR-0107064
DSR-0103534	SSR-0106786	SSR-0107065
DSR-0103535	SSR-0106787	SSR-0107066
DSR-0103536	SSR-0106788	SSR-0107067
DSR-0103537	SSR-0106789	SSR-0107068
DSR-0103538	SSR-0106790	SSR-0107069
DSR-0103539	SSR-0106791	SSR-0107070
DSR-0103540	SSR-0106792	SSR-0107071
DSR-0103541	SSR-0106793	SSR-0107072
DSR-0103542	SSR-0106794	SSR-0107073
DSR-0103543	SSR-0106795	SSR-0107074
DSR-0103544	SSR-0106796	SSR-0107075
DSR-0103545	SSR-0106797	SSR-0107076
DSR-0103546	SSR-0106798	SSR-0107077
DSR-0103547	SSR-0106799	SSR-0107078
DSR-0103548	SSR-0106800	SSR-0107079
DSR-0103549	SSR-0106801	SSR-0107080
DSR-0103550	SSR-0106802	SSR-0107081
DSR-0103551	SSR-0106803	SSR-0107082
DSR-0103552	SSR-0106804	SSR-0107083
DSR-0103553	SSR-0106805	SSR-0107084
DSR-0103554	SSR-0106806	SSR-0107085
DSR-0103555	SSR-0106807	SSR-0107086
DSR-0103556	SSR-0106808	SSR-0107087
DSR-0103557	SSR-0106809	SSR-0107088
DSR-0103558	SSR-0106810	SSR-0107089
DSR-0103559	SSR-0106811	SSR-0107090
DSR-0103560	SSR-0106812	SSR-0107091
DSR-0103561	SSR-0106813	SSR-0107092
DSR-0103562	SSR-0106814	SSR-0107093

DSR-0103563	SSR-0106815	SSR-0107094
DSR-0103564	SSR-0106816	SSR-0107095
DSR-0103565	SSR-0106817	SSR-0107096
DSR-0103566	SSR-0106818	SSR-0107097
DSR-0103567	SSR-0106819	SSR-0107098
DSR-0103568	SSR-0106820	SSR-0107099
DSR-0103569	SSR-0106821	SSR-0107100
DSR-0103570	SSR-0106822	SSR-0107101
DSR-0103571	SSR-0106823	SSR-0107102
DSR-0103572	SSR-0106824	SSR-0107103
DSR-0103573	SSR-0106825	SSR-0107104
DSR-0103574	SSR-0106826	SSR-0107105
DSR-0103575	SSR-0106827	SSR-0107106
DSR-0103576	SSR-0106828	SSR-0107107
DSR-0103577	SSR-0106829	SSR-0107108
DSR-0103578	SSR-0106830	SSR-0107109
DSR-0103579	SSR-0106831	SSR-0107110
DSR-0103580	SSR-0106832	SSR-0107111
DSR-0103581	SSR-0106833	SSR-0107112
DSR-0103582	SSR-0106834	SSR-0107113
DSR-0103583	SSR-0106835	SSR-0107114
DSR-0103584	SSR-0106836	SSR-0107115
DSR-0103585	SSR-0106837	SSR-0107116
DSR-0103586	SSR-0106838	SSR-0107117
DSR-0103587	SSR-0106839	SSR-0107118
DSR-0103588	SSR-0106840	SSR-0107119
DSR-0103589	SSR-0106841	SSR-0107120
DSR-0103590	SSR-0106842	SSR-0107121
DSR-0103591	SSR-0106843	SSR-0107122
DSR-0103592	SSR-0106844	SSR-0107123
DSR-0103593	SSR-0106845	SSR-0107124
DSR-0103594	SSR-0106846	SSR-0107125
DSR-0103595	SSR-0106847	SSR-0107126
DSR-0103596	SSR-0106848	SSR-0107127
DSR-0103597	SSR-0106849	SSR-0107128
DSR-0103598	SSR-0106850	SSR-0107129
DSR-0103599	SSR-0106851	SSR-0107130
DSR-0103600	SSR-0106852	SSR-0107131
DSR-0103601	SSR-0106853	SSR-0107132
DSR-0103602	SSR-0106854	SSR-0107133
DSR-0103603	SSR-0106855	SSR-0107134
DSR-0103604	SSR-0106856	SSR-0107135
DSR-0103605	SSR-0106857	SSR-0107136
DSR-0103606	SSR-0106858	SSR-0107137

DSR-0103607	SSR-0106859	SSR-0107138
DSR-0103608	SSR-0106860	SSR-0107139
DSR-0103609	SSR-0106861	SSR-0107140
DSR-0103610	SSR-0106862	SSR-0107141
DSR-0103611	SSR-0106863	SSR-0107142
DSR-0103612	SSR-0106864	SSR-0107143
DSR-0103613	SSR-0106865	SSR-0107144
DSR-0103614	SSR-0106866	SSR-0107145
DSR-0103615	SSR-0106867	SSR-0107146
DSR-0103616	SSR-0106868	SSR-0107147
DSR-0103617	SSR-0106869	SSR-0107148
DSR-0103618	SSR-0106870	SSR-0107149
DSR-0103619	SSR-0106871	SSR-0107150
DSR-0103620	SSR-0106872	SSR-0107151
DSR-0103621	SSR-0106873	SSR-0107152
DSR-0103622	SSR-0106874	SSR-0107153
DSR-0103623	SSR-0106875	SSR-0107154
DSR-0103624	SSR-0106876	SSR-0107155
DSR-0103625	SSR-0106877	SSR-0107156
DSR-0103626	SSR-0106878	SSR-0107157
DSR-0103627	SSR-0106879	SSR-0107158
DSR-0103628	SSR-0106880	SSR-0107159
DSR-0103629	SSR-0106881	SSR-0107160
DSR-0103630	SSR-0106882	SSR-0107161
DSR-0103631	SSR-0106883	SSR-0107162
DSR-0103632	SSR-0106884	SSR-0107163
DSR-0103633	SSR-0106885	SSR-0107164
DSR-0103634	SSR-0106886	SSR-0107165
DSR-0103635	SSR-0106887	SSR-0107166
DSR-0103636	SSR-0106888	SSR-0107167
DSR-0103637	SSR-0106889	SSR-0107168
DSR-0103638	SSR-0106890	SSR-0107169
DSR-0103639	SSR-0106891	SSR-0107170
DSR-0103640	SSR-0106892	SSR-0107171
DSR-0103641	SSR-0106893	SSR-0107172
DSR-0103642	SSR-0106894	SSR-0107173
DSR-0103643	SSR-0106895	SSR-0107174
DSR-0103644	SSR-0106896	SSR-0107175
DSR-0103645	SSR-0106897	SSR-0107176
DSR-0103646	SSR-0106898	SSR-0107177
DSR-0103647	SSR-0106899	SSR-0107178
DSR-0103648	SSR-0106900	SSR-0107179
DSR-0103649	SSR-0106901	SSR-0107180
DSR-0103650	SSR-0106902	SSR-0107181

DSR-0103651	SSR-0106903	SSR-0107182
DSR-0103652	SSR-0106904	SSR-0107183
DSR-0103653	SSR-0106905	SSR-0107184
DSR-0103654	SSR-0106906	SSR-0107185
DSR-0103655	SSR-0106907	SSR-0107186
DSR-0103656	SSR-0106908	SSR-0107187
DSR-0103657	SSR-0106909	SSR-0107188
DSR-0103658	SSR-0106910	SSR-0107189
DSR-0103659	SSR-0106911	SSR-0107190
DSR-0103660	SSR-0106912	SSR-0107191
DSR-0103661	SSR-0106913	SSR-0107192
DSR-0103662	SSR-0106914	SSR-0107193
DSR-0103663	SSR-0106915	SSR-0107194
DSR-0103664	SSR-0106916	SSR-0107195
DSR-0103665	SSR-0106917	SSR-0107196
DSR-0103666	SSR-0106918	SSR-0107197
DSR-0103667	SSR-0106919	SSR-0107198
DSR-0103668	SSR-0106920	SSR-0107199
DSR-0103669	SSR-0106921	SSR-0107200
DSR-0103670	SSR-0106922	SSR-0107201
DSR-0103671	SSR-0106923	SSR-0107202
DSR-0103672	SSR-0106924	SSR-0107203
DSR-0103673	SSR-0106925	SSR-0107204
DSR-0103674	SSR-0106926	SSR-0107205
DSR-0103675	SSR-0106927	SSR-0107206
DSR-0103676	SSR-0106928	SSR-0107207
DSR-0103677	SSR-0106929	SSR-0107208
DSR-0103678	SSR-0106930	SSR-0107209
DSR-0103679	SSR-0106931	SSR-0107210
DSR-0103680	SSR-0106932	SSR-0107211
DSR-0103681	SSR-0106933	SSR-0107212
DSR-0103682	SSR-0106934	SSR-0107213
DSR-0103683	SSR-0106935	SSR-0107214
DSR-0103684	SSR-0106936	SSR-0107215
DSR-0103685	SSR-0106937	SSR-0107216
DSR-0103686	SSR-0106938	SSR-0107217
DSR-0103687	SSR-0106939	SSR-0107218
DSR-0103688	SSR-0106940	SSR-0107219
DSR-0103689	SSR-0106941	SSR-0107220
DSR-0103690	SSR-0106942	SSR-0107221
DSR-0103691	SSR-0106943	SSR-0107222
DSR-0103692	SSR-0106944	SSR-0107223
DSR-0103693	SSR-0106945	SSR-0107224
DSR-0103694	SSR-0106946	SSR-0107225

DSR-0103695	SSR-0106947	SSR-0107226
DSR-0103696	SSR-0106948	SSR-0107227
DSR-0103697	SSR-0106949	SSR-0107228
DSR-0103698	SSR-0106950	SSR-0107229
DSR-0103699	SSR-0106951	SSR-0107230
DSR-0103700	SSR-0106952	SSR-0107231
DSR-0103701	SSR-0106953	SSR-0107232
DSR-0103702	SSR-0106954	SSR-0107233
DSR-0103703	SSR-0106955	SSR-0107234
DSR-0103704	SSR-0106956	SSR-0107235
DSR-0103705	SSR-0106957	SSR-0107236
DSR-0103706	SSR-0106958	SSR-0107237
DSR-0103707	SSR-0106959	SSR-0107238
DSR-0103708	SSR-0106960	SSR-0107239
DSR-0103709	SSR-0106961	SSR-0107240
DSR-0103710	SSR-0106962	SSR-0107241
DSR-0103711	SSR-0106963	SSR-0107242
DSR-0104067	SSR-0107998	SSR-0107999
DSR-0104068	SSR-0108000	SSR-0108001
DSR-0104069	SSR-0108010	SSR-0108045
DSR-0104070	SSR-0108011	SSR-0108046
DSR-0104071	SSR-0108012	SSR-0108047
DSR-0104072	SSR-0108013	SSR-0108048
DSR-0104073	SSR-0108014	SSR-0108049
DSR-0104074	SSR-0108015	SSR-0108050
DSR-0104075	SSR-0108016	SSR-0108051
DSR-0104076	SSR-0108017	SSR-0108052
DSR-0104077	SSR-0108018	SSR-0108053
DSR-0104078	SSR-0108019	SSR-0108054
DSR-0104079	SSR-0108020	SSR-0108055
DSR-0104080	SSR-0108021	SSR-0108056
DSR-0104081	SSR-0108022	SSR-0108057
DSR-0104082	SSR-0108023	SSR-0108058
DSR-0104083	SSR-0108024	SSR-0108059
DSR-0104084	SSR-0108025	SSR-0108060
DSR-0104085	SSR-0108026	SSR-0108061
DSR-0104086	SSR-0108027	SSR-0108062
DSR-0104087	SSR-0108028	SSR-0108063
DSR-0104088	SSR-0108029	SSR-0108064
DSR-0104089	SSR-0108030	SSR-0108065
DSR-0104090	SSR-0108031	SSR-0108066
DSR-0104091	SSR-0108032	SSR-0108067
DSR-0104092	SSR-0108033	SSR-0108068
DSR-0104093	SSR-0108034	SSR-0108069

DSR-0104094	SSR-0108035	SSR-0108070
DSR-0104095	SSR-0108036	SSR-0108071
DSR-0104096	SSR-0108037	SSR-0108072
DSR-0104097	SSR-0108038	SSR-0108073
DSR-0104098	SSR-0108039	SSR-0108074
DSR-0104099	SSR-0108040	SSR-0108075
DSR-0104100	SSR-0108041	SSR-0108076
DSR-0104101	SSR-0108042	SSR-0108077
DSR-0104102	SSR-0108043	SSR-0108078
DSR-0104103	SSR-0108044	SSR-0108079
DSR-0104108	SSR-0108095	SSR-0108001
DSR-0104159	SSR-0108099	SSR-0108059
DSR-0104291	SSR-0108322	SSR-0108059
DSR-0104293	SSR-0108324	SSR-0108059

Table 1a. Examples of Guide Sequences Targeting INHBE

GUIDE SEQUENCE	HELM	BASE SEQUENCE
SSR-0106685	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(C)p.m(A)p.[fl2r](G)p.m(C)p.m(U)p.m(C)p.m(A)p.m(U)p.m(G)p.m(U)p.[fl2r](C)p.m(U)p.[fl2r](G)p.m(G)p.m(C)p.m(U)p.m(A)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UCACAGCUCAUGUCUGGCUACUU
SSR-0106686	RNA1{m(U)[sp].[fl2r](U)[sp].m(C)p.m(A)p.m(C)p.[fl2r](A)p.m(G)p.m(C)p.m(U)p.m(C)p.m(A)p.m(U)p.m(G)p.[fl2r](U)p.m(C)p.[fl2r](U)p.m(G)p.m(G)p.m(C)p.m(U)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UUCACAGCUCAUGUCUGGCUAUU
SSR-0106687	RNA1{m(U)[sp].[fl2r](G)[sp].m(C)p.m(U)p.m(G)p.[fl2r](U)p.m(G)p.m(C)p.m(U)p.m(U)p.m(G)p.m(A)p.m(C)p.[fl2r](C)p.m(C)p.[fl2r](U)p.m(C)p.m(A)p.m(C)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGCUGUGCUUGACCCUCACAGUU
SSR-0106688	RNA1{m(U)[sp].[fl2r](U)[sp].m(A)p.m(G)p.m(C)p.[fl2r](U)p.m(G)p.m(U)p.m(G)p.m(C)p.m(U)p.m(U)p.m(G)p.[fl2r](A)p.m(C)p.[fl2r](C)p.m(C)p.m(U)p.m(C)p.m(A)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UUAGCUGUGCUUGACCCUCACUU
SSR-0106689	RNA1{m(U)[sp].[fl2r](G)[sp].m(G)p.m(A)p.m(U)p.[fl2r](A)p.m(G)p.m(C)p.m(U)p.m(G)p.m(U)p.m(G)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(A)p.m(C)p.m(C)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UGGAUAGCUGUGCUUGACCCUUU
SSR-0106690	RNA1{m(U)[sp].[fl2r](A)[sp].m(U)p.m(G)p.m(G)p.[fl2r](A)p.m(U)p.m(A)p.m(G)p.m(C)p.m(U)p.m(G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)p.m(U)p.m(G)p.m(A)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UAUGGAUAGCUGUGCUUGACCUU

SSR-0106691	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.m(G)p.m(A)p.[fl2r](U)p.m(G)p.m(G)p.m(A)p.m(U)p.m(A)p.m(G)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](U)p.m(G)p.m(C)p.m(U)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUGAUGGAUAGCUGUGCUUGUU
SSR-0106692	RNA1{m(U)[sp].[fl2r](U)[sp].m(C)p.m(U)p.m(G)p.[fl2r](A)p.m(U)p.m(G)p.m(G)p.m(A)p.m(U)p.m(A)p.m(G)p.[fl2r](C)p.m(U)p.[fl2r](G)p.m(U)p.m(G)p.m(C)p.m(U)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UUCUGAUGGAUAGCUGUGCUUUU
SSR-0106693	RNA1{m(U)[sp].[fl2r](A)[sp].m(U)p.m(C)p.m(A)p.[fl2r](U)p.m(C)p.m(U)p.m(G)p.m(A)p.m(U)p.m(G)p.m(G)p.[fl2r](A)p.m(U)p.[fl2r](A)p.m(G)p.m(C)p.m(U)p.m(G)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UAUCAUCUGAUGGAUAGCUGUUU
SSR-0106694	RNA1{m(U)[sp].[fl2r](U)[sp].m(A)p.m(G)p.m(A)p.[fl2r](U)p.m(C)p.m(A)p.m(U)p.m(C)p.m(U)p.m(G)p.m(A)p.[fl2r](U)p.m(G)p.[fl2r](G)p.m(A)p.m(U)p.m(A)p.m(G)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UUAGAUCAUCUGAUGGAUAGCUU
SSR-0106695	RNA1{m(U)[sp].[fl2r](G)[sp].m(U)p.m(A)p.m(G)p.[fl2r](A)p.m(U)p.m(C)p.m(A)p.m(U)p.m(C)p.m(U)p.m(G)p.[fl2r](A)p.m(U)p.[fl2r](G)p.m(G)p.m(A)p.m(U)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGUAGAUCAUCUGAUGGAUAGUU
SSR-0106696	RNA1{m(U)[sp].[fl2r](A)[sp].m(A)p.m(G)p.m(U)p.[fl2r](A)p.m(G)p.m(A)p.m(U)p.m(C)p.m(A)p.m(U)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](A)p.m(U)p.m(G)p.m(G)p.m(A)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UAAGUAGAUCAUCUGAUGGAUUU
SSR-0106697	RNA1{m(U)[sp].[fl2r](G)[sp].m(A)p.m(A)p.m(G)p.[fl2r](G)p.m(C)p.m(U)p.m(G)p.m(A)p.m(A)p.m(A)p.m(G)p.[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(U)p.m(C)p.m(A)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UGAAGGCUGAAAGUAGAUCAUUU
SSR-0106698	RNA1{m(U)[sp].[fl2r](A)[sp].m(G)p.m(C)p.m(A)p.[fl2r](G)p.m(A)p.m(C)p.m(A)p.m(C)p.m(C)p.m(A)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](C)p.m(C)p.m(A)p.m(C)p.m(A)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UAGCAGACACCACUGCCACACUU
SSR-0106699	RNA1{m(U)[sp].[fl2r](A)[sp].m(C)p.m(A)p.m(G)p.[fl2r](C)p.m(A)p.m(G)p.m(A)p.m(C)p.m(A)p.m(C)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](U)p.m(G)p.m(C)p.m(C)p.m(A)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UACAGCAGACACCACUGCCACUU
SSR-0106700	RNA1{m(U)[sp].[fl2r](A)[sp].m(G)p.m(U)p.m(G)p.[fl2r](A)p.m(C)p.m(A)p.m(G)p.m(C)p.m(A)p.m(G)p.m(A)p.[fl2r](C)p.m(A)p.[fl2r](C)p.m(C)p.m(A)p.m(C)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UAGUGACAGCAGACACCACUGUU
SSR-0106701	RNA1{m(U)[sp].[fl2r](A)[sp].m(G)p.m(U)p.m(U)p.[fl2r](G)p.m(C)p.m(U)p.m(C)p.m(C)p.m(G)p.m(U)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](U)p.m(U)p.m(G)p.m(A)p.m(G)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UAGUUGCUCCGUCUGUUGAGUUU
SSR-0106702	RNA1{m(U)[sp].[fl2r](G)[sp].m(C)p.m(A)p.m(G)p.[fl2r](U)p.m(U)p.m(G)p.m(C)p.m(U)p.m(C)p.m(C)p.m(G)p.[fl2r](U)p.m(C)p.[fl2r](U)p.m(G)p.m(U)p.m(U)p.m(G)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UGCAGUUGCUCCGUCUGUUGAUU

SSR-0106703	RNA1{m(U)[sp].[fl2r](G)[sp].m(G)p.m(A)p.m(U)p.[fl2r](G)p.m(G)p.m(C)p.m(A)p.m(G)p.m(U)p.m(U)p.m(G)p.[fl2r](C)p.m(U)p.[fl2r](C)p.m(C)p.m(G)p.m(U)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UGGAUGGCAGUUGCUCCGUCUUU
SSR-0106704	RNA1{m(U)[sp].[fl2r](C)[sp].m(G)p.m(G)p.m(A)p.[fl2r](U)p.m(G)p.m(G)p.m(C)p.m(A)p.m(G)p.m(U)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)p.m(C)p.m(C)p.m(G)p.m(U)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UCGGAUGGCAGUUGCUCCGUCUU
SSR-0106705	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.m(C)p.m(G)p.[fl2r](G)p.m(A)p.m(U)p.m(G)p.m(G)p.m(C)p.m(A)p.m(G)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(C)p.m(U)p.m(C)p.m(C)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUCGGAUGGCAGUUGCUCCGUU
SSR-0106706	RNA1{m(U)[sp].[fl2r](G)[sp].m(C)p.m(C)p.m(U)p.[fl2r](C)p.m(G)p.m(G)p.m(A)p.m(U)p.m(G)p.m(G)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](U)p.m(U)p.m(G)p.m(C)p.m(U)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UGCCUCGGAUGGCAGUUGCUCUU
SSR-0106707	RNA1{m(U)[sp].[fl2r](A)[sp].m(G)p.m(C)p.m(C)p.[fl2r](U)p.m(C)p.m(G)p.m(G)p.m(A)p.m(U)p.m(G)p.m(G)p.[fl2r](C)p.m(A)p.[fl2r](G)p.m(U)p.m(U)p.m(G)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UAGCCUCGGAUGGCAGUUGCUUU
SSR-0106708	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(G)p.m(C)p.[fl2r](A)p.m(G)p.m(C)p.m(A)p.m(C)p.m(C)p.m(A)p.m(G)p.[fl2r](C)p.m(C)p.[fl2r](A)p.m(G)p.m(A)p.m(G)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UCAGCAGCACCAGCCAGAGCUUU
SSR-0106709	RNA1{m(U)[sp].[fl2r](A)[sp].m(C)p.m(A)p.m(G)p.[fl2r](C)p.m(A)p.m(G)p.m(C)p.m(A)p.m(C)p.m(C)p.m(A)p.[fl2r](G)p.m(C)p.[fl2r](C)p.m(A)p.m(G)p.m(A)p.m(G)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UACAGCAGCACCAGCCAGAGCUU
SSR-0106710	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(G)p.m(U)p.[fl2r](G)p.m(C)p.m(C)p.m(C)p.m(A)p.m(C)p.m(A)p.m(G)p.[fl2r](C)p.m(A)p.[fl2r](G)p.m(C)p.m(A)p.m(C)p.m(C)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UCAGUGCCCACAGCAGCACCAUU
SSR-0106711	RNA1{m(U)[sp].[fl2r](A)[sp].m(C)p.m(C)p.m(A)p.[fl2r](G)p.m(U)p.m(G)p.m(C)p.m(C)p.m(C)p.m(A)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](C)p.m(A)p.m(G)p.m(C)p.m(A)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UACCAGUGCCCACAGCAGCACUU
SSR-0106712	RNA1{m(U)[sp].[fl2r](U)[sp].m(G)p.m(C)p.m(U)p.[fl2r](C)p.m(G)p.m(C)p.m(A)p.m(C)p.m(C)p.m(A)p.m(G)p.[fl2r](U)p.m(G)p.[fl2r](C)p.m(C)p.m(C)p.m(A)p.m(C)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UUGCUCGCACCAGUGCCCACAUU
SSR-0106713	RNA1{m(U)[sp].[fl2r](G)[sp].m(U)p.m(G)p.m(C)p.[fl2r](U)p.m(C)p.m(G)p.m(C)p.m(A)p.m(C)p.m(C)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.m(C)p.m(C)p.m(A)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UGUGCUCGCACCAGUGCCCACUU
SSR-0106714	RNA1{m(U)[sp].[fl2r](U)[sp].m(G)p.m(U)p.m(G)p.[fl2r](C)p.m(U)p.m(C)p.m(G)p.m(C)p.m(A)p.m(C)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](U)p.m(G)p.m(C)p.m(C)p.m(C)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UUGUGCUCGCACCAGUGCCCAUU

SSR-0106715	RNA1{m(U)[sp].[fl2r](A)[sp].m(C)p.m(A)p.m(G)p.[fl2r](G)p.m(A)p.m(G)p.m(G)p.m(G)p.m(A)p.m(C)p.m(A)p.[fl2r](C)p.m(A)p.[fl2r](C)p.m(A)p.m(G)p.m(A)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UACAGGAGGGACACACAGACCUU
SSR-0106716	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(C)p.m(A)p.[fl2r](G)p.m(G)p.m(A)p.m(G)p.m(G)p.m(G)p.m(A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(A)p.m(G)p.m(A)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UCACAGGAGGGACACACAGACUU
SSR-0106717	RNA1{m(U)[sp].[fl2r](G)[sp].m(C)p.m(U)p.m(G)p.[fl2r](C)p.m(U)p.m(U)p.m(G)p.m(G)p.m(C)p.m(U)p.m(A)p.[fl2r](G)p.m(C)p.[fl2r](U)p.m(C)p.m(C)p.m(A)p.m(G)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UGCUGCUUGGCUAGCUCCAGCUU
SSR-0106718	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(U)p.m(C)p.[fl2r](C)p.m(A)p.m(G)p.m(G)p.m(A)p.m(U)p.m(U)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)p.m(G)p.m(C)p.m(U)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCAUCCAGGAUUUGCUGCUUGUU
SSR-0106719	RNA1{m(U)[sp].[fl2r](C)[sp].m(C)p.m(C)p.m(A)p.[fl2r](U)p.m(C)p.m(C)p.m(A)p.m(G)p.m(G)p.m(A)p.m(U)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(C)p.m(U)p.m(G)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UCCCAUCCAGGAUUUGCUGCUUU
SSR-0106720	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(A)p.m(C)p.[fl2r](C)p.m(C)p.m(A)p.m(U)p.m(C)p.m(C)p.m(A)p.m(G)p.[fl2r](G)p.m(A)p.[fl2r](U)p.m(U)p.m(U)p.m(G)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UCAACCCAUCCAGGAUUUGCUUU
SSR-0106721	RNA1{m(U)[sp].[fl2r](G)[sp].m(C)p.m(A)p.m(A)p.[fl2r](C)p.m(C)p.m(C)p.m(A)p.m(U)p.m(C)p.m(C)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](A)p.m(U)p.m(U)p.m(U)p.m(G)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UGCAACCCAUCCAGGAUUUGCUU
SSR-0106722	RNA1{m(U)[sp].[fl2r](G)[sp].m(U)p.m(G)p.m(C)p.[fl2r](A)p.m(A)p.m(C)p.m(C)p.m(C)p.m(A)p.m(U)p.m(C)p.[fl2r](C)p.m(A)p.[fl2r](G)p.m(G)p.m(A)p.m(U)p.m(U)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UGUGCAACCCAUCCAGGAUUUUU
SSR-0106723	RNA1{m(U)[sp].[fl2r](A)[sp].m(C)p.m(G)p.m(A)p.[fl2r](C)p.m(U)p.m(G)p.m(G)p.m(U)p.m(C)p.m(A)p.m(G)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.m(A)p.m(A)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UACGACUGGUCAGGUGCAACCUU
SSR-0106724	RNA1{m(U)[sp].[fl2r](G)[sp].m(A)p.m(C)p.m(G)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(G)p.m(U)p.m(C)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](U)p.m(G)p.m(C)p.m(A)p.m(A)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UGACGACUGGUCAGGUGCAACUU
SSR-0106725	RNA1{m(U)[sp].[fl2r](U)[sp].m(U)p.m(A)p.m(U)p.[fl2r](U)p.m(C)p.m(U)p.m(G)p.m(G)p.m(G)p.m(A)p.m(C)p.[fl2r](G)p.m(A)p.[fl2r](C)p.m(U)p.m(G)p.m(G)p.m(U)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UUUAUUCUGGGACGACUGGUCUU
SSR-0106726	RNA1{m(U)[sp].[fl2r](G)[sp].m(U)p.m(U)p.m(A)p.[fl2r](U)p.m(U)p.m(C)p.m(U)p.m(G)p.m(G)p.m(G)p.m(A)p.[fl2r](C)p.m(G)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(G)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UGUUAUUCUGGGACGACUGGUUU

SSR-0106727	RNA1{m(U)[sp].[fl2r](G)[sp].m(A)p.m(G)p.m(U)p.[fl2r](U)p.m(A)p.m(U)p.m(U)p.m(C)p.m(U)p.m(G)p.m(G)p.[fl2r](G)p.m(A)p.[fl2r](C)p.m(G)p.m(A)p.m(C)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGAGUUAUUCUGGGACGACUGUU
SSR-0106728	RNA1{m(U)[sp].[fl2r](G)[sp].m(A)p.m(U)p.m(G)p.[fl2r](A)p.m(G)p.m(U)p.m(U)p.m(A)p.m(U)p.m(U)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](G)p.m(G)p.m(A)p.m(C)p.m(G)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UGAUGAGUUAUUCUGGGACGAUU
SSR-0106729	RNA1{m(U)[sp].[fl2r](U)[sp].m(C)p.m(C)p.m(G)p.[fl2r](G)p.m(A)p.m(G)p.m(G)p.m(G)p.m(C)p.m(U)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](G)p.m(U)p.m(C)p.m(A)p.m(G)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UUCCGGAGGGCUCUGGUCAGCUU
SSR-0106730	RNA1{m(U)[sp].[fl2r](A)[sp].m(C)p.m(A)p.m(C)p.[fl2r](U)p.m(C)p.m(C)p.m(C)p.m(U)p.m(G)p.m(G)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](U)p.m(A)p.m(G)p.m(U)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UACACUCCCUGGCUGUAGUCUUU
SSR-0106731	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(C)p.m(A)p.[fl2r](C)p.m(U)p.m(C)p.m(C)p.m(C)p.m(U)p.m(G)p.m(G)p.[fl2r](C)p.m(U)p.[fl2r](G)p.m(U)p.m(A)p.m(G)p.m(U)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UCACACUCCCUGGCUGUAGUCUU
SSR-0106732	RNA1{m(U)[sp].[fl2r](G)[sp].m(C)p.m(C)p.m(A)p.[fl2r](C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(C)p.m(C)p.m(U)p.[fl2r](G)p.m(G)p.[fl2r](C)p.m(U)p.m(G)p.m(U)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGCCACACUCCCUGGCUGUAGUU
SSR-0106733	RNA1{m(U)[sp].[fl2r](U)[sp].m(A)p.m(G)p.m(C)p.[fl2r](A)p.m(A)p.m(A)p.m(G)p.m(C)p.m(U)p.m(G)p.m(A)p.[fl2r](U)p.m(G)p.[fl2r](A)p.m(C)p.m(C)p.m(U)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UUAGCAAAGCUGAUGACCUCCUU
SSR-0106734	RNA1{m(U)[sp].[fl2r](G)[sp].m(U)p.m(A)p.m(G)p.[fl2r](C)p.m(A)p.m(A)p.m(A)p.m(G)p.m(C)p.m(U)p.m(G)p.[fl2r](A)p.m(U)p.[fl2r](G)p.m(A)p.m(C)p.m(C)p.m(U)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UGUAGCAAAGCUGAUGACCUCUU
SSR-0106735	RNA1{m(U)[sp].[fl2r](A)[sp].m(G)p.m(U)p.m(A)p.[fl2r](G)p.m(C)p.m(A)p.m(A)p.m(A)p.m(G)p.m(C)p.m(U)p.[fl2r](G)p.m(A)p.[fl2r](U)p.m(G)p.m(A)p.m(C)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UAGUAGCAAAGCUGAUGACCUUU
SSR-0106736	RNA1{m(U)[sp].[fl2r](A)[sp].m(C)p.m(A)p.m(G)p.[fl2r](U)p.m(A)p.m(G)p.m(C)p.m(A)p.m(A)p.m(A)p.m(G)p.[fl2r](C)p.m(U)p.[fl2r](G)p.m(A)p.m(U)p.m(G)p.m(A)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UACAGUAGCAAAGCUGAUGACUU
SSR-0106737	RNA1{m(U)[sp].[fl2r](U)[sp].m(G)p.m(A)p.m(C)p.[fl2r](A)p.m(G)p.m(U)p.m(A)p.m(G)p.m(C)p.m(A)p.m(A)p.[fl2r](A)p.m(G)p.[fl2r](C)p.m(U)p.m(G)p.m(A)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UUGACAGUAGCAAAGCUGAUGUU
SSR-0106738	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.m(G)p.m(U)p.[fl2r](G)p.m(A)p.m(C)p.m(A)p.m(G)p.m(U)p.m(A)p.m(G)p.[fl2r](C)p.m(A)p.[fl2r](A)p.m(A)p.m(G)p.m(C)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUGUGACAGUAGCAAAGCUGUU

SSR-0106739	RNA1{m(U)[sp].[fl2r](G)[sp].m(C)p.m(A)p.m(G)p.[fl2r](G)p.m(G)p.m(A)p.m(G)p.m(C)p.m(U)p.m(G)p.m(U)p.[fl2r](A)p.m(G)p.[fl2r](G)p.m(C)p.m(U)p.m(G)p.m(A)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UGCAGGGAGCUGUAGGCUGAAUU
SSR-0106740	RNA1{m(U)[sp].[fl2r](G)[sp].m(A)p.m(G)p.m(C)p.[fl2r](A)p.m(G)p.m(G)p.m(G)p.m(A)p.m(G)p.m(C)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)p.m(G)p.m(C)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGAGCAGGGAGCUGUAGGCUGUU
SSR-0106741	RNA1{m(U)[sp].[fl2r](G)[sp].m(A)p.m(A)p.m(A)p.[fl2r](A)p.m(G)p.m(U)p.m(G)p.m(A)p.m(G)p.m(C)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGAAAAGUGAGCAGGGAGCUGUU
SSR-0106742	RNA1{m(U)[sp].[fl2r](A)[sp].m(G)p.m(G)p.m(U)p.[fl2r](G)p.m(A)p.m(A)p.m(A)p.m(A)p.m(G)p.m(U)p.m(G)p.[fl2r](A)p.m(G)p.[fl2r](C)p.m(A)p.m(G)p.m(G)p.m(G)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UAGGUGAAAAGUGAGCAGGGAUU
SSR-0106743	RNA1{m(U)[sp].[fl2r](C)[sp].m(C)p.m(G)p.m(A)p.[fl2r](G)p.m(G)p.m(A)p.m(G)p.m(U)p.m(G)p.m(G)p.m(A)p.[fl2r](C)p.m(A)p.[fl2r](G)p.m(G)p.m(U)p.m(G)p.m(A)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UCCGAGGAGUGGACAGGUGAAUU
SSR-0106744	RNA1{m(U)[sp].[fl2r](A)[sp].m(C)p.m(C)p.m(G)p.[fl2r](A)p.m(G)p.m(G)p.m(A)p.m(G)p.m(U)p.m(G)p.m(G)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(G)p.m(G)p.m(U)p.m(G)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UACCGAGGAGUGGACAGGUGAUU
SSR-0106745	RNA1{m(U)[sp].[fl2r](G)[sp].m(A)p.m(C)p.m(C)p.[fl2r](G)p.m(A)p.m(G)p.m(G)p.m(A)p.m(G)p.m(U)p.m(G)p.[fl2r](G)p.m(A)p.[fl2r](C)p.m(A)p.m(G)p.m(G)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGACCGAGGAGUGGACAGGUGUU
SSR-0106746	RNA1{m(U)[sp].[fl2r](G)[sp].m(G)p.m(G)p.m(A)p.[fl2r](C)p.m(C)p.m(G)p.m(A)p.m(G)p.m(G)p.m(A)p.m(G)p.[fl2r](U)p.m(G)p.[fl2r](G)p.m(A)p.m(C)p.m(A)p.m(G)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGGGACCGAGGAGUGGACAGGUU
SSR-0106747	RNA1{m(U)[sp].[fl2r](U)[sp].m(G)p.m(G)p.m(U)p.[fl2r](G)p.m(G)p.m(G)p.m(A)p.m(C)p.m(C)p.m(G)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](A)p.m(G)p.m(U)p.m(G)p.m(G)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UUGGUGGGACCGAGGAGUGGAUU
SSR-0106748	RNA1{m(U)[sp].[fl2r](A)[sp].m(G)p.m(G)p.m(U)p.[fl2r](G)p.m(G)p.m(U)p.m(G)p.m(G)p.m(G)p.m(A)p.m(C)p.[fl2r](C)p.m(G)p.[fl2r](A)p.m(G)p.m(G)p.m(A)p.m(G)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UAGGUGGUGGGACCGAGGAGUUU
SSR-0106749	RNA1{m(U)[sp].[fl2r](C)[sp].m(G)p.m(G)p.m(G)p.[fl2r](C)p.m(A)p.m(U)p.m(G)p.m(G)p.m(U)p.m(A)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](G)p.m(U)p.m(G)p.m(G)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCGGGCAUGGUACAGGUGGUGUU
SSR-0106750	RNA1{m(U)[sp].[fl2r](A)[sp].m(C)p.m(G)p.m(U)p.[fl2r](G)p.m(C)p.m(A)p.m(G)p.m(C)p.m(C)p.m(A)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](G)p.m(C)p.m(G)p.m(G)p.m(G)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UACGUGCAGCCACAGGCGGGCUU

SSR-0106751	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.m(C)p.m(A)p.[fl2r](A)p.m(G)p.m(C)p.m(A)p.m(A)p.m(A)p.m(G)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.m(C)p.m(A)p.m(G)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUCAAGCAAAGAGUGCCAGGUU
SSR-0106752	RNA1{m(U)[sp].[fl2r](A)[sp].m(U)p.m(C)p.m(C)p.[fl2r](U)p.m(C)p.m(A)p.m(A)p.m(G)p.m(C)p.m(A)p.m(A)p.[fl2r](A)p.m(G)p.[fl2r](A)p.m(G)p.m(U)p.m(G)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UAUCCUCAAGCAAAGAGUGCCUU
SSR-0106753	RNA1{m(U)[sp].[fl2r](A)[sp].m(A)p.m(G)p.m(A)p.[fl2r](U)p.m(C)p.m(C)p.m(U)p.m(C)p.m(A)p.m(A)p.m(G)p.[fl2r](C)p.m(A)p.[fl2r](A)p.m(A)p.m(G)p.m(A)p.m(G)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UAAGAUCCUCAAGCAAAGAGUUU
SSR-0106754	RNA1{m(U)[sp].[fl2r](U)[sp].m(C)p.m(G)p.m(G)p.[fl2r](A)p.m(A)p.m(G)p.m(A)p.m(U)p.m(C)p.m(C)p.m(U)p.[fl2r](C)p.m(A)p.[fl2r](A)p.m(G)p.m(C)p.m(A)p.m(A)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UUCGGAAGAUCCUCAAGCAAAUU
SSR-0106755	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(U)p.m(C)p.[fl2r](G)p.m(G)p.m(A)p.m(A)p.m(G)p.m(A)p.m(U)p.m(C)p.[fl2r](C)p.m(U)p.[fl2r](C)p.m(A)p.m(A)p.m(G)p.m(C)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UCAUCGGAAGAUCCUCAAGCAUU
SSR-0106756	RNA1{m(U)[sp].[fl2r](C)[sp].m(C)p.m(A)p.m(U)p.[fl2r](C)p.m(G)p.m(G)p.m(A)p.m(A)p.m(G)p.m(A)p.m(U)p.[fl2r](C)p.m(C)p.[fl2r](U)p.m(C)p.m(A)p.m(A)p.m(G)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UCCAUCGGAAGAUCCUCAAGCUU
SSR-0106757	RNA1{m(U)[sp].[fl2r](C)[sp].m(C)p.m(C)p.m(A)p.[fl2r](U)p.m(C)p.m(G)p.m(G)p.m(A)p.m(A)p.m(G)p.m(A)p.[fl2r](U)p.m(C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCCCAUCGGAAGAUCCUCAAGUU
SSR-0106758	RNA1{m(U)[sp].[fl2r](U)[sp].m(G)p.m(G)p.m(C)p.[fl2r](G)p.m(C)p.m(C)p.m(U)p.m(C)p.m(C)p.m(U)p.m(C)p.[fl2r](C)p.m(U)p.[fl2r](U)p.m(G)p.m(G)p.m(U)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UUGGCGCCUCCUCCUUGGUCCUU
SSR-0106759	RNA1{m(U)[sp].[fl2r](U)[sp].m(U)p.m(G)p.m(G)p.[fl2r](C)p.m(G)p.m(C)p.m(C)p.m(U)p.m(C)p.m(C)p.m(U)p.[fl2r](C)p.m(C)p.[fl2r](U)p.m(U)p.m(G)p.m(G)p.m(U)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UUUGGCGCCUCCUCCUUGGUCUU
SSR-0106760	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.m(U)p.m(G)p.[fl2r](G)p.m(C)p.m(G)p.m(C)p.m(C)p.m(U)p.m(C)p.m(C)p.[fl2r](U)p.m(C)p.[fl2r](C)p.m(U)p.m(U)p.m(G)p.m(G)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUUGGCGCCUCCUCCUUGGUUU
SSR-0106761	RNA1{m(U)[sp].[fl2r](A)[sp].m(C)p.m(C)p.m(C)p.[fl2r](U)p.m(U)p.m(G)p.m(G)p.m(C)p.m(G)p.m(C)p.m(C)p.[fl2r](U)p.m(C)p.[fl2r](C)p.m(U)p.m(C)p.m(C)p.m(U)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UACCCUUGGCGCCUCCUCCUUUU
SSR-0106762	RNA1{m(U)[sp].[fl2r](C)[sp].m(G)p.m(G)p.m(G)p.[fl2r](A)p.m(C)p.m(C)p.m(C)p.m(U)p.m(U)p.m(G)p.m(G)p.[fl2r](C)p.m(G)p.[fl2r](C)p.m(C)p.m(U)p.m(C)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UCGGGACCCUUGGCGCCUCCUUU

SSR-0106763	RNA1{m(U)[sp].[fl2r](U)[sp].m(G)p.m(C)p.m(G)p.[fl2r](G)p.m(G)p.m(A)p.m(C)p.m(C)p.m(C)p.m(U)p.m(U)p.[fl2r](G)p.m(G)p.[fl2r](C)p.m(G)p.m(C)p.m(C)p.m(U)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UUGCGGGACCCUUGGCGCCUCUU
SSR-0106764	RNA1{m(U)[sp].[fl2r](A)[sp].m(G)p.m(U)p.m(G)p.[fl2r](C)p.m(G)p.m(G)p.m(G)p.m(A)p.m(C)p.m(C)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(G)p.m(C)p.m(G)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UAGUGCGGGACCCUUGGCGCCUU
SSR-0106765	RNA1{m(U)[sp].[fl2r](G)[sp].m(A)p.m(G)p.m(U)p.[fl2r](G)p.m(C)p.m(G)p.m(G)p.m(G)p.m(A)p.m(C)p.m(C)p.[fl2r](C)p.m(U)p.[fl2r](U)p.m(G)p.m(G)p.m(C)p.m(G)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UGAGUGCGGGACCCUUGGCGCUU
SSR-0106766	RNA1{m(U)[sp].[fl2r](G)[sp].m(U)p.m(G)p.m(A)p.[fl2r](U)p.m(G)p.m(U)p.m(G)p.m(G)p.m(U)p.m(G)p.m(C)p.[fl2r](U)p.m(C)p.[fl2r](A)p.m(G)p.m(C)p.m(C)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGUGAUGUGGUGCUCAGCCAGUU
SSR-0106767	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(G)p.m(G)p.[fl2r](U)p.m(U)p.m(G)p.m(G)p.m(U)p.m(G)p.m(A)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(G)p.m(U)p.m(G)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UCAGGUUGGUGAUGUGGUGCUUU
SSR-0106768	RNA1{m(U)[sp].[fl2r](U)[sp].m(A)p.m(U)p.m(G)p.[fl2r](C)p.m(C)p.m(A)p.m(G)p.m(C)p.m(C)p.m(C)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](U)p.m(U)p.m(G)p.m(G)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UUAUGCCAGCCCAGGUUGGUGUU
SSR-0106769	RNA1{m(U)[sp].[fl2r](G)[sp].m(C)p.m(A)p.m(G)p.[fl2r](A)p.m(G)p.m(U)p.m(U)p.m(A)p.m(A)p.m(G)p.m(G)p.[fl2r](U)p.m(A)p.[fl2r](U)p.m(G)p.m(C)p.m(C)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGCAGAGUUAAGGUAUGCCAGUU
SSR-0106770	RNA1{m(U)[sp].[fl2r](U)[sp].m(A)p.m(G)p.m(A)p.[fl2r](G)p.m(G)p.m(G)p.m(C)p.m(A)p.m(G)p.m(A)p.m(G)p.[fl2r](U)p.m(U)p.[fl2r](A)p.m(A)p.m(G)p.m(G)p.m(U)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UUAGAGGGCAGAGUUAAGGUAUU
SSR-0106771	RNA1{m(U)[sp].[fl2r](A)[sp].m(C)p.m(U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(G)p.m(G)p.m(C)p.m(A)p.m(G)p.[fl2r](A)p.m(G)p.[fl2r](U)p.m(U)p.m(A)p.m(A)p.m(G)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UACUAGAGGGCAGAGUUAAGGUU
SSR-0106772	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(C)p.m(U)p.[fl2r](A)p.m(G)p.m(A)p.m(G)p.m(G)p.m(G)p.m(C)p.m(A)p.[fl2r](G)p.m(A)p.[fl2r](G)p.m(U)p.m(U)p.m(A)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCACUAGAGGGCAGAGUUAAGUU
SSR-0106773	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.m(C)p.m(A)p.[fl2r](A)p.m(G)p.m(C)p.m(C)p.m(A)p.m(C)p.m(U)p.m(A)p.[fl2r](G)p.m(A)p.[fl2r](G)p.m(G)p.m(G)p.m(C)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUCAAGCCACUAGAGGGCAGUU
SSR-0106774	RNA1{m(U)[sp].[fl2r](U)[sp].m(U)p.m(C)p.m(A)p.[fl2r](G)p.m(G)p.m(A)p.m(C)p.m(A)p.m(C)p.m(C)p.m(A)p.[fl2r](G)p.m(A)p.[fl2r](C)p.m(U)p.m(U)p.m(C)p.m(U)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UUUCAGGACACCAGACUUCUCUU

SSR-0106775	RNA1{m(U)[sp].[fl2r](U)[sp].m(U)p.m(U)p.m(C)p.[fl2r](A)p.m(G)p.m(G)p.m(A)p.m(C)p.m(A)p.m(C)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](A)p.m(C)p.m(U)p.m(U)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UUUUCAGGACACCAGACUUCUUU
SSR-0106776	RNA1{m(U)[sp].[fl2r](G)[sp].m(U)p.m(U)p.m(U)p.[fl2r](C)p.m(A)p.m(G)p.m(G)p.m(A)p.m(C)p.m(A)p.m(C)p.[fl2r](C)p.m(A)p.[fl2r](G)p.m(A)p.m(C)p.m(U)p.m(U)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UGUUUCAGGACACCAGACUUCUU
SSR-0106777	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(G)p.m(U)p.[fl2r](U)p.m(U)p.m(C)p.m(A)p.m(G)p.m(G)p.m(A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](C)p.m(A)p.m(G)p.m(A)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UCAGUUUCAGGACACCAGACUUU
SSR-0106778	RNA1{m(U)[sp].[fl2r](G)[sp].m(C)p.m(A)p.m(G)p.[fl2r](U)p.m(U)p.m(U)p.m(C)p.m(A)p.m(G)p.m(G)p.m(A)p.[fl2r](C)p.m(A)p.[fl2r](C)p.m(C)p.m(A)p.m(G)p.m(A)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UGCAGUUUCAGGACACCAGACUU
SSR-0106779	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.m(A)p.m(G)p.[fl2r](U)p.m(U)p.m(G)p.m(C)p.m(A)p.m(G)p.m(U)p.m(U)p.[fl2r](U)p.m(C)p.[fl2r](A)p.m(G)p.m(G)p.m(A)p.m(C)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUAGUUGCAGUUUCAGGACAUU
SSR-0106780	RNA1{m(U)[sp].[fl2r](A)[sp].m(G)p.m(U)p.m(C)p.[fl2r](U)p.m(A)p.m(G)p.m(U)p.m(U)p.m(G)p.m(C)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](U)p.m(U)p.m(C)p.m(A)p.m(G)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UAGUCUAGUUGCAGUUUCAGGUU
SSR-0106781	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(G)p.m(U)p.[fl2r](C)p.m(U)p.m(A)p.m(G)p.m(U)p.m(U)p.m(G)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](U)p.m(U)p.m(U)p.m(C)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCAGUCUAGUUGCAGUUUCAGUU
SSR-0106782	RNA1{m(U)[sp].[fl2r](U)[sp].m(C)p.m(U)p.m(G)p.[fl2r](C)p.m(A)p.m(G)p.m(U)p.m(C)p.m(U)p.m(A)p.m(G)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(C)p.m(A)p.m(G)p.m(U)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UUCUGCAGUCUAGUUGCAGUUUU
SSR-0106783	RNA1{m(U)[sp].[fl2r](U)[sp].m(C)p.m(G)p.m(G)p.[fl2r](U)p.m(U)p.m(G)p.m(U)p.m(C)p.m(C)p.m(A)p.m(G)p.[fl2r](U)p.m(A)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UUCGGUUGUCCAGUAACUGUGUU
SSR-0106784	RNA1{m(U)[sp].[fl2r](C)[sp].m(C)p.m(U)p.m(C)p.[fl2r](G)p.m(G)p.m(U)p.m(U)p.m(G)p.m(U)p.m(C)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](U)p.m(A)p.m(A)p.m(C)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCCUCGGUUGUCCAGUAACUGUU
SSR-0106785	RNA1{m(U)[sp].[fl2r](G)[sp].m(C)p.m(C)p.m(U)p.[fl2r](C)p.m(G)p.m(G)p.m(U)p.m(U)p.m(G)p.m(U)p.m(C)p.[fl2r](C)p.m(A)p.[fl2r](G)p.m(U)p.m(A)p.m(A)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UGCCUCGGUUGUCCAGUAACUUU
SSR-0106786	RNA1{m(U)[sp].[fl2r](C)[sp].m(G)p.m(C)p.m(C)p.[fl2r](U)p.m(C)p.m(G)p.m(G)p.m(U)p.m(U)p.m(G)p.m(U)p.[fl2r](C)p.m(C)p.[fl2r](A)p.m(G)p.m(U)p.m(A)p.m(A)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UCGCCUCGGUUGUCCAGUAACUU

SSR-0106787	RNA1{m(U)[sp].[fl2r](G)[sp].m(A)p.m(G)p.m(C)p.[fl2r](C)p.m(G)p.m(C)p.m(C)p.m(U)p.m(C)p.m(G)p.m(G)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(U)p.m(C)p.m(C)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGAGCCGCCUCGGUUGUCCAGUU
SSR-0106788	RNA1{m(U)[sp].[fl2r](A)[sp].m(G)p.m(A)p.m(G)p.[fl2r](C)p.m(C)p.m(G)p.m(C)p.m(C)p.m(U)p.m(C)p.m(G)p.[fl2r](G)p.m(U)p.[fl2r](U)p.m(G)p.m(U)p.m(C)p.m(C)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UAGAGCCGCCUCGGUUGUCCAUU
SSR-0106789	RNA1{m(U)[sp].[fl2r](A)[sp].m(A)p.m(G)p.m(A)p.[fl2r](G)p.m(C)p.m(C)p.m(G)p.m(C)p.m(C)p.m(U)p.m(C)p.[fl2r](G)p.m(G)p.[fl2r](U)p.m(U)p.m(G)p.m(U)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UAAGAGCCGCCUCGGUUGUCCUU
SSR-0106790	RNA1{m(U)[sp].[fl2r](C)[sp].m(C)p.m(A)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(C)p.m(G)p.m(C)p.m(C)p.[fl2r](U)p.m(C)p.[fl2r](G)p.m(G)p.m(U)p.m(U)p.m(G)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UCCAAGAGCCGCCUCGGUUGUUU
SSR-0106791	RNA1{m(U)[sp].[fl2r](U)[sp].m(G)p.m(C)p.m(U)p.[fl2r](G)p.m(U)p.m(G)p.m(U)p.m(C)p.m(C)p.m(A)p.m(A)p.[fl2r](G)p.m(A)p.[fl2r](G)p.m(C)p.m(C)p.m(G)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UUGCUGUGUCCAAGAGCCGCCUU
SSR-0106792	RNA1{m(U)[sp].[fl2r](G)[sp].m(U)p.m(C)p.m(C)p.[fl2r](U)p.m(G)p.m(C)p.m(U)p.m(G)p.m(U)p.m(G)p.m(U)p.[fl2r](C)p.m(C)p.[fl2r](A)p.m(A)p.m(G)p.m(A)p.m(G)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UGUCCUGCUGUGUCCAAGAGCUU
SSR-0106793	RNA1{m(U)[sp].[fl2r](G)[sp].m(U)p.m(G)p.m(U)p.[fl2r](C)p.m(C)p.m(U)p.m(G)p.m(C)p.m(U)p.m(G)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](C)p.m(C)p.m(A)p.m(A)p.m(G)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UGUGUCCUGCUGUGUCCAAGAUU
SSR-0106794	RNA1{m(U)[sp].[fl2r](U)[sp].m(G)p.m(G)p.m(U)p.[fl2r](G)p.m(U)p.m(C)p.m(C)p.m(U)p.m(G)p.m(C)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(C)p.m(C)p.m(A)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UUGGUGUCCUGCUGUGUCCAAUU
SSR-0106795	RNA1{m(U)[sp].[fl2r](G)[sp].m(C)p.m(U)p.m(G)p.[fl2r](C)p.m(U)p.m(G)p.m(G)p.m(U)p.m(G)p.m(U)p.m(C)p.[fl2r](C)p.m(U)p.[fl2r](G)p.m(C)p.m(U)p.m(G)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGCUGCUGGUGUCCUGCUGUGUU
SSR-0106796	RNA1{m(U)[sp].[fl2r](A)[sp].m(G)p.m(C)p.m(U)p.[fl2r](C)p.m(U)p.m(A)p.m(G)p.m(G)p.m(A)p.m(A)p.m(G)p.[fl2r](G)p.m(G)p.[fl2r](C)p.m(U)p.m(G)p.m(C)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UAGCUCUAGGAAGGGCUGCUGUU
SSR-0106797	RNA1{m(U)[sp].[fl2r](U)[sp].m(C)p.m(U)p.m(U)p.[fl2r](A)p.m(A)p.m(G)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](A)p.m(A)p.m(G)p.m(G)p.m(G)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UUCUUAAGCUCUAGGAAGGGCUU
SSR-0106798	RNA1{m(U)[sp].[fl2r](C)[sp].m(G)p.m(G)p.m(A)p.[fl2r](U)p.m(C)p.m(U)p.m(U)p.m(A)p.m(A)p.m(G)p.m(C)p.[fl2r](U)p.m(C)p.[fl2r](U)p.m(A)p.m(G)p.m(G)p.m(A)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UCGGAUCUUAAGCUCUAGGAAUU

SSR-0106799	RNA1{m(U)[sp].[fl2r](U)[sp].m(C)p.m(G)p.m(G)p.[fl2r](A)p.m(U)p.m(C)p.m(U)p.m(U)p.m(A)p.m(A)p.m(G)p.[fl2r](C)p.m(U)p.[fl2r](C)p.m(U)p.m(A)p.m(G)p.m(G)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UUCGGAUCUUAAGCUCUAGGAUU
SSR-0106800	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.m(C)p.m(G)p.[fl2r](G)p.m(A)p.m(U)p.m(C)p.m(U)p.m(U)p.m(A)p.m(A)p.[fl2r](G)p.m(C)p.[fl2r](U)p.m(C)p.m(U)p.m(A)p.m(G)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUCGGAUCUUAAGCUCUAGGUU
SSR-0106801	RNA1{m(U)[sp].[fl2r](G)[sp].m(C)p.m(U)p.m(C)p.[fl2r](G)p.m(G)p.m(A)p.m(U)p.m(C)p.m(U)p.m(U)p.m(A)p.[fl2r](A)p.m(G)p.[fl2r](C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGCUCGGAUCUUAAGCUCUAGUU
SSR-0106802	RNA1{m(U)[sp].[fl2r](G)[sp].m(G)p.m(C)p.m(U)p.[fl2r](C)p.m(G)p.m(G)p.m(A)p.m(U)p.m(C)p.m(U)p.m(U)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UGGCUCGGAUCUUAAGCUCUAUU
SSR-0106803	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(U)p.m(U)p.[fl2r](G)p.m(G)p.m(C)p.m(U)p.m(C)p.m(G)p.m(G)p.m(A)p.[fl2r](U)p.m(C)p.[fl2r](U)p.m(U)p.m(A)p.m(A)p.m(G)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UCAUUGGCUCGGAUCUUAAGCUU
SSR-0106804	RNA1{m(U)[sp].[fl2r](U)[sp].m(C)p.m(A)p.m(U)p.[fl2r](U)p.m(G)p.m(G)p.m(C)p.m(U)p.m(C)p.m(G)p.m(G)p.[fl2r](A)p.m(U)p.[fl2r](C)p.m(U)p.m(U)p.m(A)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UUCAUUGGCUCGGAUCUUAAGUU
SSR-0106805	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.m(C)p.m(A)p.[fl2r](U)p.m(U)p.m(G)p.m(G)p.m(C)p.m(U)p.m(C)p.m(G)p.[fl2r](G)p.m(A)p.[fl2r](U)p.m(C)p.m(U)p.m(U)p.m(A)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUCAUUGGCUCGGAUCUUAAUU
SSR-0106806	RNA1{m(U)[sp].[fl2r](U)[sp].m(G)p.m(C)p.m(U)p.[fl2r](C)p.m(C)p.m(A)p.m(G)p.m(G)p.m(C)p.m(U)p.m(C)p.[fl2r](A)p.m(U)p.[fl2r](U)p.m(G)p.m(G)p.m(C)p.m(U)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UUGCUCCAGGCUCAUUGGCUCUU
SSR-0106807	RNA1{m(U)[sp].[fl2r](G)[sp].m(G)p.m(U)p.m(C)p.[fl2r](C)p.m(U)p.m(C)p.m(C)p.m(U)p.m(C)p.m(C)p.m(U)p.[fl2r](G)p.m(G)p.[fl2r](C)p.m(C)p.m(C)p.m(G)p.m(G)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UGGUCCUCCUCCUGGCCCGGCUU
SSR-0106808	RNA1{m(U)[sp].[fl2r](G)[sp].m(G)p.m(G)p.m(U)p.[fl2r](C)p.m(C)p.m(U)p.m(C)p.m(C)p.m(U)p.m(C)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](G)p.m(C)p.m(C)p.m(C)p.m(G)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGGGUCCUCCUCCUGGCCCGGUU
SSR-0106809	RNA1{m(U)[sp].[fl2r](G)[sp].m(U)p.m(C)p.m(G)p.[fl2r](C)p.m(A)p.m(G)p.m(G)p.m(C)p.m(U)p.m(C)p.m(A)p.[fl2r](C)p.m(A)p.[fl2r](G)p.m(G)p.m(U)p.m(G)p.m(G)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGUCGCAGGCUCACAGGUGGGUU
SSR-0106810	RNA1{m(U)[sp].[fl2r](G)[sp].m(G)p.m(G)p.m(U)p.[fl2r](C)p.m(G)p.m(C)p.m(A)p.m(G)p.m(G)p.m(C)p.m(U)p.[fl2r](C)p.m(A)p.[fl2r](C)p.m(A)p.m(G)p.m(G)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGGGUCGCAGGCUCACAGGUGUU

SSR-0106811	RNA1{m(U)[sp].[fl2r](U)[sp].m(C)p.m(U)p.m(C)p.[fl2r](G)p.m(C)p.m(C)p.m(U)p.m(G)p.m(C)p.m(A)p.m(A)p.[fl2r](C)p.m(A)p.[fl2r](U)p.m(A)p.m(A)p.m(G)p.m(G)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UUCUCGCCUGCAACAUAAGGGUU
SSR-0106812	RNA1{m(U)[sp].[fl2r](G)[sp].m(U)p.m(C)p.m(U)p.[fl2r](C)p.m(G)p.m(C)p.m(C)p.m(U)p.m(G)p.m(C)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(U)p.m(A)p.m(A)p.m(G)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGUCUCGCCUGCAACAUAAGGUU
SSR-0106813	RNA1{m(U)[sp].[fl2r](U)[sp].m(A)p.m(A)p.m(U)p.[fl2r](G)p.m(G)p.m(U)p.m(C)p.m(U)p.m(C)p.m(G)p.m(C)p.[fl2r](C)p.m(U)p.[fl2r](G)p.m(C)p.m(A)p.m(A)p.m(C)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UUAAUGGUCUCGCCUGCAACAUU
SSR-0106814	RNA1{m(U)[sp].[fl2r](G)[sp].m(U)p.m(A)p.m(A)p.[fl2r](U)p.m(G)p.m(G)p.m(U)p.m(C)p.m(U)p.m(C)p.m(G)p.[fl2r](C)p.m(C)p.[fl2r](U)p.m(G)p.m(C)p.m(A)p.m(A)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UGUAAUGGUCUCGCCUGCAACUU
SSR-0106815	RNA1{m(U)[sp].[fl2r](U)[sp].m(A)p.m(C)p.m(G)p.[fl2r](U)p.m(A)p.m(A)p.m(U)p.m(G)p.m(G)p.m(U)p.m(C)p.[fl2r](U)p.m(C)p.[fl2r](G)p.m(C)p.m(C)p.m(U)p.m(G)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UUACGUAAUGGUCUCGCCUGCUU
SSR-0106816	RNA1{m(U)[sp].[fl2r](U)[sp].m(C)p.m(U)p.m(A)p.[fl2r](C)p.m(G)p.m(U)p.m(A)p.m(A)p.m(U)p.m(G)p.m(G)p.[fl2r](U)p.m(C)p.[fl2r](U)p.m(C)p.m(G)p.m(C)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UUCUACGUAAUGGUCUCGCCUUU
SSR-0106817	RNA1{m(U)[sp].[fl2r](G)[sp].m(U)p.m(C)p.m(U)p.[fl2r](A)p.m(C)p.m(G)p.m(U)p.m(A)p.m(A)p.m(U)p.m(G)p.[fl2r](G)p.m(U)p.[fl2r](C)p.m(U)p.m(C)p.m(G)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UGUCUACGUAAUGGUCUCGCCUU
SSR-0106818	RNA1{m(U)[sp].[fl2r](G)[sp].m(C)p.m(C)p.m(A)p.[fl2r](U)p.m(C)p.m(C)p.m(C)p.m(A)p.m(G)p.m(U)p.m(U)p.[fl2r](C)p.m(C)p.[fl2r](U)p.m(G)p.m(G)p.m(A)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGCCAUCCCAGUUCCUGGAAGUU
SSR-0106819	RNA1{m(U)[sp].[fl2r](U)[sp].m(C)p.m(C)p.m(C)p.[fl2r](G)p.m(C)p.m(C)p.m(A)p.m(U)p.m(C)p.m(C)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](U)p.m(U)p.m(C)p.m(C)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UUCCCGCCAUCCCAGUUCCUGUU
SSR-0106820	RNA1{m(U)[sp].[fl2r](G)[sp].m(U)p.m(C)p.m(C)p.[fl2r](C)p.m(G)p.m(C)p.m(C)p.m(A)p.m(U)p.m(C)p.m(C)p.[fl2r](C)p.m(A)p.[fl2r](G)p.m(U)p.m(U)p.m(C)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UGUCCCGCCAUCCCAGUUCCUUU
SSR-0106821	RNA1{m(U)[sp].[fl2r](A)[sp].m(G)p.m(U)p.m(C)p.[fl2r](C)p.m(C)p.m(G)p.m(C)p.m(C)p.m(A)p.m(U)p.m(C)p.[fl2r](C)p.m(C)p.[fl2r](A)p.m(G)p.m(U)p.m(U)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UAGUCCCGCCAUCCCAGUUCCUU
SSR-0106822	RNA1{m(U)[sp].[fl2r](U)[sp].m(A)p.m(U)p.m(C)p.[fl2r](C)p.m(A)p.m(G)p.m(U)p.m(C)p.m(C)p.m(C)p.m(G)p.[fl2r](C)p.m(C)p.[fl2r](A)p.m(U)p.m(C)p.m(C)p.m(C)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UUAUCCAGUCCCGCCAUCCCAUU

SSR-0106823	RNA1{m(U)[sp].[fl2r](G)[sp].m(U)p.m(A)p.m(U)p.[fl2r](C)p.m(C)p.m(A)p.m(G)p.m(U)p.m(C)p.m(C)p.m(C)p.[fl2r](G)p.m(C)p.[fl2r](C)p.m(A)p.m(U)p.m(C)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UGUAUCCAGUCCCGCCAUCCCUU
SSR-0106824	RNA1{m(U)[sp].[fl2r](A)[sp].m(G)p.m(U)p.m(A)p.[fl2r](U)p.m(C)p.m(C)p.m(A)p.m(G)p.m(U)p.m(C)p.m(C)p.[fl2r](C)p.m(G)p.[fl2r](C)p.m(C)p.m(A)p.m(U)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UAGUAUCCAGUCCCGCCAUCCUU
SSR-0106825	RNA1{m(U)[sp].[fl2r](G)[sp].m(C)p.m(A)p.m(G)p.[fl2r](U)p.m(A)p.m(U)p.m(C)p.m(C)p.m(A)p.m(G)p.m(U)p.[fl2r](C)p.m(C)p.[fl2r](C)p.m(G)p.m(C)p.m(C)p.m(A)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UGCAGUAUCCAGUCCCGCCAUUU
SSR-0106826	RNA1{m(U)[sp].[fl2r](U)[sp].m(G)p.m(C)p.m(A)p.[fl2r](G)p.m(U)p.m(A)p.m(U)p.m(C)p.m(C)p.m(A)p.m(G)p.[fl2r](U)p.m(C)p.[fl2r](C)p.m(C)p.m(G)p.m(C)p.m(C)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UUGCAGUAUCCAGUCCCGCCAUU
SSR-0106827	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.m(C)p.m(G)p.[fl2r](G)p.m(G)p.m(C)p.m(U)p.m(G)p.m(C)p.m(A)p.m(G)p.[fl2r](U)p.m(A)p.[fl2r](U)p.m(C)p.m(C)p.m(A)p.m(G)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUCGGGCUGCAGUAUCCAGUUU
SSR-0106828	RNA1{m(U)[sp].[fl2r](C)[sp].m(C)p.m(U)p.m(C)p.[fl2r](G)p.m(G)p.m(G)p.m(C)p.m(U)p.m(G)p.m(C)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(U)p.m(C)p.m(C)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCCUCGGGCUGCAGUAUCCAGUU
SSR-0106829	RNA1{m(U)[sp].[fl2r](C)[sp].m(C)p.m(C)p.m(U)p.[fl2r](C)p.m(G)p.m(G)p.m(G)p.m(C)p.m(U)p.m(G)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](U)p.m(A)p.m(U)p.m(C)p.m(C)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UCCCUCGGGCUGCAGUAUCCAUU
SSR-0106830	RNA1{m(U)[sp].[fl2r](G)[sp].m(C)p.m(A)p.m(G)p.[fl2r](U)p.m(A)p.m(A)p.m(U)p.m(U)p.m(C)p.m(A)p.m(G)p.[fl2r](C)p.m(U)p.[fl2r](G)p.m(G)p.m(U)p.m(A)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UGCAGUAAUUCAGCUGGUACCUU
SSR-0106831	RNA1{m(U)[sp].[fl2r](U)[sp].m(G)p.m(C)p.m(A)p.[fl2r](G)p.m(U)p.m(A)p.m(A)p.m(U)p.m(U)p.m(C)p.m(A)p.[fl2r](G)p.m(C)p.[fl2r](U)p.m(G)p.m(G)p.m(U)p.m(A)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UUGCAGUAAUUCAGCUGGUACUU
SSR-0106832	RNA1{m(U)[sp].[fl2r](A)[sp].m(A)p.m(U)p.m(G)p.[fl2r](C)p.m(C)p.m(U)p.m(G)p.m(G)p.m(G)p.m(C)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](C)p.m(A)p.m(G)p.m(C)p.m(C)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UAAUGCCUGGGCUGCCAGCCAUU
SSR-0106833	RNA1{m(U)[sp].[fl2r](A)[sp].m(G)p.m(A)p.m(C)p.[fl2r](G)p.m(G)p.m(C)p.m(A)p.m(G)p.m(A)p.m(A)p.m(U)p.[fl2r](G)p.m(G)p.[fl2r](A)p.m(A)p.m(A)p.m(G)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UAGACGGCAGAAUGGAAAGAGUU
SSR-0106834	RNA1{m(U)[sp].[fl2r](A)[sp].m(A)p.m(G)p.m(A)p.[fl2r](C)p.m(G)p.m(G)p.m(C)p.m(A)p.m(G)p.m(A)p.m(A)p.[fl2r](U)p.m(G)p.[fl2r](G)p.m(A)p.m(A)p.m(A)p.m(G)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UAAGACGGCAGAAUGGAAAGAUU

SSR-0106835	RNA1{m(U)[sp].[fl2r](G)[sp].m(A)p.m(A)p.m(G)p.[fl2r](A)p.m(C)p.m(G)p.m(G)p.m(C)p.m(A)p.m(G)p.m(A)p.[fl2r](A)p.m(U)p.[fl2r](G)p.m(G)p.m(A)p.m(A)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGAAGACGGCAGAAUGGAAAGUU
SSR-0106836	RNA1{m(U)[sp].[fl2r](U)[sp].m(U)p.m(G)p.m(A)p.[fl2r](G)p.m(G)p.m(A)p.m(G)p.m(G)p.m(C)p.m(U)p.m(G)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(A)p.m(C)p.m(G)p.m(G)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UUUGAGGAGGCUGAAGACGGCUU
SSR-0106837	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.m(U)p.m(U)p.[fl2r](G)p.m(A)p.m(G)p.m(G)p.m(A)p.m(G)p.m(G)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](A)p.m(A)p.m(G)p.m(A)p.m(C)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUUUGAGGAGGCUGAAGACGUU
SSR-0106838	RNA1{m(U)[sp].[fl2r](G)[sp].m(C)p.m(U)p.m(U)p.[fl2r](U)p.m(G)p.m(A)p.m(G)p.m(G)p.m(A)p.m(G)p.m(G)p.[fl2r](C)p.m(U)p.[fl2r](G)p.m(A)p.m(A)p.m(G)p.m(A)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UGCUUUGAGGAGGCUGAAGACUU
SSR-0106839	RNA1{m(U)[sp].[fl2r](G)[sp].m(G)p.m(C)p.m(U)p.[fl2r](U)p.m(U)p.m(G)p.m(A)p.m(G)p.m(G)p.m(A)p.m(G)p.[fl2r](G)p.m(C)p.[fl2r](U)p.m(G)p.m(A)p.m(A)p.m(G)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UGGCUUUGAGGAGGCUGAAGAUU
SSR-0106840	RNA1{m(U)[sp].[fl2r](G)[sp].m(G)p.m(A)p.m(U)p.[fl2r](U)p.m(G)p.m(U)p.m(U)p.m(G)p.m(G)p.m(C)p.m(U)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(A)p.m(G)p.m(G)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGGAUUGUUGGCUUUGAGGAGUU
SSR-0106841	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(A)p.m(G)p.[fl2r](G)p.m(A)p.m(U)p.m(U)p.m(G)p.m(U)p.m(U)p.m(G)p.[fl2r](G)p.m(C)p.[fl2r](U)p.m(U)p.m(U)p.m(G)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCAAGGAUUGUUGGCUUUGAGUU
SSR-0106842	RNA1{m(U)[sp].[fl2r](C)[sp].m(C)p.m(A)p.m(A)p.[fl2r](G)p.m(G)p.m(A)p.m(U)p.m(U)p.m(G)p.m(U)p.m(U)p.[fl2r](G)p.m(G)p.[fl2r](C)p.m(U)p.m(U)p.m(U)p.m(G)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UCCAAGGAUUGUUGGCUUUGAUU
SSR-0106843	RNA1{m(U)[sp].[fl2r](G)[sp].m(C)p.m(A)p.m(G)p.[fl2r](G)p.m(C)p.m(C)p.m(A)p.m(A)p.m(G)p.m(G)p.m(A)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(G)p.m(G)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UGCAGGCCAAGGAUUGUUGGCUU
SSR-0106844	RNA1{m(U)[sp].[fl2r](G)[sp].m(A)p.m(G)p.m(G)p.[fl2r](U)p.m(A)p.m(C)p.m(U)p.m(G)p.m(G)p.m(C)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](C)p.m(C)p.m(A)p.m(A)p.m(G)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGAGGUACUGGCAGGCCAAGGUU
SSR-0106845	RNA1{m(U)[sp].[fl2r](A)[sp].m(C)p.m(A)p.m(A)p.[fl2r](C)p.m(A)p.m(G)p.m(G)p.m(A)p.m(G)p.m(G)p.m(U)p.[fl2r](A)p.m(C)p.[fl2r](U)p.m(G)p.m(G)p.m(C)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UACAACAGGAGGUACUGGCAGUU
SSR-0106846	RNA1{m(U)[sp].[fl2r](A)[sp].m(G)p.m(U)p.m(A)p.[fl2r](G)p.m(G)p.m(G)p.m(A)p.m(C)p.m(A)p.m(C)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(G)p.m(G)p.m(A)p.m(G)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UAGUAGGGACACAACAGGAGGUU

SSR-0106847	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(G)p.m(U)p.[fl2r](A)p.m(G)p.m(G)p.m(G)p.m(A)p.m(C)p.m(A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](C)p.m(A)p.m(G)p.m(G)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCAGUAGGGACACAACAGGAGUU
SSR-0106848	RNA1{m(U)[sp].[fl2r](G)[sp].m(C)p.m(A)p.m(G)p.[fl2r](U)p.m(A)p.m(G)p.m(G)p.m(G)p.m(A)p.m(C)p.m(A)p.[fl2r](C)p.m(A)p.[fl2r](A)p.m(C)p.m(A)p.m(G)p.m(G)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UGCAGUAGGGACACAACAGGAUU
SSR-0106849	RNA1{m(U)[sp].[fl2r](G)[sp].m(G)p.m(C)p.m(A)p.[fl2r](G)p.m(U)p.m(A)p.m(G)p.m(G)p.m(G)p.m(A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)p.m(C)p.m(A)p.m(G)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGGCAGUAGGGACACAACAGGUU
SSR-0106850	RNA1{m(U)[sp].[fl2r](U)[sp].m(U)p.m(C)p.m(G)p.[fl2r](G)p.m(G)p.m(C)p.m(A)p.m(G)p.m(U)p.m(A)p.m(G)p.[fl2r](G)p.m(G)p.[fl2r](A)p.m(C)p.m(A)p.m(C)p.m(A)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UUUCGGGCAGUAGGGACACAAUU
SSR-0106851	RNA1{m(U)[sp].[fl2r](C)[sp].m(C)p.m(U)p.m(U)p.[fl2r](C)p.m(G)p.m(G)p.m(G)p.m(C)p.m(A)p.m(G)p.m(U)p.[fl2r](A)p.m(G)p.[fl2r](G)p.m(G)p.m(A)p.m(C)p.m(A)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UCCUUCGGGCAGUAGGGACACUU
SSR-0106852	RNA1{m(U)[sp].[fl2r](G)[sp].m(G)p.m(G)p.m(C)p.[fl2r](C)p.m(U)p.m(U)p.m(C)p.m(G)p.m(G)p.m(G)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](U)p.m(A)p.m(G)p.m(G)p.m(G)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UGGGCCUUCGGGCAGUAGGGAUU
SSR-0106853	RNA1{m(U)[sp].[fl2r](U)[sp].m(U)p.m(A)p.m(U)p.[fl2r](G)p.m(A)p.m(U)p.m(C)p.m(C)p.m(A)p.m(G)p.m(G)p.[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(G)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UUUAUGAUCCAGGUAGAGGAGUU
SSR-0106854	RNA1{m(U)[sp].[fl2r](A)[sp].m(U)p.m(U)p.m(A)p.[fl2r](U)p.m(G)p.m(A)p.m(U)p.m(C)p.m(C)p.m(A)p.m(G)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)p.m(A)p.m(G)p.m(G)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UAUUAUGAUCCAGGUAGAGGAUU
SSR-0106855	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(U)p.m(U)p.[fl2r](A)p.m(U)p.m(G)p.m(A)p.m(U)p.m(C)p.m(C)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](U)p.m(A)p.m(G)p.m(A)p.m(G)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCAUUAUGAUCCAGGUAGAGGUU
SSR-0106856	RNA1{m(U)[sp].[fl2r](A)[sp].m(U)p.m(U)p.m(G)p.[fl2r](C)p.m(C)p.m(A)p.m(U)p.m(U)p.m(A)p.m(U)p.m(G)p.[fl2r](A)p.m(U)p.[fl2r](C)p.m(C)p.m(A)p.m(G)p.m(G)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UAUUGCCAUUAUGAUCCAGGUUU
SSR-0106857	RNA1{m(U)[sp].[fl2r](A)[sp].m(C)p.m(A)p.m(U)p.[fl2r](U)p.m(G)p.m(C)p.m(C)p.m(A)p.m(U)p.m(U)p.m(A)p.[fl2r](U)p.m(G)p.[fl2r](A)p.m(U)p.m(C)p.m(C)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UACAUUGCCAUUAUGAUCCAGUU
SSR-0106858	RNA1{m(U)[sp].[fl2r](U)[sp].m(G)p.m(A)p.m(C)p.[fl2r](C)p.m(A)p.m(C)p.m(A)p.m(U)p.m(U)p.m(G)p.m(C)p.[fl2r](C)p.m(A)p.[fl2r](U)p.m(U)p.m(A)p.m(U)p.m(G)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UUGACCACAUUGCCAUUAUGAUU

SSR-0106859	RNA1{m(U)[sp].[fl2r](C)[sp].m(G)p.m(U)p.m(C)p.[fl2r](U)p.m(U)p.m(G)p.m(A)p.m(C)p.m(C)p.m(A)p.m(C)p.[fl2r](A)p.m(U)p.[fl2r](U)p.m(G)p.m(C)p.m(C)p.m(A)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UCGUCUUGACCACAUUGCCAUUU
SSR-0106860	RNA1{m(U)[sp].[fl2r](C)[sp].m(C)p.m(G)p.m(U)p.[fl2r](C)p.m(U)p.m(U)p.m(G)p.m(A)p.m(C)p.m(C)p.m(A)p.[fl2r](C)p.m(A)p.[fl2r](U)p.m(U)p.m(G)p.m(C)p.m(C)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UCCGUCUUGACCACAUUGCCAUU
SSR-0106861	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(U)p.m(C)p.[fl2r](C)p.m(G)p.m(U)p.m(C)p.m(U)p.m(U)p.m(G)p.m(A)p.[fl2r](C)p.m(C)p.[fl2r](A)p.m(C)p.m(A)p.m(U)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCAUCCGUCUUGACCACAUUGUU
SSR-0106862	RNA1{m(U)[sp].[fl2r](A)[sp].m(C)p.m(A)p.m(U)p.[fl2r](C)p.m(C)p.m(G)p.m(U)p.m(C)p.m(U)p.m(U)p.m(G)p.[fl2r](A)p.m(C)p.[fl2r](C)p.m(A)p.m(C)p.m(A)p.m(U)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UACAUCCGUCUUGACCACAUUUU
SSR-0106863	RNA1{m(U)[sp].[fl2r](U)[sp].m(C)p.m(U)p.m(G)p.[fl2r](G)p.m(C)p.m(A)p.m(C)p.m(A)p.m(U)p.m(C)p.m(C)p.[fl2r](G)p.m(U)p.[fl2r](C)p.m(U)p.m(U)p.m(G)p.m(A)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UUCUGGCACAUCCGUCUUGACUU
SSR-0106864	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(U)p.m(A)p.[fl2r](U)p.m(C)p.m(U)p.m(G)p.m(G)p.m(C)p.m(A)p.m(C)p.[fl2r](A)p.m(U)p.[fl2r](C)p.m(C)p.m(G)p.m(U)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UCAUAUCUGGCACAUCCGUCUUU
SSR-0106865	RNA1{m(U)[sp].[fl2r](C)[sp].m(C)p.m(A)p.m(U)p.[fl2r](A)p.m(U)p.m(C)p.m(U)p.m(G)p.m(G)p.m(C)p.m(A)p.[fl2r](C)p.m(A)p.[fl2r](U)p.m(C)p.m(C)p.m(G)p.m(U)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UCCAUAUCUGGCACAUCCGUCUU
SSR-0106866	RNA1{m(U)[sp].[fl2r](U)[sp].m(C)p.m(C)p.m(A)p.[fl2r](C)p.m(C)p.m(A)p.m(C)p.m(C)p.m(A)p.m(U)p.m(A)p.[fl2r](U)p.m(C)p.[fl2r](U)p.m(G)p.m(G)p.m(C)p.m(A)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UUCCACCACCAUAUCUGGCACUU
SSR-0106867	RNA1{m(U)[sp].[fl2r](U)[sp].m(U)p.m(G)p.m(G)p.[fl2r](U)p.m(C)p.m(U)p.m(C)p.m(U)p.m(U)p.m(C)p.m(A)p.[fl2r](C)p.m(U)p.[fl2r](C)p.m(C)p.m(A)p.m(A)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UUUGGUCUCUUCACUCCAAAGUU
SSR-0106868	RNA1{m(U)[sp].[fl2r](A)[sp].m(A)p.m(C)p.m(U)p.[fl2r](U)p.m(C)p.m(A)p.m(U)p.m(C)p.m(U)p.m(U)p.m(G)p.[fl2r](G)p.m(U)p.[fl2r](C)p.m(U)p.m(C)p.m(U)p.m(U)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UAACUUCAUCUUGGUCUCUUCUU
SSR-0106869	RNA1{m(U)[sp].[fl2r](G)[sp].m(G)p.m(G)p.m(A)p.[fl2r](A)p.m(A)p.m(C)p.m(U)p.m(U)p.m(C)p.m(A)p.m(U)p.[fl2r](C)p.m(U)p.[fl2r](U)p.m(G)p.m(G)p.m(U)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UGGGAAACUUCAUCUUGGUCUUU
SSR-0106870	RNA1{m(U)[sp].[fl2r](G)[sp].m(A)p.m(U)p.m(G)p.[fl2r](C)p.m(C)p.m(C)p.m(U)p.m(G)p.m(U)p.m(G)p.m(C)p.[fl2r](C)p.m(U)p.[fl2r](G)p.m(G)p.m(G)p.m(A)p.m(A)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UGAUGCCCUGUGCCUGGGAAAUU

SSR-0106871	RNA1{m(U)[sp].[fl2r](A)[sp].m(G)p.m(U)p.m(C)p.[fl2r](A)p.m(C)p.m(A)p.m(G)p.m(A)p.m(U)p.m(G)p.m(C)p.[fl2r](C)p.m(C)p.[fl2r](U)p.m(G)p.m(U)p.m(G)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UAGUCACAGAUGCCCUGUGCCUU
SSR-0106872	RNA1{m(U)[sp].[fl2r](U)[sp].m(C)p.m(U)p.m(G)p.[fl2r](A)p.m(U)p.m(G)p.m(C)p.m(C)p.m(U)p.m(C)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](U)p.m(C)p.m(A)p.m(C)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UUCUGAUGCCUCCAGUCACAGUU
SSR-0106873	RNA1{m(U)[sp].[fl2r](A)[sp].m(G)p.m(G)p.m(A)p.[fl2r](A)p.m(U)p.m(C)p.m(U)p.m(G)p.m(A)p.m(U)p.m(G)p.[fl2r](C)p.m(C)p.[fl2r](U)p.m(C)p.m(C)p.m(A)p.m(G)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UAGGAAUCUGAUGCCUCCAGUUU
SSR-0106874	RNA1{m(U)[sp].[fl2r](U)[sp].m(U)p.m(G)p.m(C)p.[fl2r](C)p.m(A)p.m(G)p.m(G)p.m(U)p.m(G)p.m(G)p.m(U)p.[fl2r](U)p.m(G)p.[fl2r](U)p.m(U)p.m(G)p.m(G)p.m(G)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UUUGCCAGGUGGUUGUUGGGUUU
SSR-0106875	RNA1{m(U)[sp].[fl2r](A)[sp].m(U)p.m(U)p.m(G)p.[fl2r](C)p.m(C)p.m(A)p.m(G)p.m(G)p.m(U)p.m(G)p.m(G)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(G)p.m(G)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UAUUGCCAGGUGGUUGUUGGGUU
SSR-0106876	RNA1{m(U)[sp].[fl2r](U)[sp].m(C)p.m(A)p.m(U)p.[fl2r](A)p.m(U)p.m(U)p.m(G)p.m(C)p.m(C)p.m(A)p.m(G)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(G)p.m(U)p.m(U)p.m(G)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UUCAUAUUGCCAGGUGGUUGUUU
SSR-0106877	RNA1{m(U)[sp].[fl2r](A)[sp].m(G)p.m(U)p.m(C)p.[fl2r](A)p.m(U)p.m(A)p.m(U)p.m(U)p.m(G)p.m(C)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](G)p.m(U)p.m(G)p.m(G)p.m(U)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UAGUCAUAUUGCCAGGUGGUUUU
SSR-0106878	RNA1{m(U)[sp].[fl2r](G)[sp].m(A)p.m(G)p.m(U)p.[fl2r](C)p.m(A)p.m(U)p.m(A)p.m(U)p.m(U)p.m(G)p.m(C)p.[fl2r](C)p.m(A)p.[fl2r](G)p.m(G)p.m(U)p.m(G)p.m(G)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UGAGUCAUAUUGCCAGGUGGUUU
SSR-0106879	RNA1{m(U)[sp].[fl2r](G)[sp].m(U)p.m(G)p.m(A)p.[fl2r](G)p.m(U)p.m(C)p.m(A)p.m(U)p.m(A)p.m(U)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](C)p.m(A)p.m(G)p.m(G)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGUGAGUCAUAUUGCCAGGUGUU
SSR-0106880	RNA1{m(U)[sp].[fl2r](G)[sp].m(A)p.m(A)p.m(A)p.[fl2r](G)p.m(U)p.m(G)p.m(C)p.m(C)p.m(C)p.m(A)p.m(U)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(G)p.m(G)p.m(U)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UGAAAGUGCCCAUUUGGGUCCUU
SSR-0106881	RNA1{m(U)[sp].[fl2r](A)[sp].m(C)p.m(A)p.m(A)p.[fl2r](G)p.m(A)p.m(A)p.m(A)p.m(G)p.m(U)p.m(G)p.m(C)p.[fl2r](C)p.m(C)p.[fl2r](A)p.m(U)p.m(U)p.m(U)p.m(G)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UACAAGAAAGUGCCCAUUUGGUU
SSR-0106882	RNA1{m(U)[sp].[fl2r](G)[sp].m(A)p.m(C)p.m(A)p.[fl2r](A)p.m(G)p.m(A)p.m(A)p.m(A)p.m(G)p.m(U)p.m(G)p.[fl2r](C)p.m(C)p.[fl2r](C)p.m(A)p.m(U)p.m(U)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGACAAGAAAGUGCCCAUUUGUU

SSR-0106883	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(G)p.m(A)p.[fl2r](C)p.m(A)p.m(A)p.m(G)p.m(A)p.m(A)p.m(A)p.m(G)p.[fl2r](U)p.m(G)p.[fl2r](C)p.m(C)p.m(C)p.m(A)p.m(U)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UCAGACAAGAAAGUGCCCAUUUU
SSR-0106884	RNA1{m(U)[sp].[fl2r](U)[sp].m(C)p.m(A)p.m(G)p.[fl2r](A)p.m(C)p.m(A)p.m(A)p.m(G)p.m(A)p.m(A)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.m(C)p.m(C)p.m(A)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UUCAGACAAGAAAGUGCCCAUUU
SSR-0106885	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.m(C)p.m(A)p.[fl2r](G)p.m(A)p.m(C)p.m(A)p.m(A)p.m(G)p.m(A)p.m(A)p.[fl2r](A)p.m(G)p.[fl2r](U)p.m(G)p.m(C)p.m(C)p.m(C)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUCAGACAAGAAAGUGCCCAUU
SSR-0106886	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(U)p.m(C)p.[fl2r](A)p.m(G)p.m(C)p.m(C)p.m(A)p.m(A)p.m(C)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](G)p.m(A)p.m(A)p.m(U)p.m(A)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UCAUCAGCCAACCUGGAAUAAUU
SSR-0106887	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(C)p.m(A)p.[fl2r](U)p.m(C)p.m(A)p.m(G)p.m(C)p.m(C)p.m(A)p.m(A)p.[fl2r](C)p.m(C)p.[fl2r](U)p.m(G)p.m(G)p.m(A)p.m(A)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UCACAUCAGCCAACCUGGAAUUU
SSR-0106888	RNA1{m(U)[sp].[fl2r](A)[sp].m(U)p.m(C)p.m(U)p.[fl2r](C)p.m(C)p.m(C)p.m(A)p.m(A)p.m(C)p.m(A)p.m(C)p.[fl2r](A)p.m(U)p.[fl2r](C)p.m(A)p.m(G)p.m(C)p.m(C)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UAUCUCCCAACACAUCAGCCAUU
SSR-0106889	RNA1{m(U)[sp].[fl2r](A)[sp].m(G)p.m(A)p.m(A)p.[fl2r](A)p.m(C)p.m(G)p.m(C)p.m(U)p.m(U)p.m(U)p.m(A)p.[fl2r](C)p.m(C)p.[fl2r](C)p.m(A)p.m(U)p.m(C)p.m(U)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UAGAAACGCUUUACCCAUCUCUU
SSR-0106890	RNA1{m(U)[sp].[fl2r](U)[sp].m(A)p.m(G)p.m(A)p.[fl2r](A)p.m(G)p.m(A)p.m(A)p.m(A)p.m(C)p.m(G)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](U)p.m(A)p.m(C)p.m(C)p.m(C)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UUAGAAGAAACGCUUUACCCAUU
SSR-0106891	RNA1{m(U)[sp].[fl2r](U)[sp].m(U)p.m(U)p.m(A)p.[fl2r](G)p.m(A)p.m(A)p.m(G)p.m(A)p.m(A)p.m(A)p.m(C)p.[fl2r](G)p.m(C)p.[fl2r](U)p.m(U)p.m(U)p.m(A)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UUUUAGAAGAAACGCUUUACCUU
SSR-0106892	RNA1{m(U)[sp].[fl2r](U)[sp].m(A)p.m(G)p.m(G)p.[fl2r](G)p.m(C)p.m(A)p.m(G)p.m(G)p.m(A)p.m(A)p.m(A)p.[fl2r](U)p.m(C)p.[fl2r](A)p.m(U)p.m(G)p.m(C)p.m(U)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UUAGGGCAGGAAAUCAUGCUUUU
SSR-0106893	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.m(U)p.m(A)p.[fl2r](G)p.m(G)p.m(G)p.m(C)p.m(A)p.m(G)p.m(G)p.m(A)p.[fl2r](A)p.m(A)p.[fl2r](U)p.m(C)p.m(A)p.m(U)p.m(G)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUUAGGGCAGGAAAUCAUGCUU
SSR-0106894	RNA1{m(U)[sp].[fl2r](A)[sp].m(C)p.m(U)p.m(U)p.[fl2r](A)p.m(G)p.m(G)p.m(G)p.m(C)p.m(A)p.m(G)p.m(G)p.[fl2r](A)p.m(A)p.[fl2r](A)p.m(U)p.m(C)p.m(A)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UACUUAGGGCAGGAAAUCAUGUU

SSR-0106895	RNA1{m(U)[sp].[fl2r](G)[sp].m(A)p.m(C)p.m(U)p.[fl2r](U)p.m(A)p.m(G)p.m(G)p.m(G)p.m(C)p.m(A)p.m(G)p.[fl2r](G)p.m(A)p.[fl2r](A)p.m(A)p.m(U)p.m(C)p.m(A)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UGACUUAGGGCAGGAAAUCAUUU
SSR-0106896	RNA1{m(U)[sp].[fl2r](G)[sp].m(G)p.m(A)p.m(C)p.[fl2r](U)p.m(U)p.m(A)p.m(G)p.m(G)p.m(G)p.m(C)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](A)p.m(A)p.m(A)p.m(U)p.m(C)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UGGACUUAGGGCAGGAAAUCAUU
SSR-0106897	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(C)p.m(A)p.[fl2r](G)p.m(G)p.m(A)p.m(C)p.m(U)p.m(U)p.m(A)p.m(G)p.[fl2r](G)p.m(G)p.[fl2r](C)p.m(A)p.m(G)p.m(G)p.m(A)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UCACAGGACUUAGGGCAGGAAUU
SSR-0106898	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(U)p.m(C)p.[fl2r](U)p.m(U)p.m(C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](A)p.m(C)p.m(U)p.m(U)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCAUCUUCUCACAGGACUUAGUU
SSR-0106899	RNA1{m(U)[sp].[fl2r](C)[sp].m(C)p.m(U)p.m(G)p.[fl2r](A)p.m(C)p.m(A)p.m(U)p.m(C)p.m(U)p.m(U)p.m(C)p.[fl2r](U)p.m(C)p.[fl2r](A)p.m(C)p.m(A)p.m(G)p.m(G)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UCCUGACAUCUUCUCACAGGAUU
SSR-0106900	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.m(C)p.m(C)p.[fl2r](C)p.m(U)p.m(A)p.m(G)p.m(U)p.m(C)p.m(C)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](A)p.m(C)p.m(A)p.m(U)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUCCCUAGUCCCUGACAUCUUU
SSR-0106901	RNA1{m(U)[sp].[fl2r](C)[sp].m(C)p.m(C)p.m(U)p.[fl2r](C)p.m(C)p.m(C)p.m(U)p.m(A)p.m(G)p.m(U)p.m(C)p.[fl2r](C)p.m(C)p.[fl2r](U)p.m(G)p.m(A)p.m(C)p.m(A)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UCCCUCCCUAGUCCCUGACAUUU
SSR-0106902	RNA1{m(U)[sp].[fl2r](C)[sp].m(C)p.m(C)p.m(U)p.[fl2r](C)p.m(C)p.m(C)p.m(U)p.m(C)p.m(C)p.m(C)p.m(U)p.[fl2r](A)p.m(G)p.[fl2r](U)p.m(C)p.m(C)p.m(C)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCCCUCCCUCCCUAGUCCCUGUU
SSR-0106903	RNA1{m(U)[sp].[fl2r](C)[sp].m(C)p.m(C)p.m(U)p.[fl2r](C)p.m(C)p.m(C)p.m(U)p.m(C)p.m(C)p.m(C)p.m(U)p.[fl2r](C)p.m(C)p.[fl2r](C)p.m(U)p.m(A)p.m(G)p.m(U)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UCCCUCCCUCCCUCCCUAGUCUU
SSR-0106904	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.m(A)p.m(A)p.[fl2r](G)p.m(U)p.m(A)p.m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](U)p.m(C)p.[fl2r](U)p.m(C)p.m(U)p.m(G)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUAAGUAAUUUUUCUCUGCCUU
SSR-0106905	RNA1{m(U)[sp].[fl2r](A)[sp].m(G)p.m(G)p.m(C)p.[fl2r](U)p.m(A)p.m(A)p.m(G)p.m(U)p.m(A)p.m(A)p.m(U)p.[fl2r](U)p.m(U)p.[fl2r](U)p.m(U)p.m(C)p.m(U)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UAGGCUAAGUAAUUUUUCUCUUU
SSR-0106906	RNA1{m(U)[sp].[fl2r](U)[sp].m(U)p.m(C)p.m(U)p.[fl2r](C)p.m(A)p.m(U)p.m(C)p.m(U)p.m(U)p.m(G)p.m(G)p.[fl2r](G)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(G)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UUUCUCAUCUUGGGAGAGGCUUU

SSR-0106907	RNA1{m(U)[sp].[fl2r](U)[sp].m(U)p.m(U)p.m(C)p.[fl2r](U)p.m(C)p.m(A)p.m(U)p.m(C)p.m(U)p.m(U)p.m(G)p.[fl2r](G)p.m(G)p.[fl2r](A)p.m(G)p.m(A)p.m(G)p.m(G)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UUUUCUCAUCUUGGGAGAGGCUU
SSR-0106908	RNA1{m(U)[sp].[fl2r](U)[sp].m(U)p.m(G)p.m(A)p.[fl2r](G)p.m(G)p.m(A)p.m(C)p.m(U)p.m(U)p.m(U)p.m(C)p.[fl2r](U)p.m(C)p.[fl2r](A)p.m(U)p.m(C)p.m(U)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UUUGAGGACUUUCUCAUCUUGUU
SSR-0106909	RNA1{m(U)[sp].[fl2r](C)[sp].m(C)p.m(U)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(U)p.m(G)p.m(A)p.m(G)p.m(G)p.[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.m(U)p.m(C)p.m(U)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UCCUCACUUGAGGACUUUCUCUU
SSR-0106910	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.m(G)p.m(C)p.[fl2r](U)p.m(U)p.m(C)p.m(A)p.m(A)p.m(G)p.m(C)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](C)p.m(U)p.m(G)p.m(G)p.m(A)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUGCUUCAAGCCUGCUGGACUU
SSR-0106911	RNA1{m(U)[sp].[fl2r](U)[sp].m(A)p.m(C)p.m(C)p.[fl2r](C)p.m(U)p.m(G)p.m(C)p.m(U)p.m(U)p.m(C)p.m(A)p.[fl2r](A)p.m(G)p.[fl2r](C)p.m(C)p.m(U)p.m(G)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UUACCCUGCUUCAAGCCUGCUUU
SSR-0106912	RNA1{m(U)[sp].[fl2r](G)[sp].m(C)p.m(U)p.m(U)p.[fl2r](A)p.m(C)p.m(C)p.m(C)p.m(U)p.m(G)p.m(C)p.m(U)p.[fl2r](U)p.m(C)p.[fl2r](A)p.m(A)p.m(G)p.m(C)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UGCUUACCCUGCUUCAAGCCUUU
SSR-0106913	RNA1{m(U)[sp].[fl2r](U)[sp].m(G)p.m(C)p.m(U)p.[fl2r](U)p.m(A)p.m(C)p.m(C)p.m(C)p.m(U)p.m(G)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](C)p.m(A)p.m(A)p.m(G)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UUGCUUACCCUGCUUCAAGCCUU
SSR-0106914	RNA1{m(U)[sp].[fl2r](G)[sp].m(G)p.m(C)p.m(C)p.[fl2r](A)p.m(G)p.m(C)p.m(C)p.m(U)p.m(G)p.m(C)p.m(U)p.[fl2r](U)p.m(A)p.[fl2r](C)p.m(C)p.m(C)p.m(U)p.m(G)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UGGCCAGCCUGCUUACCCUGCUU
SSR-0106915	RNA1{m(U)[sp].[fl2r](C)[sp].m(C)p.m(U)p.m(U)p.[fl2r](A)p.m(C)p.m(C)p.m(C)p.m(U)p.m(G)p.m(G)p.m(G)p.[fl2r](C)p.m(C)p.[fl2r](A)p.m(G)p.m(C)p.m(C)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCCUUACCCUGGGCCAGCCUGUU
SSR-0106916	RNA1{m(U)[sp].[fl2r](C)[sp].m(C)p.m(C)p.m(U)p.[fl2r](U)p.m(A)p.m(C)p.m(C)p.m(C)p.m(U)p.m(G)p.m(G)p.[fl2r](G)p.m(C)p.[fl2r](C)p.m(A)p.m(G)p.m(C)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UCCCUUACCCUGGGCCAGCCUUU
SSR-0106917	RNA1{m(U)[sp].[fl2r](A)[sp].m(A)p.m(C)p.m(A)p.[fl2r](G)p.m(C)p.m(C)p.m(C)p.m(U)p.m(U)p.m(A)p.m(C)p.[fl2r](C)p.m(C)p.[fl2r](U)p.m(G)p.m(G)p.m(G)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UAACAGCCCUUACCCUGGGCCUU
SSR-0106918	RNA1{m(U)[sp].[fl2r](G)[sp].m(U)p.m(A)p.m(C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(A)p.m(C)p.m(A)p.m(G)p.[fl2r](C)p.m(C)p.[fl2r](C)p.m(U)p.m(U)p.m(A)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UGUACCUCAACAGCCCUUACCUU

SSR-0106919	RNA1{m(U)[sp].[fl2r](A)[sp].m(U)p.m(C)p.m(U)p.[fl2r](C)p.m(C)p.m(C)p.m(U)p.m(C)p.m(U)p.m(U)p.m(G)p.[fl2r](A)p.m(C)p.[fl2r](C)p.m(U)p.m(U)p.m(C)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UAUCUCCCUCUUGACCUUCCCUU
SSR-0106920	RNA1{m(U)[sp].[fl2r](G)[sp].m(C)p.m(C)p.m(C)p.[fl2r](A)p.m(U)p.m(C)p.m(U)p.m(C)p.m(C)p.m(C)p.m(U)p.[fl2r](C)p.m(U)p.[fl2r](U)p.m(G)p.m(A)p.m(C)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UGCCCAUCUCCCUCUUGACCUUU
SSR-0106921	RNA1{m(U)[sp].[fl2r](A)[sp].m(G)p.m(C)p.m(G)p.[fl2r](C)p.m(C)p.m(U)p.m(U)p.m(G)p.m(C)p.m(C)p.m(C)p.[fl2r](A)p.m(U)p.[fl2r](C)p.m(U)p.m(C)p.m(C)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UAGCGCCUUGCCCAUCUCCCUUU
SSR-0106922	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(G)p.m(C)p.[fl2r](G)p.m(C)p.m(C)p.m(U)p.m(U)p.m(G)p.m(C)p.m(C)p.[fl2r](C)p.m(A)p.[fl2r](U)p.m(C)p.m(U)p.m(C)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UCAGCGCCUUGCCCAUCUCCCUU
SSR-0106923	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.m(C)p.m(A)p.[fl2r](G)p.m(C)p.m(G)p.m(C)p.m(C)p.m(U)p.m(U)p.m(G)p.[fl2r](C)p.m(C)p.[fl2r](C)p.m(A)p.m(U)p.m(C)p.m(U)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUCAGCGCCUUGCCCAUCUCUU
SSR-0106924	RNA1{m(U)[sp].[fl2r](G)[sp].m(C)p.m(A)p.m(U)p.[fl2r](C)p.m(C)p.m(U)p.m(C)p.m(C)p.m(C)p.m(U)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](C)p.m(G)p.m(C)p.m(C)p.m(U)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UGCAUCCUCCCUCAGCGCCUUUU
SSR-0106925	RNA1{m(U)[sp].[fl2r](A)[sp].m(G)p.m(C)p.m(A)p.[fl2r](U)p.m(C)p.m(C)p.m(U)p.m(C)p.m(C)p.m(C)p.m(U)p.[fl2r](C)p.m(A)p.[fl2r](G)p.m(C)p.m(G)p.m(C)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UAGCAUCCUCCCUCAGCGCCUUU
SSR-0106926	RNA1{m(U)[sp].[fl2r](A)[sp].m(A)p.m(G)p.m(C)p.[fl2r](A)p.m(U)p.m(C)p.m(C)p.m(U)p.m(C)p.m(C)p.m(C)p.[fl2r](U)p.m(C)p.[fl2r](A)p.m(G)p.m(C)p.m(G)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UAAGCAUCCUCCCUCAGCGCCUU
SSR-0106927	RNA1{m(U)[sp].[fl2r](U)[sp].m(A)p.m(A)p.m(G)p.[fl2r](C)p.m(A)p.m(U)p.m(C)p.m(C)p.m(U)p.m(C)p.m(C)p.[fl2r](C)p.m(U)p.[fl2r](C)p.m(A)p.m(G)p.m(C)p.m(G)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UUAAGCAUCCUCCCUCAGCGCUU
SSR-0106928	RNA1{m(U)[sp].[fl2r](U)[sp].m(U)p.m(U)p.m(C)p.[fl2r](C)p.m(U)p.m(G)p.m(A)p.m(C)p.m(U)p.m(C)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](U)p.m(U)p.m(U)p.m(C)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UUUUCCUGACUCCUGUUUCUGUU
SSR-0106929	RNA1{m(U)[sp].[fl2r](A)[sp].m(U)p.m(U)p.m(U)p.[fl2r](U)p.m(C)p.m(C)p.m(U)p.m(G)p.m(A)p.m(C)p.m(U)p.[fl2r](C)p.m(C)p.[fl2r](U)p.m(G)p.m(U)p.m(U)p.m(U)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UAUUUUCCUGACUCCUGUUUCUU
SSR-0106930	RNA1{m(U)[sp].[fl2r](U)[sp].m(C)p.m(A)p.m(U)p.[fl2r](U)p.m(U)p.m(U)p.m(C)p.m(C)p.m(U)p.m(G)p.m(A)p.[fl2r](C)p.m(U)p.[fl2r](C)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UUCAUUUUCCUGACUCCUGUUUU

SSR-0106931	RNA1{m(U)[sp].[fl2r](G)[sp].m(C)p.m(C)p.m(U)p.[fl2r](C)p.m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.m(C)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](A)p.m(C)p.m(U)p.m(C)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UGCCUCAUUUUCCUGACUCCUUU
SSR-0106932	RNA1{m(U)[sp].[fl2r](G)[sp].m(U)p.m(G)p.m(C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](C)p.m(C)p.[fl2r](U)p.m(G)p.m(A)p.m(C)p.m(U)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UGUGCCUCAUUUUCCUGACUCUUU
SSR-0106933	RNA1{m(U)[sp].[fl2r](G)[sp].m(C)p.m(U)p.m(U)p.[fl2r](A)p.m(G)p.m(U)p.m(G)p.m(C)p.m(C)p.m(U)p.m(C)p.[fl2r](A)p.m(U)p.[fl2r](U)p.m(U)p.m(U)p.m(C)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UGCUUAGUGCCUCAUUUUCCUUU
SSR-0106934	RNA1{m(U)[sp].[fl2r](U)[sp].m(U)p.m(A)p.m(G)p.[fl2r](G)p.m(C)p.m(U)p.m(U)p.m(A)p.m(G)p.m(U)p.m(G)p.[fl2r](C)p.m(C)p.[fl2r](U)p.m(C)p.m(A)p.m(U)p.m(U)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UUUAGGCUUAGUGCCUCAUUUUU
SSR-0106935	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.m(U)p.m(A)p.[fl2r](G)p.m(G)p.m(C)p.m(U)p.m(U)p.m(A)p.m(G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(U)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUUAGGCUUAGUGCCUCAUUUU
SSR-0106936	RNA1{m(U)[sp].[fl2r](U)[sp].m(C)p.m(U)p.m(U)p.[fl2r](A)p.m(G)p.m(G)p.m(C)p.m(U)p.m(U)p.m(A)p.m(G)p.[fl2r](U)p.m(G)p.[fl2r](C)p.m(C)p.m(U)p.m(C)p.m(A)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UUCUUAGGCUUAGUGCCUCAUUU
SSR-0106937	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.m(U)p.m(C)p.[fl2r](U)p.m(U)p.m(A)p.m(G)p.m(G)p.m(C)p.m(U)p.m(U)p.[fl2r](A)p.m(G)p.[fl2r](U)p.m(G)p.m(C)p.m(C)p.m(U)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUUCUUAGGCUUAGUGCCUCUU
SSR-0106938	RNA1{m(U)[sp].[fl2r](A)[sp].m(C)p.m(U)p.m(U)p.[fl2r](C)p.m(U)p.m(U)p.m(A)p.m(G)p.m(G)p.m(C)p.m(U)p.[fl2r](U)p.m(A)p.[fl2r](G)p.m(U)p.m(G)p.m(C)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UACUUCUUAGGCUUAGUGCCUUU
SSR-0106939	RNA1{m(U)[sp].[fl2r](G)[sp].m(A)p.m(A)p.m(C)p.[fl2r](U)p.m(U)p.m(C)p.m(U)p.m(U)p.m(A)p.m(G)p.m(G)p.[fl2r](C)p.m(U)p.[fl2r](U)p.m(A)p.m(G)p.m(U)p.m(G)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UGAACUUCUUAGGCUUAGUGCUU
SSR-0106940	RNA1{m(U)[sp].[fl2r](A)[sp].m(A)p.m(A)p.m(C)p.[fl2r](C)p.m(A)p.m(G)p.m(G)p.m(G)p.m(A)p.m(A)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](C)p.m(U)p.m(U)p.m(A)p.m(G)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UAAACCAGGGAACUUCUUAGGUU
SSR-0106941	RNA1{m(U)[sp].[fl2r](G)[sp].m(A)p.m(A)p.m(A)p.[fl2r](A)p.m(A)p.m(C)p.m(C)p.m(A)p.m(G)p.m(G)p.m(G)p.[fl2r](A)p.m(A)p.[fl2r](C)p.m(U)p.m(U)p.m(C)p.m(U)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UGAAAAACCAGGGAACUUCUUUU
SSR-0106942	RNA1{m(U)[sp].[fl2r](A)[sp].m(A)p.m(U)p.m(G)p.[fl2r](C)p.m(U)p.m(U)p.m(G)p.m(U)p.m(C)p.m(U)p.m(C)p.[fl2r](C)p.m(C)p.[fl2r](A)p.m(G)p.m(U)p.m(G)p.m(G)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UAAUGCUUGUCUCCCAGUGGGUU

SSR-0106943	RNA1{m(U)[sp].[fl2r](A)[sp].m(A)p.m(A)p.m(U)p.[fl2r](G)p.m(C)p.m(U)p.m(U)p.m(G)p.m(U)p.m(C)p.m(U)p.[fl2r](C)p.m(C)p.[fl2r](C)p.m(A)p.m(G)p.m(U)p.m(G)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UAAAUGCUUGUCUCCCAGUGGUU
SSR-0106944	RNA1{m(U)[sp].[fl2r](U)[sp].m(A)p.m(A)p.m(A)p.[fl2r](U)p.m(G)p.m(C)p.m(U)p.m(U)p.m(G)p.m(U)p.m(C)p.[fl2r](U)p.m(C)p.[fl2r](C)p.m(C)p.m(A)p.m(G)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UUAAAUGCUUGUCUCCCAGUGUU
SSR-0106945	RNA1{m(U)[sp].[fl2r](G)[sp].m(U)p.m(A)p.m(U)p.[fl2r](A)p.m(A)p.m(A)p.m(U)p.m(G)p.m(C)p.m(U)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](C)p.m(U)p.m(C)p.m(C)p.m(C)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UGUAUAAAUGCUUGUCUCCCAUU
SSR-0106946	RNA1{m(U)[sp].[fl2r](A)[sp].m(G)p.m(U)p.m(A)p.[fl2r](U)p.m(A)p.m(A)p.m(A)p.m(U)p.m(G)p.m(C)p.m(U)p.[fl2r](U)p.m(G)p.[fl2r](U)p.m(C)p.m(U)p.m(C)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UAGUAUAAAUGCUUGUCUCCCUU
SSR-0106947	RNA1{m(U)[sp].[fl2r](A)[sp].m(A)p.m(G)p.m(U)p.[fl2r](A)p.m(U)p.m(A)p.m(A)p.m(A)p.m(U)p.m(G)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(U)p.m(C)p.m(U)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UAAGUAUAAAUGCUUGUCUCCUU
SSR-0106948	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.m(C)p.m(C)p.[fl2r](U)p.m(U)p.m(U)p.m(U)p.m(U)p.m(A)p.m(U)p.m(U)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(A)p.m(A)p.m(A)p.m(G)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUCCUUUUUAUUAAGAAAGUUU
SSR-0106949	RNA1{m(U)[sp].[fl2r](U)[sp].m(G)p.m(U)p.m(U)p.[fl2r](G)p.m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.m(C)p.m(U)p.[fl2r](U)p.m(U)p.[fl2r](C)p.m(U)p.m(C)p.m(C)p.m(U)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UUGUUGAUUUUCUUUCUCCUUUU
SSR-0106950	RNA1{m(U)[sp].[fl2r](U)[sp].m(U)p.m(U)p.m(G)p.[fl2r](U)p.m(U)p.m(G)p.m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](C)p.m(U)p.[fl2r](U)p.m(U)p.m(C)p.m(U)p.m(C)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UUUUGUUGAUUUUCUUUCUCCUU
SSR-0106951	RNA1{m(U)[sp].[fl2r](A)[sp].m(C)p.m(A)p.m(U)p.[fl2r](U)p.m(U)p.m(G)p.m(U)p.m(U)p.m(G)p.m(A)p.m(U)p.[fl2r](U)p.m(U)p.[fl2r](U)p.m(C)p.m(U)p.m(U)p.m(U)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UACAUUUGUUGAUUUUCUUUCUU
SSR-0106952	RNA1{m(U)[sp].[fl2r](C)[sp].m(A)p.m(C)p.m(A)p.[fl2r](U)p.m(U)p.m(U)p.m(G)p.m(U)p.m(U)p.m(G)p.m(A)p.[fl2r](U)p.m(U)p.[fl2r](U)p.m(U)p.m(C)p.m(U)p.m(U)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UCACAUUUGUUGAUUUUCUUUUU
SSR-0106953	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.m(C)p.m(A)p.[fl2r](C)p.m(A)p.m(U)p.m(U)p.m(U)p.m(G)p.m(U)p.m(U)p.[fl2r](G)p.m(A)p.[fl2r](U)p.m(U)p.m(U)p.m(U)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUCACAUUUGUUGAUUUUCUUU
SSR-0106954	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.m(U)p.m(U)p.[fl2r](A)p.m(U)p.m(G)p.m(A)p.m(C)p.m(U)p.m(C)p.m(A)p.[fl2r](C)p.m(A)p.[fl2r](U)p.m(U)p.m(U)p.m(G)p.m(U)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUUUAUGACUCACAUUUGUUUU

SSR-0106955	RNA1{m(U)[sp].[fl2r](U)[sp].m(C)p.m(U)p.m(U)p.[fl2r](U)p.m(A)p.m(U)p.m(G)p.m(A)p.m(C)p.m(U)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(U)p.m(U)p.m(U)p.m(G)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UUCUUUAUGACUCACAUUUGUUU
SSR-0106956	RNA1{m(U)[sp].[fl2r](A)[sp].m(C)p.m(C)p.m(C)p.[fl2r](U)p.m(U)p.m(C)p.m(U)p.m(U)p.m(U)p.m(A)p.m(U)p.[fl2r](G)p.m(A)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UACCCUUCUUUAUGACUCACAUU
SSR-0106957	RNA1{m(U)[sp].[fl2r](U)[sp].m(A)p.m(A)p.m(C)p.[fl2r](C)p.m(C)p.m(U)p.m(U)p.m(C)p.m(U)p.m(U)p.m(U)p.[fl2r](A)p.m(U)p.[fl2r](G)p.m(A)p.m(C)p.m(U)p.m(C)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UUAACCCUUCUUUAUGACUCAUU
SSR-0106958	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.m(A)p.m(A)p.[fl2r](C)p.m(C)p.m(C)p.m(U)p.m(U)p.m(C)p.m(U)p.m(U)p.[fl2r](U)p.m(A)p.[fl2r](U)p.m(G)p.m(A)p.m(C)p.m(U)p.m(C)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUAACCCUUCUUUAUGACUCUU
SSR-0106959	RNA1{m(U)[sp].[fl2r](C)[sp].m(C)p.m(U)p.m(A)p.[fl2r](A)p.m(C)p.m(C)p.m(C)p.m(U)p.m(U)p.m(C)p.m(U)p.[fl2r](U)p.m(U)p.[fl2r](A)p.m(U)p.m(G)p.m(A)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UCCUAACCCUUCUUUAUGACUUU
SSR-0106960	RNA1{m(U)[sp].[fl2r](A)[sp].m(C)p.m(C)p.m(C)p.[fl2r](U)p.m(A)p.m(A)p.m(C)p.m(C)p.m(C)p.m(U)p.m(U)p.[fl2r](C)p.m(U)p.[fl2r](U)p.m(U)p.m(A)p.m(U)p.m(G)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UACCCUAACCCUUCUUUAUGAUU
SSR-0106961	RNA1{m(U)[sp].[fl2r](U)[sp].m(C)p.m(A)p.m(C)p.[fl2r](C)p.m(C)p.m(U)p.m(A)p.m(A)p.m(C)p.m(C)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](C)p.m(U)p.m(U)p.m(U)p.m(A)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UUCACCCUAACCCUUCUUUAUUU
SSR-0106962	RNA1{m(U)[sp].[fl2r](A)[sp].m(U)p.m(C)p.m(A)p.[fl2r](C)p.m(C)p.m(C)p.m(U)p.m(A)p.m(A)p.m(C)p.m(C)p.[fl2r](C)p.m(U)p.[fl2r](U)p.m(C)p.m(U)p.m(U)p.m(U)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UAUCACCCUAACCCUUCUUUAUU
SSR-0106963	RNA1{m(U)[sp].[fl2r](G)[sp].m(U)p.m(A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(U)p.m(G)p.m(A)p.m(A)p.m(G)p.[fl2r](A)p.m(A)p.[fl2r](C)p.m(U)p.m(G)p.m(U)p.m(U)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UGUACACUUGAAGAACUGUUGUU
SSR-0107998	RNA1{m(U)[sp].[fl2r](A)[sp].m(A)p.[fl2r](G)p.m(A)p.[fl2r](C)p.m(G)p.m(G)p.m(C)p.m(A)p.[fl2r](G)p.m(A)p.m(A)p.[fl2r](U)p.m(G)p.[fl2r](G)p.m(A)p.m(A)p.m(G)p.m(G)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UAAGACGGCAGAAUGGAAGGAUU
SSR-0108000	RNA1{m(U)[Ssp].[fl2r](A)[Rsp].m(A)[n001S].[fl2r](G)p.m(A)p.[fl2r](C)p.m(G)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](G)p.m(A)p.m(A)p.[fl2r](U)p.m(G)p.[fl2r](G)p.m(A)p.m(A)p.m(G)p.m(G)p.m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UAAGACGGCAGAAUGGAAGGAUU
SSR-0108010	RNA1{m(U)[Ssp].[fl2r](G)[Rsp].m(U)[n001S].[fl2r](U)p.m(A)p.[fl2r](U)p.m(U)p.m(C)p.m(U)p.m(G)[n001R].[fl2r](G)p.m(G)p.m(A)p.[fl2r](C)p.m(G)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(G)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UGUUAUUCUGGGACGACUGGUUU

SSR-0108011	RNA1{m(U)[Ssp].[fl2r](G)[Rsp].m(A)[n001S].[fl2r](U)p.m(G)p.[fl2r](A)p.m(G)p.m(U)p.m(U)p.m(A)[n001R].[fl2r](U)p.m(U)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](G)p.m(G)p.m(A)p.m(C)p.m(G)p.m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UGAUGAGUUAUUCUGGGACGAUU
SSR-0108012	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](G)p.m(C)p.[fl2r](A)p.m(A)p.m(A)p.m(G)p.m(C)[n001R].[fl2r](U)p.m(G)p.m(A)p.[fl2r](U)p.m(G)p.[fl2r](A)p.m(C)p.m(C)p.m(U)p.m(C)p.m(C)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAGCAAAGCUGAUGACCUCCUU
SSR-0108013	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(G)[n001S].[fl2r](A)p.m(C)p.[fl2r](A)p.m(G)p.m(U)p.m(A)p.m(G)[n001R].[fl2r](C)p.m(A)p.m(A)p.[fl2r](A)p.m(G)p.[fl2r](C)p.m(U)p.m(G)p.m(A)p.m(U)p.m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUGACAGUAGCAAAGCUGAUGUU
SSR-0108014	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(U)[n001S].[fl2r](C)p.m(A)p.[fl2r](G)p.m(G)p.m(A)p.m(C)p.m(A)[n001R].[fl2r](C)p.m(C)p.m(A)p.[fl2r](G)p.m(A)p.[fl2r](C)p.m(U)p.m(U)p.m(C)p.m(U)p.m(C)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUUCAGGACACCAGACUUCUCUU
SSR-0108015	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](C)p.m(G)p.[fl2r](U)p.m(A)p.m(A)p.m(U)p.m(G)[n001R].[fl2r](G)p.m(U)p.m(C)p.[fl2r](U)p.m(C)p.[fl2r](G)p.m(C)p.m(C)p.m(U)p.m(G)p.m(C)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUACGUAAUGGUCUCGCCUGCUU
SSR-0108016	RNA1{m(U)[Ssp].[fl2r](A)[Rsp].m(A)[n001S].[fl2r](G)p.m(A)p.[fl2r](C)p.m(G)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](G)p.m(A)p.m(A)p.[fl2r](U)p.m(G)p.[fl2r](G)p.m(A)p.m(A)p.m(A)p.m(G)p.m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UAAGACGGCAGAAUGGAAAGAUU
SSR-0108017	RNA1{m(U)[Ssp].[fl2r](A)[Rsp].m(C)[n001S].[fl2r](A)p.m(U)p.[fl2r](U)p.m(G)p.m(C)p.m(C)p.m(A)[n001R].[fl2r](U)p.m(U)p.m(A)p.[fl2r](U)p.m(G)p.[fl2r](A)p.m(U)p.m(C)p.m(C)p.m(A)p.m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UACAUUGCCAUUAUGAUCCAGUU
SSR-0108018	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(U)[n001S].[fl2r](G)p.m(G)p.[fl2r](U)p.m(C)p.m(U)p.m(C)p.m(U)[n001R].[fl2r](U)p.m(C)p.m(A)p.[fl2r](C)p.m(U)p.[fl2r](C)p.m(C)p.m(A)p.m(A)p.m(A)p.m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUUGGUCUCUUCACUCCAAAGUU
SSR-0108019	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(C)[n001S].[fl2r](U)p.m(G)p.[fl2r](A)p.m(U)p.m(G)p.m(C)p.m(C)[n001R].[fl2r](U)p.m(C)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](U)p.m(C)p.m(A)p.m(C)p.m(A)p.m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUCUGAUGCCUCCAGUCACAGUU
SSR-0108020	RNA1{m(U)[Ssp].[fl2r](A)[Rsp].m(G)[n001S].[fl2r](G)p.m(A)p.[fl2r](A)p.m(U)p.m(C)p.m(U)p.m(G)[n001R].[fl2r](A)p.m(U)p.m(G)p.[fl2r](C)p.m(C)p.[fl2r](U)p.m(C)p.m(C)p.m(A)p.m(G)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UAGGAAUCUGAUGCCUCCAGUUU
SSR-0108021	RNA1{m(U)[Ssp].[fl2r](A)[Rsp].m(C)[n001S].[fl2r](A)p.m(A)p.[fl2r](G)p.m(A)p.m(A)p.m(A)p.m(G)[n001R].[fl2r](U)p.m(G)p.m(C)p.[fl2r](C)p.m(C)p.[fl2r](A)p.m(U)p.m(U)p.m(U)p.m(G)p.m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UACAAGAAAGUGCCCAUUUGGUU
SSR-0108022	RNA1{m(U)[Ssp].[fl2r](G)[Rsp].m(A)[n001S].[fl2r](C)p.m(A)p.[fl2r](A)p.m(G)p.m(A)p.m(A)p.m(A)[n001R].[fl2r](G)p.m(U)p.m(G)p.[fl2r](C)p.m(C)p.[fl2r](C)p.m(A)p.m(U)p.m(U)p.m(U)p.m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UGACAAGAAAGUGCCCAUUUGUU

SSR-0108023	RNA1{m(U)[Ssp].[fl2r](C)[Rsp].m(A)[n001S].[fl2r](G)p.m(A)p.[fl2r](C)p.m(A)p.m(A)p.m(G)p.m(A)[n001R].[fl2r](A)p.m(A)p.m(G)p.[fl2r](U)p.m(G)p.[fl2r](C)p.m(C)p.m(C)p.m(A)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCAGACAAGAAAGUGCCCAUUUU
SSR-0108024	RNA1{m(U)[Ssp].[fl2r](C)[Rsp].m(U)[n001S].[fl2r](C)p.m(A)p.[fl2r](G)p.m(A)p.m(C)p.m(A)p.m(A)[n001R].[fl2r](G)p.m(A)p.m(A)p.[fl2r](A)p.m(G)p.[fl2r](U)p.m(G)p.m(C)p.m(C)p.m(C)p.m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUCAGACAAGAAAGUGCCCAUU
SSR-0108025	RNA1{m(U)[Ssp].[fl2r](C)[Rsp].m(A)[n001S].[fl2r](U)p.m(C)p.[fl2r](A)p.m(G)p.m(C)p.m(C)p.m(A)[n001R].[fl2r](A)p.m(C)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](G)p.m(A)p.m(A)p.m(U)p.m(A)p.m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCAUCAGCCAACCUGGAAUAAUU
SSR-0108026	RNA1{m(U)[Ssp].[fl2r](A)[Rsp].m(G)[n001S].[fl2r](A)p.m(A)p.[fl2r](A)p.m(C)p.m(G)p.m(C)p.m(U)[n001R].[fl2r](U)p.m(U)p.m(A)p.[fl2r](C)p.m(C)p.[fl2r](C)p.m(A)p.m(U)p.m(C)p.m(U)p.m(C)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UAGAAACGCUUUACCCAUCUCUU
SSR-0108027	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](G)p.m(A)p.[fl2r](A)p.m(G)p.m(A)p.m(A)p.m(A)[n001R].[fl2r](C)p.m(G)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](U)p.m(A)p.m(C)p.m(C)p.m(C)p.m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAGAAGAAACGCUUUACCCAUU
SSR-0108028	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(U)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(A)p.m(G)p.m(A)[n001R].[fl2r](A)p.m(A)p.m(C)p.[fl2r](G)p.m(C)p.[fl2r](U)p.m(U)p.m(U)p.m(A)p.m(C)p.m(C)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUUUAGAAGAAACGCUUUACCUU
SSR-0108029	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(U)[n001S].[fl2r](G)p.m(A)p.[fl2r](G)p.m(G)p.m(A)p.m(C)p.m(U)[n001R].[fl2r](U)p.m(U)p.m(C)p.[fl2r](U)p.m(C)p.[fl2r](A)p.m(U)p.m(C)p.m(U)p.m(U)p.m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUUGAGGACUUUCUCAUCUUGUU
SSR-0108030	RNA1{m(U)[Ssp].[fl2r](A)[Rsp].m(U)[n001S].[fl2r](U)p.m(U)p.[fl2r](U)p.m(C)p.m(C)p.m(U)p.m(G)[n001R].[fl2r](A)p.m(C)p.m(U)p.[fl2r](C)p.m(C)p.[fl2r](U)p.m(G)p.m(U)p.m(U)p.m(U)p.m(C)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UAUUUUCCUGACUCCUGUUUCUU
SSR-0108031	RNA1{m(U)[Ssp].[fl2r](A)[Rsp].m(A)[n001S].[fl2r](A)p.m(U)p.[fl2r](G)p.m(C)p.m(U)p.m(U)p.m(G)[n001R].[fl2r](U)p.m(C)p.m(U)p.[fl2r](C)p.m(C)p.[fl2r](C)p.m(A)p.m(G)p.m(U)p.m(G)p.m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UAAAUGCUUGUCUCCCAGUGGUU
SSR-0108032	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](A)p.m(A)p.[fl2r](U)p.m(G)p.m(C)p.m(U)p.m(U)[n001R].[fl2r](G)p.m(U)p.m(C)p.[fl2r](U)p.m(C)p.[fl2r](C)p.m(C)p.m(A)p.m(G)p.m(U)p.m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAAAUGCUUGUCUCCCAGUGUU
SSR-0108033	RNA1{m(U)[Ssp].[fl2r](G)[Rsp].m(U)[n001S].[fl2r](A)p.m(U)p.[fl2r](A)p.m(A)p.m(A)p.m(U)p.m(G)[n001R].[fl2r](C)p.m(U)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](C)p.m(U)p.m(C)p.m(C)p.m(C)p.m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UGUAUAAAUGCUUGUCUCCCAUU
SSR-0108034	RNA1{m(U)[Ssp].[fl2r](A)[Rsp].m(A)[n001S].[fl2r](G)p.m(U)p.[fl2r](A)p.m(U)p.m(A)p.m(A)p.m(A)[n001R].[fl2r](U)p.m(G)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(U)p.m(C)p.m(U)p.m(C)p.m(C)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UAAGUAUAAAUGCUUGUCUCCUU

SSR-0108035	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(U)[n001S].[fl2r](U)p.m(G)p.[fl2r](U)p.m(U)p.m(G)p.m(A)p.m(U)[n001R].[fl2r](U)p.m(U)p.m(U)p.[fl2r](C)p.m(U)p.[fl2r](U)p.m(U)p.m(C)p.m(U)p.m(C)p.m(C)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUUUGUUGAUUUUCUUUCUCCUU
SSR-0108036	RNA1{m(U)[Ssp].[fl2r](A)[Rsp].m(C)[n001S].[fl2r](A)p.m(U)p.[fl2r](U)p.m(U)p.m(G)p.m(U)p.m(U)[n001R].[fl2r](G)p.m(A)p.m(U)p.[fl2r](U)p.m(U)p.[fl2r](U)p.m(C)p.m(U)p.m(U)p.m(U)p.m(C)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UACAUUUGUUGAUUUUCUUUCUU
SSR-0108037	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(C)[n001S].[fl2r](U)p.m(U)p.[fl2r](U)p.m(A)p.m(U)p.m(G)p.m(A)[n001R].[fl2r](C)p.m(U)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(U)p.m(U)p.m(U)p.m(G)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUCUUUAUGACUCACAUUUGUUU
SSR-0108038	RNA1{m(U)[Ssp].[fl2r](G)[Rsp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(U)p.m(G)[n001R].[fl2r](A)p.m(A)p.m(G)p.[fl2r](A)p.m(A)p.[fl2r](C)p.m(U)p.m(G)p.m(U)p.m(U)p.m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UGUACACUUGAAGAACUGUUGUU
SSR-0108039	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(G)[n001S].[fl2r](G)p.m(A)p.[fl2r](G)p.m(G)p.m(A)p.m(U)p.m(G)[n001R].[fl2r](A)p.m(G)p.m(U)p.[fl2r](U)p.m(A)p.[fl2r](U)p.m(U)p.m(C)p.m(U)p.m(G)p.m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUGGAGGAUGAGUUAUUCUGGUU
SSR-0108040	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(G)[n001S].[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.m(G)p.m(G)p.m(A)[n001R].[fl2r](G)p.m(U)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](U)p.m(G)p.m(A)p.m(C)p.m(A)p.m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUGAAGUGGAGUCUGUGACAGUU
SSR-0108041	RNA1{m(U)[Ssp].[fl2r](C)[Rsp].m(U)[n001S].[fl2r](G)p.m(A)p.[fl2r](A)p.m(G)p.m(U)p.m(G)p.m(G)[n001R].[fl2r](A)p.m(G)p.m(U)p.[fl2r](C)p.m(U)p.[fl2r](G)p.m(U)p.m(G)p.m(A)p.m(C)p.m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUGAAGUGGAGUCUGUGACAUU
SSR-0108042	RNA1{m(U)[Ssp].[fl2r](C)[Rsp].m(G)[n001S].[fl2r](G)p.m(A)p.[fl2r](A)p.m(G)p.m(A)p.m(U)p.m(C)[n001R].[fl2r](C)p.m(U)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(C)p.m(A)p.m(A)p.m(A)p.m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCGGAAGAUCCUCAAGCAAAGUU
SSR-0108043	RNA1{m(U)[Ssp].[fl2r](A)[Rsp].m(G)[n001S].[fl2r](A)p.m(A)p.[fl2r](A)p.m(G)p.m(U)p.m(A)p.m(U)[n001R].[fl2r](A)p.m(A)p.m(A)p.[fl2r](U)p.m(G)p.[fl2r](C)p.m(U)p.m(U)p.m(G)p.m(U)p.m(C)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UAGAAAGUAUAAAUGCUUGUCUU
SSR-0108044	RNA1{m(U)[Ssp].[fl2r](A)[Rsp].m(A)[n001S].[fl2r](G)p.m(A)p.[fl2r](A)p.m(A)p.m(G)p.m(U)p.m(A)[n001R].[fl2r](U)p.m(A)p.m(A)p.[fl2r](A)p.m(U)p.[fl2r](G)p.m(C)p.m(U)p.m(U)p.m(G)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UAAGAAAGUAUAAAUGCUUGUUU
SSR-0108095	RNA1{p.[Rm5d5m](U)[Ssp].[fl2r](A)[Rsp].m(A)[n001S].[fl2r](G)p.m(A)p.[fl2r](C)p.m(G)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](G)p.m(A)p.m(A)p.[fl2r](U)p.m(G)p.[fl2r](G)p.m(A)p.m(A)p.m(G)p.m(G)p.m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UAAGACGGCAGAAUGGAAGGAUU
SSR-0108099	RNA1{p.[Rm5d5m](U)[Ssp].[fl2r](C)[Rsp].m(U)[n001S].[fl2r](C)p.m(A)p.[fl2r](G)p.m(A)p.m(C)p.m(A)p.m(A)[n001R].[fl2r](G)p.m(A)p.m(A)p.[fl2r](A)p.m(G)p.[fl2r](U)p.m(G)p.m(C)p.m(C)p.m(C)p.m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUCAGACAAGAAAGUGCCCAUU

SSR-0108322	RNA1{[vped5m](U)[Ssp].[fl2r](C)[Rsp].m(U)[n001S].[fl2r](C)p.m(A)p.[fl2r](G)p.m(A)p.m(C)p.m(A)p.m(A)[n001R].[fl2r](G)p.m(A)p.m(A)p.[fl2r](A)p.m(G)p.[fl2r](U)p.m(G)p.m(C)p.m(C)p.m(C)p.m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUCAGACAAGAAAGUGCCCAUU
SSR-0108324	RNA1{[d5m](U)[Ssp].[fl2r](C)[Rsp].m(U)[n001S].[fl2r](C)p.m(A)p.[fl2r](G)p.m(A)p.m(C)p.m(A)p.m(A)[n001R].[fl2r](G)p.m(A)p.m(A)p.[fl2r](A)p.m(G)p.[fl2r](U)p.m(G)p.m(C)p.m(C)p.m(C)p.m(A)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	UCUCAGACAAGAAAGUGCCCAUU

Table 1b. Examples of Passenger Sequences Targeting INHBE

PASSENGER SEQUENCE	HELM	BASE SEQUENCE
SSR-0106964	RNA1{p.m(G)[sp].m(U)p.m(A)p.m(G)p.m(C)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](A)p.[fl2r](C)p.[fl2r](A)p.m(U)p.m(G)p.m(A)p.m(G)p.m(C)p.m(U)p.m(G)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GUAGCCAGACAUGAGCUGUGA
SSR-0106965	RNA1{p.m(U)[sp].m(A)p.m(G)p.m(C)p.m(C)p.m(A)p.[fl2r](G)p.m(A)p.[fl2r](C)p.[fl2r](A)p.[fl2r](U)p.m(G)p.m(A)p.m(G)p.m(C)p.m(U)p.m(G)p.m(U)p.m(G)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UAGCCAGACAUGAGCUGUGAA
SSR-0106966	RNA1{p.m(C)[sp].m(U)p.m(G)p.m(U)p.m(G)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](G)p.[fl2r](U)p.[fl2r](C)p.m(A)p.m(A)p.m(G)p.m(C)p.m(A)p.m(C)p.m(A)p.m(G)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUGUGAGGGUCAAGCACAGCA
SSR-0106967	RNA1{p.m(G)[sp].m(U)p.m(G)p.m(A)p.m(G)p.m(G)p.[fl2r](G)p.m(U)p.[fl2r](C)p.[fl2r](A)p.[fl2r](A)p.m(G)p.m(C)p.m(A)p.m(C)p.m(A)p.m(G)p.m(C)p.m(U)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GUGAGGGUCAAGCACAGCUAA
SSR-0106968	RNA1{p.m(A)[sp].m(G)p.m(G)p.m(G)p.m(U)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.[fl2r](C)p.[fl2r](A)p.m(C)p.m(A)p.m(G)p.m(C)p.m(U)p.m(A)p.m(U)p.m(C)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGGGUCAAGCACAGCUAUCCA

SSR-0106969	RNA1{p.m(G)[sp].m(G)p.m(U)p.m(C)p.m(A)p.m(A)p.[fl2r](G)p.m(C)p.[fl2r](A)p.[fl2r](C)p.[fl2r](A)p.m(G)p.m(C)p.m(U)p.m(A)p.m(U)p.m(C)p.m(C)p.m(A)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGUC AAGC ACAG CUAU CCAU A
SSR-0106970	RNA1{p.m(C)[sp].m(A)p.m(A)p.m(G)p.m(C)p.m(A)p.[fl2r](C)p.m(A)p.[fl2r](G)p.[fl2r](C)p.[fl2r](U)p.m(A)p.m(U)p.m(C)p.m(C)p.m(A)p.m(U)p.m(C)p.m(A)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CAAG CACA GCUA UCCA UCAG A
SSR-0106971	RNA1{p.m(A)[sp].m(A)p.m(G)p.m(C)p.m(A)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](C)p.[fl2r](U)p.[fl2r](A)p.m(U)p.m(C)p.m(C)p.m(A)p.m(U)p.m(C)p.m(A)p.m(G)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AAGC ACAG CUAU CCAU CAGA A
SSR-0106972	RNA1{p.m(A)[sp].m(C)p.m(A)p.m(G)p.m(C)p.m(U)p.[fl2r](A)p.m(U)p.[fl2r](C)p.[fl2r](C)p.[fl2r](A)p.m(U)p.m(C)p.m(A)p.m(G)p.m(A)p.m(U)p.m(G)p.m(A)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	ACAG CUAU CCAU CAGA UGAU A
SSR-0106973	RNA1{p.m(G)[sp].m(C)p.m(U)p.m(A)p.m(U)p.m(C)p.[fl2r](C)p.m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](A)p.m(G)p.m(A)p.m(U)p.m(G)p.m(A)p.m(U)p.m(C)p.m(U)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GCUA UCCA UCAG AUGA UCUA A
SSR-0106974	RNA1{p.m(C)[sp].m(U)p.m(A)p.m(U)p.m(C)p.m(C)p.[fl2r](A)p.m(U)p.[fl2r](C)p.[fl2r](A)p.[fl2r](G)p.m(A)p.m(U)p.m(G)p.m(A)p.m(U)p.m(C)p.m(U)p.m(A)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUAU CCAU CAGA UGAU CUAC A
SSR-0106975	RNA1{p.m(A)[sp].m(U)p.m(C)p.m(C)p.m(A)p.m(U)p.[fl2r](C)p.m(A)p.[fl2r](G)p.[fl2r](A)p.[fl2r](U)p.m(G)p.m(A)p.m(U)p.m(C)p.m(U)p.m(A)p.m(C)p.m(U)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AUCC AUCA GAUG AUCU ACUU A
SSR-0106976	RNA1{p.m(A)[sp].m(U)p.m(G)p.m(A)p.m(U)p.m(C)p.[fl2r](U)p.m(A)p.[fl2r](C)p.[fl2r](U)p.[fl2r](U)p.m(U)p.m(C)p.m(A)p.m(G)p.m(C)p.m(C)p.m(U)p.m(U)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AUGA UCUA CUUU CAGC CUUC A
SSR-0106977	RNA1{p.m(G)[sp].m(U)p.m(G)p.m(U)p.m(G)p.m(G)p.[fl2r](C)p.m(A)p.[fl2r](G)p.[fl2r](U)p.[fl2r](G)p.m(G)p.m(U)p.m(G)p.	GUGU GGCA

	m(U)p.m(C)p.m(U)p.m(G)p.m(C)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GUGG UGUC UGCU A
SSR-0106978	RNA1{p.m(G)[sp].m(U)p.m(G)p.m(G)p.m(C)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](G)p.[fl2r](G)p.[fl2r](U)p.m(G)p.m(U)p.m(C)p.m(U)p.m(G)p.m(C)p.m(U)p.m(G)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GUGG CAGU GGUG UCUG CUGU A
SSR-0106979	RNA1{p.m(C)[sp].m(A)p.m(G)p.m(U)p.m(G)p.m(G)p.[fl2r](U)p.m(G)p.[fl2r](U)p.[fl2r](C)p.[fl2r](U)p.m(G)p.m(C)p.m(U)p.m(G)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CAGU GGUG UCUG CUGU CACU A
SSR-0106980	RNA1{p.m(A)[sp].m(C)p.m(U)p.m(C)p.m(A)p.m(A)p.[fl2r](C)p.m(A)p.[fl2r](G)p.[fl2r](A)p.[fl2r](C)p.m(G)p.m(G)p.m(A)p.m(G)p.m(C)p.m(A)p.m(A)p.m(C)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	ACUC AACA GACG GAGC AACU A
SSR-0106981	RNA1{p.m(U)[sp].m(C)p.m(A)p.m(A)p.m(C)p.m(A)p.[fl2r](G)p.m(A)p.[fl2r](C)p.[fl2r](G)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)p.m(A)p.m(C)p.m(U)p.m(G)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UCAA CAGA CGGA GCAA CUGC A
SSR-0106982	RNA1{p.m(A)[sp].m(G)p.m(A)p.m(C)p.m(G)p.m(G)p.[fl2r](A)p.m(G)p.[fl2r](C)p.[fl2r](A)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(C)p.m(C)p.m(A)p.m(U)p.m(C)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGAC GGAG CAAC UGCC AUCC A
SSR-0106983	RNA1{p.m(G)[sp].m(A)p.m(C)p.m(G)p.m(G)p.m(A)p.[fl2r](G)p.m(C)p.[fl2r](A)p.[fl2r](A)p.[fl2r](C)p.m(U)p.m(G)p.m(C)p.m(C)p.m(A)p.m(U)p.m(C)p.m(C)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GACG GAGC AACU GCCA UCCG A
SSR-0106984	RNA1{p.m(C)[sp].m(G)p.m(G)p.m(A)p.m(G)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](C)p.[fl2r](U)p.[fl2r](G)p.m(C)p.m(C)p.m(A)p.m(U)p.m(C)p.m(C)p.m(G)p.m(A)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CGGA GCAA CUGC CAUC CGAG A
SSR-0106985	RNA1{p.m(G)[sp].m(A)p.m(G)p.m(C)p.m(A)p.m(A)p.[fl2r](C)p.m(U)p.[fl2r](G)p.[fl2r](C)p.[fl2r](C)p.m(A)p.m(U)p.m(C)p.m(C)p.m(G)p.m(A)p.m(G)p.m(G)p.m(C)[sp].m(A)}|CHEM1{[	GAGC AACU GCCA UCCG

	nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGGCA
SSR-0106986	RNA1{p.m(A)[sp].m(G)p.m(C)p.m(A)p.m(A)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](C)p.[fl2r](C)p.[fl2r](A)p.m(U)p.m(C)p.m(C)p.m(G)p.m(A)p.m(G)p.m(G)p.m(C)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGCAACUGCCAUCCGAGGCUA
SSR-0106987	RNA1{p.m(A)[sp].m(G)p.m(C)p.m(U)p.m(C)p.m(U)p.[fl2r](G)p.m(G)p.[fl2r](C)p.[fl2r](U)p.[fl2r](G)p.m(G)p.m(U)p.m(G)p.m(C)p.m(U)p.m(G)p.m(C)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGCUCUGGCUGGUGCUGCUGA
SSR-0106988	RNA1{p.m(G)[sp].m(C)p.m(U)p.m(C)p.m(U)p.m(G)p.[fl2r](G)p.m(C)p.[fl2r](U)p.[fl2r](G)p.[fl2r](G)p.m(U)p.m(G)p.m(C)p.m(U)p.m(G)p.m(C)p.m(U)p.m(G)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GCUCUGGCUGGUGCUGCUGUA
SSR-0106989	RNA1{p.m(U)[sp].m(G)p.m(G)p.m(U)p.m(G)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](C)p.[fl2r](U)p.[fl2r](G)p.m(U)p.m(G)p.m(G)p.m(G)p.m(C)p.m(A)p.m(C)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGGUGCUGCUGUGGGCACUGA
SSR-0106990	RNA1{p.m(G)[sp].m(U)p.m(G)p.m(C)p.m(U)p.m(G)p.[fl2r](C)p.m(U)p.[fl2r](G)p.[fl2r](U)p.[fl2r](G)p.m(G)p.m(G)p.m(C)p.m(A)p.m(C)p.m(U)p.m(G)p.m(G)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GUGCUGCUGUGGGCACUGGUA
SSR-0106991	RNA1{p.m(U)[sp].m(G)p.m(U)p.m(G)p.m(G)p.m(G)p.[fl2r](C)p.m(A)p.[fl2r](C)p.[fl2r](U)p.[fl2r](G)p.m(G)p.m(U)p.m(G)p.m(C)p.m(G)p.m(A)p.m(G)p.m(C)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGUGGGCACUGGUGCGAGCAA
SSR-0106992	RNA1{p.m(G)[sp].m(U)p.m(G)p.m(G)p.m(G)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](U)p.[fl2r](G)p.[fl2r](G)p.m(U)p.m(G)p.m(C)p.m(G)p.m(A)p.m(G)p.m(C)p.m(A)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GUGGGCACUGGUGCGAGCACA
SSR-0106993	RNA1{p.m(U)[sp].m(G)p.m(G)p.m(G)p.m(C)p.m(A)p.[fl2r](C)p.m(U)p.[fl2r](G)p.[fl2r](G)p.[fl2r](U)p.m(G)p.m(C)p.m(G)p.m(A)p.m(G)p.m(C)p.m(A)p.m(C)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGGGCACUGGUGCGAGCACAA

SSR-0106994	RNA1{p.m(G)[sp].m(G)p.m(U)p.m(C)p.m(U)p.m(G)p.[fl2r](U)p.m(G)p.[fl2r](U)p.[fl2r](G)p.[fl2r](U)p.m(C)p.m(C)p.m(C)p.m(U)p.m(C)p.m(C)p.m(U)p.m(G)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGUC UGUG UGUC CCUCC UGUA
SSR-0106995	RNA1{p.m(G)[sp].m(U)p.m(C)p.m(U)p.m(G)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.[fl2r](U)p.[fl2r](C)p.m(C)p.m(C)p.m(U)p.m(C)p.m(C)p.m(U)p.m(G)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GUCU GUGU GUCC CUCC UGUG A
SSR-0106996	RNA1{p.m(G)[sp].m(C)p.m(U)p.m(G)p.m(G)p.m(A)p.[fl2r](G)p.m(C)p.[fl2r](U)p.[fl2r](A)p.[fl2r](G)p.m(C)p.m(C)p.m(A)p.m(A)p.m(G)p.m(C)p.m(A)p.m(G)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GCUG GAGC UAGC CAAG CAGC A
SSR-0106997	RNA1{p.m(C)[sp].m(A)p.m(A)p.m(G)p.m(C)p.m(A)p.[fl2r](G)p.m(C)p.[fl2r](A)p.[fl2r](A)p.[fl2r](A)p.m(U)p.m(C)p.m(C)p.m(U)p.m(G)p.m(G)p.m(A)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CAAG CAGC AAAU CCUG GAUG A
SSR-0106998	RNA1{p.m(A)[sp].m(G)p.m(C)p.m(A)p.m(G)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](A)p.[fl2r](U)p.[fl2r](C)p.m(C)p.m(U)p.m(G)p.m(G)p.m(A)p.m(U)p.m(G)p.m(G)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGCA GCAA AUCC UGGA UGGG A
SSR-0106999	RNA1{p.m(A)[sp].m(G)p.m(C)p.m(A)p.m(A)p.m(A)p.[fl2r](U)p.m(C)p.[fl2r](C)p.[fl2r](U)p.[fl2r](G)p.m(G)p.m(A)p.m(U)p.m(G)p.m(G)p.m(G)p.m(U)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGCA AAUC CUGG AUGG GUUG A
SSR-0107000	RNA1{p.m(G)[sp].m(C)p.m(A)p.m(A)p.m(A)p.m(U)p.[fl2r](C)p.m(C)p.[fl2r](U)p.[fl2r](G)p.[fl2r](G)p.m(A)p.m(U)p.m(G)p.m(G)p.m(G)p.m(U)p.m(U)p.m(G)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GCAA AUCC UGGA UGGG UUGC A
SSR-0107001	RNA1{p.m(A)[sp].m(A)p.m(A)p.m(U)p.m(C)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](G)p.[fl2r](A)p.[fl2r](U)p.m(G)p.m(G)p.m(G)p.m(U)p.m(U)p.m(G)p.m(C)p.m(A)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AAAU CCUG GAUG GGUU GCAC A
SSR-0107002	RNA1{p.m(G)[sp].m(G)p.m(U)p.m(U)p.m(G)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](C)p.[fl2r](U)p.[fl2r](G)p.m(A)p.m(C)p.m(C)p.m(A)p.m(G)p.m(U)p.m(C)p.m(G)p.m(U)[sp].m(A)}|CHEM1{[	GGUU GCAC CUGA

	nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CCAG UCGU A
SSR-0107003	RNA1{p.m(G)[sp].m(U)p.m(U)p.m(G)p.m(C)p.m(A)p.[fl2r](C)p.m(C)p.[fl2r](U)p.[fl2r](G)p.[fl2r](A)p.m(C)p.m(C)p.m(A)p.m(G)p.m(U)p.m(C)p.m(G)p.m(U)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GUUG CACC UGAC CAGU CGUC A
SSR-0107004	RNA1{p.m(G)[sp].m(A)p.m(C)p.m(C)p.m(A)p.m(G)p.[fl2r](U)p.m(C)p.[fl2r](G)p.[fl2r](U)p.[fl2r](C)p.m(C)p.m(C)p.m(A)p.m(G)p.m(A)p.m(A)p.m(U)p.m(A)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GACC AGUC GUCC CAGA AUAA A
SSR-0107005	RNA1{p.m(A)[sp].m(C)p.m(C)p.m(A)p.m(G)p.m(U)p.[fl2r](C)p.m(G)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(C)p.m(A)p.m(G)p.m(A)p.m(A)p.m(U)p.m(A)p.m(A)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	ACCA GUCG UCCC AGAA UAAC A
SSR-0107006	RNA1{p.m(C)[sp].m(A)p.m(G)p.m(U)p.m(C)p.m(G)p.[fl2r](U)p.m(C)p.[fl2r](C)p.[fl2r](C)p.[fl2r](A)p.m(G)p.m(A)p.m(A)p.m(U)p.m(A)p.m(A)p.m(C)p.m(U)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CAGU CGUC CCAG AAUA ACUC A
SSR-0107007	RNA1{p.m(U)[sp].m(C)p.m(G)p.m(U)p.m(C)p.m(C)p.[fl2r](C)p.m(A)p.[fl2r](G)p.[fl2r](A)p.[fl2r](A)p.m(U)p.m(A)p.m(A)p.m(C)p.m(U)p.m(C)p.m(A)p.m(U)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UCGU CCCA GAAU AACU CAUC A
SSR-0107008	RNA1{p.m(G)[sp].m(C)p.m(U)p.m(G)p.m(A)p.m(C)p.[fl2r](C)p.m(A)p.[fl2r](G)p.[fl2r](A)p.[fl2r](G)p.m(C)p.m(C)p.m(C)p.m(U)p.m(C)p.m(C)p.m(G)p.m(G)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GCUG ACCA GAGC CCUCC GGAA
SSR-0107009	RNA1{p.m(A)[sp].m(G)p.m(A)p.m(C)p.m(U)p.m(A)p.[fl2r](C)p.m(A)p.[fl2r](G)p.[fl2r](C)p.[fl2r](C)p.m(A)p.m(G)p.m(G)p.m(G)p.m(A)p.m(G)p.m(U)p.m(G)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGAC UACA GCCA GGGA GUGU A
SSR-0107010	RNA1{p.m(G)[sp].m(A)p.m(C)p.m(U)p.m(A)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](C)p.[fl2r](C)p.[fl2r](A)p.m(G)p.m(G)p.m(G)p.m(A)p.m(G)p.m(U)p.m(G)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GACU ACAG CCAG GGAG UGUG A

SSR-0107011	RNA1{p.m(C)[sp].m(U)p.m(A)p.m(C)p.m(A)p.m(G)p.[fl2r](C)p.m(C)p.[fl2r](A)p.[fl2r](G)p.[fl2r](G)p.m(G)p.m(A)p.m(G)p.m(U)p.m(G)p.m(U)p.m(G)p.m(G)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUAC AGCC AGGG AGUG UGGC A
SSR-0107012	RNA1{p.m(G)[sp].m(G)p.m(A)p.m(G)p.m(G)p.m(U)p.[fl2r](C)p.m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](A)p.m(G)p.m(C)p.m(U)p.m(U)p.m(U)p.m(G)p.m(C)p.m(U)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGAG GUCA UCAG CUUU GCUA A
SSR-0107013	RNA1{p.m(G)[sp].m(A)p.m(G)p.m(G)p.m(U)p.m(C)p.[fl2r](A)p.m(U)p.[fl2r](C)p.[fl2r](A)p.[fl2r](G)p.m(C)p.m(U)p.m(U)p.m(U)p.m(G)p.m(C)p.m(U)p.m(A)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GAGG UCAU CAGC UUUG CUAC A
SSR-0107014	RNA1{p.m(A)[sp].m(G)p.m(G)p.m(U)p.m(C)p.m(A)p.[fl2r](U)p.m(C)p.[fl2r](A)p.[fl2r](G)p.[fl2r](C)p.m(U)p.m(U)p.m(U)p.m(G)p.m(C)p.m(U)p.m(A)p.m(C)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGGU CAUC AGCU UUGC UACU A
SSR-0107015	RNA1{p.m(G)[sp].m(U)p.m(C)p.m(A)p.m(U)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](C)p.[fl2r](U)p.[fl2r](U)p.m(U)p.m(G)p.m(C)p.m(U)p.m(A)p.m(C)p.m(U)p.m(G)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GUCA UCAG CUUU GCUA CUGU A
SSR-0107016	RNA1{p.m(C)[sp].m(A)p.m(U)p.m(C)p.m(A)p.m(G)p.[fl2r](C)p.m(U)p.[fl2r](U)p.[fl2r](U)p.[fl2r](G)p.m(C)p.m(U)p.m(A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(C)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CAUC AGCU UUGC UACU GUCA A
SSR-0107017	RNA1{p.m(C)[sp].m(A)p.m(G)p.m(C)p.m(U)p.m(U)p.[fl2r](U)p.m(G)p.[fl2r](C)p.[fl2r](U)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(C)p.m(A)p.m(C)p.m(A)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CAGC UUUG CUAC UGUC ACAG A
SSR-0107018	RNA1{p.m(U)[sp].m(U)p.m(C)p.m(A)p.m(G)p.m(C)p.[fl2r](C)p.m(U)p.[fl2r](A)p.[fl2r](C)p.[fl2r](A)p.m(G)p.m(C)p.m(U)p.m(C)p.m(C)p.m(C)p.m(U)p.m(G)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UUCA GCCU ACAG CUCCC UGCA
SSR-0107019	RNA1{p.m(C)[sp].m(A)p.m(G)p.m(C)p.m(C)p.m(U)p.[fl2r](A)p.m(C)p.[fl2r](A)p.[fl2r](G)p.[fl2r](C)p.m(U)p.m(C)p.m(C)p.m(C)p.m(U)p.m(G)p.m(C)p.m(U)p.m(C)[sp].m(A)}|CHEM1{[	CAGC CUAC AGCU

	nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CCCU GCUC A
SSR-0107020	RNA1{p.m(C)[sp].m(A)p.m(G)p.m(C)p.m(U)p.m(C)p.[fl2r](C)p.m(C)p.[fl2r](U)p.[fl2r](G)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(U)p.m(U)p.m(U)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CAGC UCCC UGCU CACU UUUC A
SSR-0107021	RNA1{p.m(U)[sp].m(C)p.m(C)p.m(C)p.m(U)p.m(G)p.[fl2r](C)p.m(U)p.[fl2r](C)p.[fl2r](A)p.[fl2r](C)p.m(U)p.m(U)p.m(U)p.m(U)p.m(C)p.m(A)p.m(C)p.m(C)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UCCC UGCU CACU UUUC ACCU A
SSR-0107022	RNA1{p.m(U)[sp].m(U)p.m(C)p.m(A)p.m(C)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(C)p.m(U)p.m(C)p.m(G)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UUCA CCUG UCCA CUCC UCGG A
SSR-0107023	RNA1{p.m(U)[sp].m(C)p.m(A)p.m(C)p.m(C)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](C)p.[fl2r](C)p.[fl2r](A)p.m(C)p.m(U)p.m(C)p.m(C)p.m(U)p.m(C)p.m(G)p.m(G)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UCAC CUGU CCAC UCCU CGGU A
SSR-0107024	RNA1{p.m(C)[sp].m(A)p.m(C)p.m(C)p.m(U)p.m(G)p.[fl2r](U)p.m(C)p.[fl2r](C)p.[fl2r](A)p.[fl2r](C)p.m(U)p.m(C)p.m(C)p.m(U)p.m(C)p.m(G)p.m(G)p.m(U)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CACC UGUC CACU CCUC GGUC A
SSR-0107025	RNA1{p.m(C)[sp].m(C)p.m(U)p.m(G)p.m(U)p.m(C)p.[fl2r](C)p.m(A)p.[fl2r](C)p.[fl2r](U)p.[fl2r](C)p.m(C)p.m(U)p.m(C)p.m(G)p.m(G)p.m(U)p.m(C)p.m(C)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CCUG UCCA CUCC UCGG UCCC A
SSR-0107026	RNA1{p.m(U)[sp].m(C)p.m(C)p.m(A)p.m(C)p.m(U)p.[fl2r](C)p.m(C)p.[fl2r](U)p.[fl2r](C)p.[fl2r](G)p.m(G)p.m(U)p.m(C)p.m(C)p.m(C)p.m(A)p.m(C)p.m(C)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UCCA CUCC UCGG UCCC ACCA A
SSR-0107027	RNA1{p.m(A)[sp].m(C)p.m(U)p.m(C)p.m(C)p.m(U)p.[fl2r](C)p.m(G)p.[fl2r](G)p.[fl2r](U)p.[fl2r](C)p.m(C)p.m(C)p.m(A)p.m(C)p.m(C)p.m(A)p.m(C)p.m(C)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	ACUC CUCG GUCC CACC

		ACCU A
SSR- 0107028	RNA1{p.m(C)[sp].m(A)p.m(C)p.m(C)p.m(A)p.m(C)p.[fl2r](C) p.m(U)p.[fl2r](G)p.[fl2r](U)p.[fl2r](A)p.m(C)p.m(C)p.m(A)p. m(U)p.m(G)p.m(C)p.m(C)p.m(C)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1- 1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CACC ACCU GUAC CAUG CCCG A
SSR- 0107029	RNA1{p.m(G)[sp].m(C)p.m(C)p.m(C)p.m(G)p.m(C)p.[fl2r](C) p.m(U)p.[fl2r](G)p.[fl2r](U)p.[fl2r](G)p.m(G)p.m(C)p.m(U)p. m(G)p.m(C)p.m(A)p.m(C)p.m(G)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1- 1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GCCC GCCU GUGG CUGC ACGU A
SSR- 0107030	RNA1{p.m(C)[sp].m(C)p.m(U)p.m(G)p.m(G)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](U)p.[fl2r](C)p.[fl2r](U)p.m(U)p.m(U)p.m(G)p. m(C)p.m(U)p.m(U)p.m(G)p.m(A)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1- 1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CCUG GCAC UCUU UGCU UGAG A
SSR- 0107031	RNA1{p.m(G)[sp].m(G)p.m(C)p.m(A)p.m(C)p.m(U)p.[fl2r](C)p.m(U)p.[fl2r](U)p.[fl2r](U)p.[fl2r](G)p.m(C)p.m(U)p.m(U)p. m(G)p.m(A)p.m(G)p.m(G)p.m(A)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1- 1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGCA CUCU UUGC UUGA GGAU A
SSR- 0107032	RNA1{p.m(A)[sp].m(C)p.m(U)p.m(C)p.m(U)p.m(U)p.[fl2r](U)p.m(G)p.[fl2r](C)p.[fl2r](U)p.[fl2r](U)p.m(G)p.m(A)p.m(G)p. m(G)p.m(A)p.m(U)p.m(C)p.m(U)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1- 1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	ACUC UUUG CUUG AGGA UCUU A
SSR- 0107033	RNA1{p.m(U)[sp].m(U)p.m(U)p.m(G)p.m(C)p.m(U)p.[fl2r](U)p.m(G)p.[fl2r](A)p.[fl2r](G)p.[fl2r](G)p.m(A)p.m(U)p.m(C)p. m(U)p.m(U)p.m(C)p.m(C)p.m(G)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1- 1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UUUG CUUG AGGA UCUU CCGA A
SSR- 0107034	RNA1{p.m(U)[sp].m(G)p.m(C)p.m(U)p.m(U)p.m(G)p.[fl2r](A)p.m(G)p.[fl2r](G)p.[fl2r](A)p.[fl2r](U)p.m(C)p.m(U)p.m(U)p. m(C)p.m(C)p.m(G)p.m(A)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1- 1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGCU UGAG GAUC UUCC GAUG A
SSR- 0107035	RNA1{p.m(G)[sp].m(C)p.m(U)p.m(U)p.m(G)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](A)p.[fl2r](U)p.[fl2r](C)p.m(U)p.m(U)p.m(C)p. m(C)p.m(G)p.m(A)p.m(U)p.m(G)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1- 1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GCUU GAGG AUCU UCCG AUGG A

SSR-0107036	RNA1{p.m(C)[sp].m(U)p.m(U)p.m(G)p.m(A)p.m(G)p.[fl2r](G)p.m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](U)p.m(U)p.m(C)p.m(C)p.m(G)p.m(A)p.m(U)p.m(G)p.m(G)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUUGAGGAUCUUCCGAUGGGA
SSR-0107037	RNA1{p.m(G)[sp].m(G)p.m(A)p.m(C)p.m(C)p.m(A)p.[fl2r](A)p.m(G)p.[fl2r](G)p.[fl2r](A)p.[fl2r](G)p.m(G)p.m(A)p.m(G)p.m(G)p.m(C)p.m(G)p.m(C)p.m(C)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGACCAAGGAGGAGGCGCCAA
SSR-0107038	RNA1{p.m(G)[sp].m(A)p.m(C)p.m(C)p.m(A)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](A)p.[fl2r](G)p.[fl2r](G)p.m(A)p.m(G)p.m(G)p.m(C)p.m(G)p.m(C)p.m(C)p.m(A)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GACCAAGGAGGAGGCGCCAAA
SSR-0107039	RNA1{p.m(A)[sp].m(C)p.m(C)p.m(A)p.m(A)p.m(G)p.[fl2r](G)p.m(A)p.[fl2r](G)p.[fl2r](G)p.[fl2r](A)p.m(G)p.m(G)p.m(C)p.m(G)p.m(C)p.m(C)p.m(A)p.m(A)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	ACCAAGGAGGAGCGCCAAGA
SSR-0107040	RNA1{p.m(A)[sp].m(A)p.m(G)p.m(G)p.m(A)p.m(G)p.[fl2r](G)p.m(A)p.[fl2r](G)p.[fl2r](G)p.[fl2r](C)p.m(G)p.m(C)p.m(C)p.m(A)p.m(A)p.m(G)p.m(G)p.m(G)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AAGGAGGAGGCGCCAAGGGUA
SSR-0107041	RNA1{p.m(A)[sp].m(G)p.m(G)p.m(A)p.m(G)p.m(G)p.[fl2r](C)p.m(G)p.[fl2r](C)p.[fl2r](C)p.[fl2r](A)p.m(A)p.m(G)p.m(G)p.m(G)p.m(U)p.m(C)p.m(C)p.m(C)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGGAGGCGCCAAGGGUCCCGA
SSR-0107042	RNA1{p.m(G)[sp].m(A)p.m(G)p.m(G)p.m(C)p.m(G)p.[fl2r](C)p.m(C)p.[fl2r](A)p.[fl2r](A)p.[fl2r](G)p.m(G)p.m(G)p.m(U)p.m(C)p.m(C)p.m(C)p.m(G)p.m(C)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GAGGCGCCAAGGGUCCCGCA
SSR-0107043	RNA1{p.m(G)[sp].m(G)p.m(C)p.m(G)p.m(C)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.[fl2r](G)p.[fl2r](G)p.m(U)p.m(C)p.m(C)p.m(C)p.m(G)p.m(C)p.m(A)p.m(C)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGCGCCAAGGGUCCCGCACUA
SSR-0107044	RNA1{p.m(G)[sp].m(C)p.m(G)p.m(C)p.m(C)p.m(A)p.[fl2r](A)p.m(G)p.[fl2r](G)p.[fl2r](G)p.[fl2r](U)p.m(C)p.m(C)p.m(C)p.m(G)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)[sp].m(A)}|CHEM1{[	GCGCCAAGGGUC

	nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CCGC ACUC A
SSR-0107045	RNA1{p.m(C)[sp].m(U)p.m(G)p.m(G)p.m(C)p.m(U)p.[fl2r](G)p.m(A)p.[fl2r](G)p.[fl2r](C)p.[fl2r](A)p.m(C)p.m(C)p.m(A)p.m(C)p.m(A)p.m(U)p.m(C)p.m(A)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUGG CUGA GCAC CACA UCAC A
SSR-0107046	RNA1{p.m(A)[sp].m(G)p.m(C)p.m(A)p.m(C)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.[fl2r](U)p.[fl2r](C)p.m(A)p.m(C)p.m(C)p.m(A)p.m(A)p.m(C)p.m(C)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGCA CCAC AUCA CCAA CCUG A
SSR-0107047	RNA1{p.m(C)[sp].m(A)p.m(C)p.m(C)p.m(A)p.m(A)p.[fl2r](C)p.m(C)p.[fl2r](U)p.[fl2r](G)p.[fl2r](G)p.m(G)p.m(C)p.m(U)p.m(G)p.m(G)p.m(C)p.m(A)p.m(U)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CACC AACC UGGG CUGG CAUA A
SSR-0107048	RNA1{p.m(C)[sp].m(U)p.m(G)p.m(G)p.m(C)p.m(A)p.[fl2r](U)p.m(A)p.[fl2r](C)p.[fl2r](C)p.[fl2r](U)p.m(U)p.m(A)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(G)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUGG CAUA CCUU AACU CUGC A
SSR-0107049	RNA1{p.m(U)[sp].m(A)p.m(C)p.m(C)p.m(U)p.m(U)p.[fl2r](A)p.m(A)p.[fl2r](C)p.[fl2r](U)p.[fl2r](C)p.m(U)p.m(G)p.m(C)p.m(C)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UACC UUAA CUCU GCCC UCUA A
SSR-0107050	RNA1{p.m(C)[sp].m(C)p.m(U)p.m(U)p.m(A)p.m(A)p.[fl2r](C)p.m(U)p.[fl2r](C)p.[fl2r](U)p.[fl2r](G)p.m(C)p.m(C)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(G)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CCUU AACU CUGC CCUC UAGU A
SSR-0107051	RNA1{p.m(C)[sp].m(U)p.m(U)p.m(A)p.m(A)p.m(C)p.[fl2r](U)p.m(C)p.[fl2r](U)p.[fl2r](G)p.[fl2r](C)p.m(C)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(G)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUUA ACUC UGCC CUCU AGUG A
SSR-0107052	RNA1{p.m(C)[sp].m(U)p.m(G)p.m(C)p.m(C)p.m(C)p.[fl2r](U)p.m(C)p.[fl2r](U)p.[fl2r](A)p.[fl2r](G)p.m(U)p.m(G)p.m(G)p.m(C)p.m(U)p.m(U)p.m(G)p.m(A)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUGC CCUC UAGU GGCU

		UGAG A
SSR-0107053	RNA1{p.m(G)[sp].m(A)p.m(G)p.m(A)p.m(A)p.m(G)p.[fl2r](U)p.m(C)p.[fl2r](U)p.[fl2r](G)p.[fl2r](G)p.m(U)p.m(G)p.m(U)p.m(C)p.m(C)p.m(U)p.m(G)p.m(A)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GAGA AGUC UGGU GUCC UGAA A
SSR-0107054	RNA1{p.m(A)[sp].m(G)p.m(A)p.m(A)p.m(G)p.m(U)p.[fl2r](C)p.m(U)p.[fl2r](G)p.[fl2r](G)p.[fl2r](U)p.m(G)p.m(U)p.m(C)p.m(C)p.m(U)p.m(G)p.m(A)p.m(A)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGAA GUCU GGUG UCCU GAAA A
SSR-0107055	RNA1{p.m(G)[sp].m(A)p.m(A)p.m(G)p.m(U)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](G)p.[fl2r](U)p.[fl2r](G)p.m(U)p.m(C)p.m(C)p.m(U)p.m(G)p.m(A)p.m(A)p.m(A)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GAAG UCUG GUGU CCUG AAAC A
SSR-0107056	RNA1{p.m(A)[sp].m(G)p.m(U)p.m(C)p.m(U)p.m(G)p.[fl2r](G)p.m(U)p.[fl2r](G)p.[fl2r](U)p.[fl2r](C)p.m(C)p.m(U)p.m(G)p.m(A)p.m(A)p.m(A)p.m(C)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGUC UGGU GUCC UGAA ACUG A
SSR-0107057	RNA1{p.m(G)[sp].m(U)p.m(C)p.m(U)p.m(G)p.m(G)p.[fl2r](U)p.m(G)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(G)p.m(A)p.m(A)p.m(A)p.m(C)p.m(U)p.m(G)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GUCU GGUG UCCU GAAA CUGC A
SSR-0107058	RNA1{p.m(U)[sp].m(G)p.m(U)p.m(C)p.m(C)p.m(U)p.[fl2r](G)p.m(A)p.[fl2r](A)p.[fl2r](A)p.[fl2r](C)p.m(U)p.m(G)p.m(C)p.m(A)p.m(A)p.m(C)p.m(U)p.m(A)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGUC CUGA AACU GCAA CUAG A
SSR-0107059	RNA1{p.m(C)[sp].m(C)p.m(U)p.m(G)p.m(A)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](U)p.[fl2r](G)p.[fl2r](C)p.m(A)p.m(A)p.m(C)p.m(U)p.m(A)p.m(G)p.m(A)p.m(C)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CCUG AAAC UGCA ACUA GACU A
SSR-0107060	RNA1{p.m(C)[sp].m(U)p.m(G)p.m(A)p.m(A)p.m(A)p.[fl2r](C)p.m(U)p.[fl2r](G)p.[fl2r](C)p.[fl2r](A)p.m(A)p.m(C)p.m(U)p.m(A)p.m(G)p.m(A)p.m(C)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUGA AACU GCAA CUAG ACUG A

SSR-0107061	RNA1{p.m(A)[sp].m(A)p.m(C)p.m(U)p.m(G)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](C)p.[fl2r](U)p.[fl2r](A)p.m(G)p.m(A)p.m(C)p.m(U)p.m(G)p.m(C)p.m(A)p.m(G)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AACUGCAACUAGACUGCAGAA
SSR-0107062	RNA1{p.m(C)[sp].m(A)p.m(C)p.m(A)p.m(G)p.m(U)p.[fl2r](U)p.m(A)p.[fl2r](C)p.[fl2r](U)p.[fl2r](G)p.m(G)p.m(A)p.m(C)p.m(A)p.m(A)p.m(C)p.m(C)p.m(G)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CACAGUUACUGGACAACCGAA
SSR-0107063	RNA1{p.m(C)[sp].m(A)p.m(G)p.m(U)p.m(U)p.m(A)p.[fl2r](C)p.m(U)p.[fl2r](G)p.[fl2r](G)p.[fl2r](A)p.m(C)p.m(A)p.m(A)p.m(C)p.m(C)p.m(G)p.m(A)p.m(G)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CAGUUACUGGACAACCGAGGA
SSR-0107064	RNA1{p.m(A)[sp].m(G)p.m(U)p.m(U)p.m(A)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](G)p.[fl2r](A)p.[fl2r](C)p.m(A)p.m(A)p.m(C)p.m(C)p.m(G)p.m(A)p.m(G)p.m(G)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGUUACUGGACAACCGAGGCA
SSR-0107065	RNA1{p.m(G)[sp].m(U)p.m(U)p.m(A)p.m(C)p.m(U)p.[fl2r](G)p.m(G)p.[fl2r](A)p.[fl2r](C)p.[fl2r](A)p.m(A)p.m(C)p.m(C)p.m(G)p.m(A)p.m(G)p.m(G)p.m(C)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GUUACUGGACAACCGAGGCGA
SSR-0107066	RNA1{p.m(C)[sp].m(U)p.m(G)p.m(G)p.m(A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](C)p.[fl2r](C)p.[fl2r](G)p.m(A)p.m(G)p.m(G)p.m(C)p.m(G)p.m(G)p.m(C)p.m(U)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUGGACAACCGAGGCGGCUCA
SSR-0107067	RNA1{p.m(U)[sp].m(G)p.m(G)p.m(A)p.m(C)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](C)p.[fl2r](G)p.[fl2r](A)p.m(G)p.m(G)p.m(C)p.m(G)p.m(G)p.m(C)p.m(U)p.m(C)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGGACAACCGAGGCGGCUCUA
SSR-0107068	RNA1{p.m(G)[sp].m(G)p.m(A)p.m(C)p.m(A)p.m(A)p.[fl2r](C)p.m(C)p.[fl2r](G)p.[fl2r](A)p.[fl2r](G)p.m(G)p.m(C)p.m(G)p.m(G)p.m(C)p.m(U)p.m(C)p.m(U)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGACAACCGAGGCGGCUCUUA
SSR-0107069	RNA1{p.m(A)[sp].m(C)p.m(A)p.m(A)p.m(C)p.m(C)p.[fl2r](G)p.m(A)p.[fl2r](G)p.[fl2r](G)p.[fl2r](C)p.m(G)p.m(G)p.m(C)p.	ACAACCGA

	m(U)p.m(C)p.m(U)p.m(U)p.m(G)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGCG GCUC UUGG A
SSR-0107070	RNA1{p.m(G)[sp].m(G)p.m(C)p.m(G)p.m(G)p.m(C)p.[fl2r](U)p.m(C)p.[fl2r](U)p.[fl2r](U)p.[fl2r](G)p.m(G)p.m(A)p.m(C)p.m(A)p.m(C)p.m(A)p.m(G)p.m(C)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGCG GCUC UUGG ACAC AGCA A
SSR-0107071	RNA1{p.m(G)[sp].m(C)p.m(U)p.m(C)p.m(U)p.m(U)p.[fl2r](G)p.m(G)p.[fl2r](A)p.[fl2r](C)p.[fl2r](A)p.m(C)p.m(A)p.m(G)p.m(C)p.m(A)p.m(G)p.m(G)p.m(A)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GCUC UUGG ACAC AGCA GGAC A
SSR-0107072	RNA1{p.m(U)[sp].m(C)p.m(U)p.m(U)p.m(G)p.m(G)p.[fl2r](A)p.m(C)p.[fl2r](A)p.[fl2r](C)p.[fl2r](A)p.m(G)p.m(C)p.m(A)p.m(G)p.m(G)p.m(A)p.m(C)p.m(A)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UCUU GGAC ACAG CAGG ACAC A
SSR-0107073	RNA1{p.m(U)[sp].m(U)p.m(G)p.m(G)p.m(A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.[fl2r](G)p.[fl2r](C)p.m(A)p.m(G)p.m(G)p.m(A)p.m(C)p.m(A)p.m(C)p.m(C)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UUGG ACAC AGCA GGAC ACCA A
SSR-0107074	RNA1{p.m(C)[sp].m(A)p.m(C)p.m(A)p.m(G)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](G)p.[fl2r](A)p.[fl2r](C)p.m(A)p.m(C)p.m(C)p.m(A)p.m(G)p.m(C)p.m(A)p.m(G)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CACA GCAG GACA CCAG CAGC A
SSR-0107075	RNA1{p.m(C)[sp].m(A)p.m(G)p.m(C)p.m(A)p.m(G)p.[fl2r](C)p.m(C)p.[fl2r](C)p.[fl2r](U)p.[fl2r](U)p.m(C)p.m(C)p.m(U)p.m(A)p.m(G)p.m(A)p.m(G)p.m(C)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CAGC AGCC CUUC CUAG AGCU A
SSR-0107076	RNA1{p.m(G)[sp].m(C)p.m(C)p.m(C)p.m(U)p.m(U)p.[fl2r](C)p.m(C)p.[fl2r](U)p.[fl2r](A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(U)p.m(U)p.m(A)p.m(A)p.m(G)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GCCC UUCC UAGA GCUU AAGA A
SSR-0107077	RNA1{p.m(U)[sp].m(U)p.m(C)p.m(C)p.m(U)p.m(A)p.[fl2r](G)p.m(A)p.[fl2r](G)p.[fl2r](C)p.[fl2r](U)p.m(U)p.m(A)p.m(A)p.m(G)p.m(A)p.m(U)p.m(C)p.m(C)p.m(G)[sp].m(A)}|CHEM1{[	UUCC UAGA GCUU AAGA

	nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UCCGA
SSR-0107078	RNA1{p.m(U)[sp].m(C)p.m(C)p.m(U)p.m(A)p.m(G)p.[fl2r](A)p.m(G)p.[fl2r](C)p.[fl2r](U)p.[fl2r](U)p.m(A)p.m(A)p.m(G)p.m(A)p.m(U)p.m(C)p.m(C)p.m(G)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UCCUAGAGCUUAAGAUCCGAA
SSR-0107079	RNA1{p.m(C)[sp].m(C)p.m(U)p.m(A)p.m(G)p.m(A)p.[fl2r](G)p.m(C)p.[fl2r](U)p.[fl2r](U)p.[fl2r](A)p.m(A)p.m(G)p.m(A)p.m(U)p.m(C)p.m(C)p.m(G)p.m(A)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CCUAGAGCUUAAGAUCCGAGA
SSR-0107080	RNA1{p.m(C)[sp].m(U)p.m(A)p.m(G)p.m(A)p.m(G)p.[fl2r](C)p.m(U)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(G)p.m(A)p.m(U)p.m(C)p.m(C)p.m(G)p.m(A)p.m(G)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUAGAGCUUAAGAUCCGAGCA
SSR-0107081	RNA1{p.m(U)[sp].m(A)p.m(G)p.m(A)p.m(G)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](A)p.[fl2r](A)p.[fl2r](G)p.m(A)p.m(U)p.m(C)p.m(C)p.m(G)p.m(A)p.m(G)p.m(C)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UAGAGCUUAAGAUCCGAGCCA
SSR-0107082	RNA1{p.m(G)[sp].m(C)p.m(U)p.m(U)p.m(A)p.m(A)p.[fl2r](G)p.m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(G)p.m(A)p.m(G)p.m(C)p.m(C)p.m(A)p.m(A)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GCUUAAGAUCCGAGCCAAUGA
SSR-0107083	RNA1{p.m(C)[sp].m(U)p.m(U)p.m(A)p.m(A)p.m(G)p.[fl2r](A)p.m(U)p.[fl2r](C)p.[fl2r](C)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(C)p.m(A)p.m(A)p.m(U)p.m(G)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUUAAGAUCCGAGCCAAUGAA
SSR-0107084	RNA1{p.m(U)[sp].m(U)p.m(A)p.m(A)p.m(G)p.m(A)p.[fl2r](U)p.m(C)p.[fl2r](C)p.[fl2r](G)p.[fl2r](A)p.m(G)p.m(C)p.m(C)p.m(A)p.m(A)p.m(U)p.m(G)p.m(A)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UUAAGAUCCGAGCCAAUGAGA
SSR-0107085	RNA1{p.m(G)[sp].m(A)p.m(G)p.m(C)p.m(C)p.m(A)p.[fl2r](A)p.m(U)p.[fl2r](G)p.[fl2r](A)p.[fl2r](G)p.m(C)p.m(C)p.m(U)p.m(G)p.m(G)p.m(A)p.m(G)p.m(C)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GAGCCAAUGAGCCUGGAGCAA

SSR-0107086	RNA1{p.m(G)[sp].m(C)p.m(C)p.m(G)p.m(G)p.m(G)p.[fl2r](C)p.m(C)p.[fl2r](A)p.[fl2r](G)p.[fl2r](G)p.m(A)p.m(G)p.m(G)p.m(A)p.m(G)p.m(G)p.m(A)p.m(C)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GCCGGGCCAGGAGGAGGACCA
SSR-0107087	RNA1{p.m(C)[sp].m(C)p.m(G)p.m(G)p.m(G)p.m(C)p.[fl2r](C)p.m(A)p.[fl2r](G)p.[fl2r](G)p.[fl2r](A)p.m(G)p.m(G)p.m(A)p.m(G)p.m(G)p.m(A)p.m(C)p.m(C)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CCGGGCCAGGAGGAGGACCCA
SSR-0107088	RNA1{p.m(C)[sp].m(C)p.m(C)p.m(A)p.m(C)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](U)p.[fl2r](G)p.[fl2r](A)p.m(G)p.m(C)p.m(C)p.m(U)p.m(G)p.m(C)p.m(G)p.m(A)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CCCACCUGUGAGCCUGCGACA
SSR-0107089	RNA1{p.m(C)[sp].m(A)p.m(C)p.m(C)p.m(U)p.m(G)p.[fl2r](U)p.m(G)p.[fl2r](A)p.[fl2r](G)p.[fl2r](C)p.m(C)p.m(U)p.m(G)p.m(C)p.m(G)p.m(A)p.m(C)p.m(C)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CACCUGUGAGCCUGCGACCCA
SSR-0107090	RNA1{p.m(C)[sp].m(C)p.m(C)p.m(U)p.m(U)p.m(A)p.[fl2r](U)p.m(G)p.[fl2r](U)p.[fl2r](U)p.[fl2r](G)p.m(C)p.m(A)p.m(G)p.m(G)p.m(C)p.m(G)p.m(A)p.m(G)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CCCUUAUGUUGCAGGCGAGAA
SSR-0107091	RNA1{p.m(C)[sp].m(C)p.m(U)p.m(U)p.m(A)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](U)p.[fl2r](G)p.[fl2r](C)p.m(A)p.m(G)p.m(G)p.m(C)p.m(G)p.m(A)p.m(G)p.m(A)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CCUUAUGUUGCAGGCGAGACA
SSR-0107092	RNA1{p.m(U)[sp].m(G)p.m(U)p.m(U)p.m(G)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](G)p.[fl2r](C)p.[fl2r](G)p.m(A)p.m(G)p.m(A)p.m(C)p.m(C)p.m(A)p.m(U)p.m(U)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGUUGCAGGCGAGACCAUUAA
SSR-0107093	RNA1{p.m(G)[sp].m(U)p.m(U)p.m(G)p.m(C)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](C)p.[fl2r](G)p.[fl2r](A)p.m(G)p.m(A)p.m(C)p.m(C)p.m(A)p.m(U)p.m(U)p.m(A)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GUUGCAGGCGAGACCAUUACA
SSR-0107094	RNA1{p.m(G)[sp].m(C)p.m(A)p.m(G)p.m(G)p.m(C)p.[fl2r](G)p.m(A)p.[fl2r](G)p.[fl2r](A)p.[fl2r](C)p.m(C)p.m(A)p.m(U)p.m(U)p.m(A)p.m(C)p.m(G)p.m(U)p.m(A)[sp].m(A)}|CHEM1{[	GCAGGCGAGACC

	nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AUUACGUAA
SSR-0107095	RNA1{p.m(A)[sp].m(G)p.m(G)p.m(C)p.m(G)p.m(A)p.[fl2r](G)p.m(A)p.[fl2r](C)p.[fl2r](C)p.[fl2r](A)p.m(U)p.m(U)p.m(A)p.m(C)p.m(G)p.m(U)p.m(A)p.m(G)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGGCGAGACCAUUACGUAGAA
SSR-0107096	RNA1{p.m(G)[sp].m(G)p.m(C)p.m(G)p.m(A)p.m(G)p.[fl2r](A)p.m(C)p.[fl2r](C)p.[fl2r](A)p.[fl2r](U)p.m(U)p.m(A)p.m(C)p.m(G)p.m(U)p.m(A)p.m(G)p.m(A)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGCGAGACCAUUACGUAGACA
SSR-0107097	RNA1{p.m(C)[sp].m(U)p.m(U)p.m(C)p.m(C)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](A)p.[fl2r](A)p.[fl2r](C)p.m(U)p.m(G)p.m(G)p.m(G)p.m(A)p.m(U)p.m(G)p.m(G)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUUCCAGGAACUGGGAUGGCA
SSR-0107098	RNA1{p.m(C)[sp].m(A)p.m(G)p.m(G)p.m(A)p.m(A)p.[fl2r](C)p.m(U)p.[fl2r](G)p.[fl2r](G)p.[fl2r](G)p.m(A)p.m(U)p.m(G)p.m(G)p.m(C)p.m(G)p.m(G)p.m(G)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CAGGAACUGGGAUGGCGGGAA
SSR-0107099	RNA1{p.m(A)[sp].m(G)p.m(G)p.m(A)p.m(A)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](G)p.[fl2r](G)p.[fl2r](A)p.m(U)p.m(G)p.m(G)p.m(C)p.m(G)p.m(G)p.m(G)p.m(A)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGGAACUGGGAUGGCGGACA
SSR-0107100	RNA1{p.m(G)[sp].m(G)p.m(A)p.m(A)p.m(C)p.m(U)p.[fl2r](G)p.m(G)p.[fl2r](G)p.[fl2r](A)p.[fl2r](U)p.m(G)p.m(G)p.m(C)p.m(G)p.m(G)p.m(G)p.m(A)p.m(C)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGAACUGGGAUGGCGGGACUA
SSR-0107101	RNA1{p.m(U)[sp].m(G)p.m(G)p.m(G)p.m(A)p.m(U)p.[fl2r](G)p.m(G)p.[fl2r](C)p.[fl2r](G)p.[fl2r](G)p.m(G)p.m(A)p.m(C)p.m(U)p.m(G)p.m(G)p.m(A)p.m(U)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGGGAUGGCGGGACUGGAUAA
SSR-0107102	RNA1{p.m(G)[sp].m(G)p.m(G)p.m(A)p.m(U)p.m(G)p.[fl2r](G)p.m(C)p.[fl2r](G)p.[fl2r](G)p.[fl2r](G)p.m(A)p.m(C)p.m(U)p.m(G)p.m(G)p.m(A)p.m(U)p.m(A)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGGAUGGCGGGACUGG

		AUAC A
SSR-0107103	RNA1{p.m(G)[sp].m(G)p.m(A)p.m(U)p.m(G)p.m(G)p.[fl2r](C)p.m(G)p.[fl2r](G)p.[fl2r](G)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(G)p.m(A)p.m(U)p.m(A)p.m(C)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGAU GGCG GGAC UGGA UACU A
SSR-0107104	RNA1{p.m(A)[sp].m(U)p.m(G)p.m(G)p.m(C)p.m(G)p.[fl2r](G)p.m(G)p.[fl2r](A)p.[fl2r](C)p.[fl2r](U)p.m(G)p.m(G)p.m(A)p.m(U)p.m(A)p.m(C)p.m(U)p.m(G)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AUGG CGGG ACUG GAUA CUGC A
SSR-0107105	RNA1{p.m(U)[sp].m(G)p.m(G)p.m(C)p.m(G)p.m(G)p.[fl2r](G)p.m(A)p.[fl2r](C)p.[fl2r](U)p.[fl2r](G)p.m(G)p.m(A)p.m(U)p.m(A)p.m(C)p.m(U)p.m(G)p.m(C)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGGC GGGA CUGG AUAC UGCA A
SSR-0107106	RNA1{p.m(A)[sp].m(C)p.m(U)p.m(G)p.m(G)p.m(A)p.[fl2r](U)p.m(A)p.[fl2r](C)p.[fl2r](U)p.[fl2r](G)p.m(C)p.m(A)p.m(G)p.m(C)p.m(C)p.m(C)p.m(G)p.m(A)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	ACUG GAUA CUGC AGCC CGAG A
SSR-0107107	RNA1{p.m(C)[sp].m(U)p.m(G)p.m(G)p.m(A)p.m(U)p.[fl2r](A)p.m(C)p.[fl2r](U)p.[fl2r](G)p.[fl2r](C)p.m(A)p.m(G)p.m(C)p.m(C)p.m(C)p.m(G)p.m(A)p.m(G)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUGG AUAC UGCA GCCC GAGG A
SSR-0107108	RNA1{p.m(U)[sp].m(G)p.m(G)p.m(A)p.m(U)p.m(A)p.[fl2r](C)p.m(U)p.[fl2r](G)p.[fl2r](C)p.[fl2r](A)p.m(G)p.m(C)p.m(C)p.m(C)p.m(G)p.m(A)p.m(G)p.m(G)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGGA UACU GCAG CCCG AGGG A
SSR-0107109	RNA1{p.m(G)[sp].m(G)p.m(U)p.m(A)p.m(C)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](C)p.[fl2r](U)p.[fl2r](G)p.m(A)p.m(A)p.m(U)p.m(U)p.m(A)p.m(C)p.m(U)p.m(G)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGUA CCAG CUGA AUUA CUGC A
SSR-0107110	RNA1{p.m(G)[sp].m(U)p.m(A)p.m(C)p.m(C)p.m(A)p.[fl2r](G)p.m(C)p.[fl2r](U)p.[fl2r](G)p.[fl2r](A)p.m(A)p.m(U)p.m(U)p.m(A)p.m(C)p.m(U)p.m(G)p.m(C)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GUAC CAGC UGAA UUAC UGCA A

SSR-0107111	RNA1{p.m(U)[sp].m(G)p.m(G)p.m(C)p.m(U)p.m(G)p.[fl2r](G)p.m(C)p.[fl2r](A)p.[fl2r](G)p.[fl2r](C)p.m(C)p.m(C)p.m(A)p.m(G)p.m(G)p.m(C)p.m(A)p.m(U)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGGC UGGC AGCC CAGG CAUU A
SSR-0107112	RNA1{p.m(C)[sp].m(U)p.m(C)p.m(U)p.m(U)p.m(U)p.[fl2r](C)p.m(C)p.[fl2r](A)p.[fl2r](U)p.[fl2r](U)p.m(C)p.m(U)p.m(G)p.m(C)p.m(C)p.m(G)p.m(U)p.m(C)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUCU UUCC AUUC UGCC GUCU A
SSR-0107113	RNA1{p.m(U)[sp].m(C)p.m(U)p.m(U)p.m(U)p.m(C)p.[fl2r](C)p.m(A)p.[fl2r](U)p.[fl2r](U)p.[fl2r](C)p.m(U)p.m(G)p.m(C)p.m(C)p.m(G)p.m(U)p.m(C)p.m(U)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UCUU UCCA UUCU GCCG UCUU A
SSR-0107114	RNA1{p.m(C)[sp].m(U)p.m(U)p.m(U)p.m(C)p.m(C)p.[fl2r](A)p.m(U)p.[fl2r](U)p.[fl2r](C)p.[fl2r](U)p.m(G)p.m(C)p.m(C)p.m(G)p.m(U)p.m(C)p.m(U)p.m(U)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUUU CCAU UCUG CCGU CUUC A
SSR-0107115	RNA1{p.m(G)[sp].m(C)p.m(C)p.m(G)p.m(U)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](C)p.[fl2r](A)p.[fl2r](G)p.m(C)p.m(C)p.m(U)p.m(C)p.m(C)p.m(U)p.m(C)p.m(A)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GCCG UCUU CAGC CUCC UCAA A
SSR-0107116	RNA1{p.m(C)[sp].m(G)p.m(U)p.m(C)p.m(U)p.m(U)p.[fl2r](C)p.m(A)p.[fl2r](G)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(C)p.m(U)p.m(C)p.m(A)p.m(A)p.m(A)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CGUC UUCA GCCU CCUC AAAG A
SSR-0107117	RNA1{p.m(G)[sp].m(U)p.m(C)p.m(U)p.m(U)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](C)p.[fl2r](C)p.[fl2r](U)p.m(C)p.m(C)p.m(U)p.m(C)p.m(A)p.m(A)p.m(A)p.m(G)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GUCU UCAG CCUCC UCAA AGCA
SSR-0107118	RNA1{p.m(U)[sp].m(C)p.m(U)p.m(U)p.m(C)p.m(A)p.[fl2r](G)p.m(C)p.[fl2r](C)p.[fl2r](U)p.[fl2r](C)p.m(C)p.m(U)p.m(C)p.m(A)p.m(A)p.m(A)p.m(G)p.m(C)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UCUU CAGC CUCC UCAA AGCC A
SSR-0107119	RNA1{p.m(C)[sp].m(U)p.m(C)p.m(C)p.m(U)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](A)p.[fl2r](G)p.[fl2r](C)p.m(C)p.m(A)p.m(A)p.m(C)p.m(A)p.m(A)p.m(U)p.m(C)p.m(C)[sp].m(A)}|CHEM1{[	CUCC UCAA AGCC

	nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AACAAUCCA
SSR-0107120	RNA1{p.m(C)[sp].m(U)p.m(C)p.m(A)p.m(A)p.m(A)p.[fl2r](G)p.m(C)p.[fl2r](C)p.[fl2r](A)p.[fl2r](A)p.m(C)p.m(A)p.m(A)p.m(U)p.m(C)p.m(C)p.m(U)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUCAAAGCCAACAAUCCUUGA
SSR-0107121	RNA1{p.m(U)[sp].m(C)p.m(A)p.m(A)p.m(A)p.m(G)p.[fl2r](C)p.m(C)p.[fl2r](A)p.[fl2r](A)p.[fl2r](C)p.m(A)p.m(A)p.m(U)p.m(C)p.m(C)p.m(U)p.m(U)p.m(G)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UCAAAGCCAACAAUCCUUGGA
SSR-0107122	RNA1{p.m(G)[sp].m(C)p.m(C)p.m(A)p.m(A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(U)p.m(G)p.m(G)p.m(C)p.m(C)p.m(U)p.m(G)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GCCAACAAUCCUUGGCCUGCA
SSR-0107123	RNA1{p.m(C)[sp].m(C)p.m(U)p.m(U)p.m(G)p.m(G)p.[fl2r](C)p.m(C)p.[fl2r](U)p.[fl2r](G)p.[fl2r](C)p.m(C)p.m(A)p.m(G)p.m(U)p.m(A)p.m(C)p.m(C)p.m(U)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CCUUGGCCUGCCAGUACCUCA
SSR-0107124	RNA1{p.m(C)[sp].m(U)p.m(G)p.m(C)p.m(C)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)p.m(G)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUGCCAGUACCUCCUGUUGUA
SSR-0107125	RNA1{p.m(C)[sp].m(C)p.m(U)p.m(C)p.m(C)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](U)p.[fl2r](G)p.[fl2r](U)p.m(G)p.m(U)p.m(C)p.m(C)p.m(C)p.m(U)p.m(A)p.m(C)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CCUCCUGUUGUGUCCCUACUA
SSR-0107126	RNA1{p.m(C)[sp].m(U)p.m(C)p.m(C)p.m(U)p.m(G)p.[fl2r](U)p.m(U)p.[fl2r](G)p.[fl2r](U)p.[fl2r](G)p.m(U)p.m(C)p.m(C)p.m(C)p.m(U)p.m(A)p.m(C)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUCCUGUUGUGUCCCUACUGA
SSR-0107127	RNA1{p.m(U)[sp].m(C)p.m(C)p.m(U)p.m(G)p.m(U)p.[fl2r](U)p.m(G)p.[fl2r](U)p.[fl2r](G)p.[fl2r](U)p.m(C)p.m(C)p.m(C)p.m(U)p.m(A)p.m(C)p.m(U)p.m(G)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UCCUGUUGUGUCCCUACUGCA

SSR-0107128	RNA1{p.m(C)[sp].m(C)p.m(U)p.m(G)p.m(U)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.[fl2r](U)p.[fl2r](C)p.m(C)p.m(C)p.m(U)p.m(A)p.m(C)p.m(U)p.m(G)p.m(C)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CCUG UUGU GUCC CUAC UGCC A
SSR-0107129	RNA1{p.m(U)[sp].m(U)p.m(G)p.m(U)p.m(G)p.m(U)p.[fl2r](C)p.m(C)p.[fl2r](C)p.[fl2r](U)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(C)p.m(C)p.m(C)p.m(G)p.m(A)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UUGU GUCC CUAC UGCC CGAA A
SSR-0107130	RNA1{p.m(G)[sp].m(U)p.m(G)p.m(U)p.m(C)p.m(C)p.[fl2r](C)p.m(U)p.[fl2r](A)p.[fl2r](C)p.[fl2r](U)p.m(G)p.m(C)p.m(C)p.m(C)p.m(G)p.m(A)p.m(A)p.m(G)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GUGU CCCU ACUG CCCG AAGG A
SSR-0107131	RNA1{p.m(U)[sp].m(C)p.m(C)p.m(C)p.m(U)p.m(A)p.[fl2r](C)p.m(U)p.[fl2r](G)p.[fl2r](C)p.[fl2r](C)p.m(C)p.m(G)p.m(A)p.m(A)p.m(G)p.m(G)p.m(C)p.m(C)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UCCC UACU GCCC GAAG GCCC A
SSR-0107132	RNA1{p.m(C)[sp].m(U)p.m(C)p.m(C)p.m(U)p.m(C)p.[fl2r](U)p.m(A)p.[fl2r](C)p.[fl2r](C)p.[fl2r](U)p.m(G)p.m(G)p.m(A)p.m(U)p.m(C)p.m(A)p.m(U)p.m(A)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUCC UCUA CCUG GAUC AUAA A
SSR-0107133	RNA1{p.m(U)[sp].m(C)p.m(C)p.m(U)p.m(C)p.m(U)p.[fl2r](A)p.m(C)p.[fl2r](C)p.[fl2r](U)p.[fl2r](G)p.m(G)p.m(A)p.m(U)p.m(C)p.m(A)p.m(U)p.m(A)p.m(A)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UCCU CUAC CUGG AUCA UAAU A
SSR-0107134	RNA1{p.m(C)[sp].m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.[fl2r](C)p.m(C)p.[fl2r](U)p.[fl2r](G)p.[fl2r](G)p.m(A)p.m(U)p.m(C)p.m(A)p.m(U)p.m(A)p.m(A)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CCUC UACC UGGA UCAU AAUG A
SSR-0107135	RNA1{p.m(A)[sp].m(C)p.m(C)p.m(U)p.m(G)p.m(G)p.[fl2r](A)p.m(U)p.[fl2r](C)p.[fl2r](A)p.[fl2r](U)p.m(A)p.m(A)p.m(U)p.m(G)p.m(G)p.m(C)p.m(A)p.m(A)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	ACCU GGAU CAUA AUGG CAAU A
SSR-0107136	RNA1{p.m(C)[sp].m(U)p.m(G)p.m(G)p.m(A)p.m(U)p.[fl2r](C)p.m(A)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(U)p.m(G)p.m(G)p.	CUGG AUCA

	m(C)p.m(A)p.m(A)p.m(U)p.m(G)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UAAUGGCAAUGUA
SSR-0107137	RNA1{p.m(U)[sp].m(C)p.m(A)p.m(U)p.m(A)p.m(A)p.[fl2r](U)p.m(G)p.[fl2r](G)p.[fl2r](C)p.[fl2r](A)p.m(A)p.m(U)p.m(G)p.m(U)p.m(G)p.m(G)p.m(U)p.m(C)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UCAUAAUGGCAAUGUGGUCAA
SSR-0107138	RNA1{p.m(A)[sp].m(U)p.m(G)p.m(G)p.m(C)p.m(A)p.[fl2r](A)p.m(U)p.[fl2r](G)p.[fl2r](U)p.[fl2r](G)p.m(G)p.m(U)p.m(C)p.m(A)p.m(A)p.m(G)p.m(A)p.m(C)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AUGGCAAUGUGGUCAAGACGA
SSR-0107139	RNA1{p.m(U)[sp].m(G)p.m(G)p.m(C)p.m(A)p.m(A)p.[fl2r](U)p.m(G)p.[fl2r](U)p.[fl2r](G)p.[fl2r](G)p.m(U)p.m(C)p.m(A)p.m(A)p.m(G)p.m(A)p.m(C)p.m(G)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGGCAAUGUGGUCAAGACGGA
SSR-0107140	RNA1{p.m(C)[sp].m(A)p.m(A)p.m(U)p.m(G)p.m(U)p.[fl2r](G)p.m(G)p.[fl2r](U)p.[fl2r](C)p.[fl2r](A)p.m(A)p.m(G)p.m(A)p.m(C)p.m(G)p.m(G)p.m(A)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CAAUGUGGUCAAGACGGAUGA
SSR-0107141	RNA1{p.m(A)[sp].m(A)p.m(U)p.m(G)p.m(U)p.m(G)p.[fl2r](G)p.m(U)p.[fl2r](C)p.[fl2r](A)p.[fl2r](A)p.m(G)p.m(A)p.m(C)p.m(G)p.m(G)p.m(A)p.m(U)p.m(G)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AAUGUGGUCAAGACGGAUGUA
SSR-0107142	RNA1{p.m(G)[sp].m(U)p.m(C)p.m(A)p.m(A)p.m(G)p.[fl2r](A)p.m(C)p.[fl2r](G)p.[fl2r](G)p.[fl2r](A)p.m(U)p.m(G)p.m(U)p.m(G)p.m(C)p.m(C)p.m(A)p.m(G)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GUCAAGACGGAUGUGCCAGAA
SSR-0107143	RNA1{p.m(A)[sp].m(G)p.m(A)p.m(C)p.m(G)p.m(G)p.[fl2r](A)p.m(U)p.[fl2r](G)p.[fl2r](U)p.[fl2r](G)p.m(C)p.m(C)p.m(A)p.m(G)p.m(A)p.m(U)p.m(A)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGACGGAUGUGCCAGAUAUGA
SSR-0107144	RNA1{p.m(G)[sp].m(A)p.m(C)p.m(G)p.m(G)p.m(A)p.[fl2r](U)p.m(G)p.[fl2r](U)p.[fl2r](G)p.[fl2r](C)p.m(C)p.m(A)p.m(G)p.m(A)p.m(U)p.m(A)p.m(U)p.m(G)p.m(G)[sp].m(A)}|CHEM1{[	GACGGAUGUGCCAGAU

	nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AUGGA
SSR-0107145	RNA1{p.m(G)[sp].m(U)p.m(G)p.m(C)p.m(C)p.m(A)p.[fl2r](G)p.m(A)p.[fl2r](U)p.[fl2r](A)p.[fl2r](U)p.m(G)p.m(G)p.m(U)p.m(G)p.m(G)p.m(U)p.m(G)p.m(G)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GUGCCAGAUAUGGUGGUGGAA
SSR-0107146	RNA1{p.m(C)[sp].m(U)p.m(U)p.m(U)p.m(G)p.m(G)p.[fl2r](A)p.m(G)p.[fl2r](U)p.[fl2r](G)p.[fl2r](A)p.m(A)p.m(G)p.m(A)p.m(G)p.m(A)p.m(C)p.m(C)p.m(A)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUUUGGAGUGAAGAGACCAAA
SSR-0107147	RNA1{p.m(G)[sp].m(A)p.m(A)p.m(G)p.m(A)p.m(G)p.[fl2r](A)p.m(C)p.[fl2r](C)p.[fl2r](A)p.[fl2r](A)p.m(G)p.m(A)p.m(U)p.m(G)p.m(A)p.m(A)p.m(G)p.m(U)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GAAGAGACCAAGAUGAAGUUA
SSR-0107148	RNA1{p.m(A)[sp].m(G)p.m(A)p.m(C)p.m(C)p.m(A)p.[fl2r](A)p.m(G)p.[fl2r](A)p.[fl2r](U)p.[fl2r](G)p.m(A)p.m(A)p.m(G)p.m(U)p.m(U)p.m(U)p.m(C)p.m(C)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGACCAAGAUGAAGUUUCCCA
SSR-0107149	RNA1{p.m(U)[sp].m(U)p.m(U)p.m(C)p.m(C)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](G)p.[fl2r](C)p.[fl2r](A)p.m(C)p.m(A)p.m(G)p.m(G)p.m(G)p.m(C)p.m(A)p.m(U)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UUUCCCAGGCACAGGGCAUCA
SSR-0107150	RNA1{p.m(G)[sp].m(G)p.m(C)p.m(A)p.m(C)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](G)p.[fl2r](C)p.[fl2r](A)p.m(U)p.m(C)p.m(U)p.m(G)p.m(U)p.m(G)p.m(A)p.m(C)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGCACAGGGCAUCUGUGACUA
SSR-0107151	RNA1{p.m(C)[sp].m(U)p.m(G)p.m(U)p.m(G)p.m(A)p.[fl2r](C)p.m(U)p.[fl2r](G)p.[fl2r](G)p.[fl2r](A)p.m(G)p.m(G)p.m(C)p.m(A)p.m(U)p.m(C)p.m(A)p.m(G)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUGUGACUGGAGGCAUCAGAA
SSR-0107152	RNA1{p.m(A)[sp].m(C)p.m(U)p.m(G)p.m(G)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](C)p.[fl2r](A)p.[fl2r](U)p.m(C)p.m(A)p.m(G)p.m(A)p.m(U)p.m(U)p.m(C)p.m(C)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	ACUGGAGGCAUCAGAUUCCUA

SSR-0107153	RNA1{p.m(A)[sp].m(C)p.m(C)p.m(C)p.m(A)p.m(A)p.[fl2r](C)p.m(A)p.[fl2r](A)p.[fl2r](C)p.[fl2r](C)p.m(A)p.m(C)p.m(C)p.m(U)p.m(G)p.m(G)p.m(C)p.m(A)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	ACCC AACA ACCA CCUG GCAA A
SSR-0107154	RNA1{p.m(C)[sp].m(C)p.m(C)p.m(A)p.m(A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](C)p.[fl2r](C)p.[fl2r](A)p.m(C)p.m(C)p.m(U)p.m(G)p.m(G)p.m(C)p.m(A)p.m(A)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CCCA ACAA CCACC UGGC AAUA
SSR-0107155	RNA1{p.m(A)[sp].m(C)p.m(A)p.m(A)p.m(C)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](C)p.[fl2r](U)p.[fl2r](G)p.m(G)p.m(C)p.m(A)p.m(A)p.m(U)p.m(A)p.m(U)p.m(G)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	ACAA CCACC UGGC AAUA UGAA
SSR-0107156	RNA1{p.m(A)[sp].m(A)p.m(C)p.m(C)p.m(A)p.m(C)p.[fl2r](C)p.m(U)p.[fl2r](G)p.[fl2r](G)p.[fl2r](C)p.m(A)p.m(A)p.m(U)p.m(A)p.m(U)p.m(G)p.m(A)p.m(C)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AACC ACCU GGCA AUAU GACU A
SSR-0107157	RNA1{p.m(A)[sp].m(C)p.m(C)p.m(A)p.m(C)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](G)p.[fl2r](C)p.[fl2r](A)p.m(A)p.m(U)p.m(A)p.m(U)p.m(G)p.m(A)p.m(C)p.m(U)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	ACCA CCUG GCAA UAUG ACUC A
SSR-0107158	RNA1{p.m(C)[sp].m(A)p.m(C)p.m(C)p.m(U)p.m(G)p.[fl2r](G)p.m(C)p.[fl2r](A)p.[fl2r](A)p.[fl2r](U)p.m(A)p.m(U)p.m(G)p.m(A)p.m(C)p.m(U)p.m(C)p.m(A)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CACC UGGC AAUA UGAC UCAC A
SSR-0107159	RNA1{p.m(G)[sp].m(G)p.m(A)p.m(C)p.m(C)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](A)p.[fl2r](U)p.[fl2r](G)p.m(G)p.m(G)p.m(C)p.m(A)p.m(C)p.m(U)p.m(U)p.m(U)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGAC CCAA AUGG GCAC UUUC A
SSR-0107160	RNA1{p.m(C)[sp].m(C)p.m(A)p.m(A)p.m(A)p.m(U)p.[fl2r](G)p.m(G)p.[fl2r](G)p.[fl2r](C)p.[fl2r](A)p.m(C)p.m(U)p.m(U)p.m(U)p.m(C)p.m(U)p.m(U)p.m(G)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CCAA AUGG GCAC UUUC UUGU A
SSR-0107161	RNA1{p.m(C)[sp].m(A)p.m(A)p.m(A)p.m(U)p.m(G)p.[fl2r](G)p.m(G)p.[fl2r](C)p.[fl2r](A)p.[fl2r](C)p.m(U)p.m(U)p.m(U)p.m(C)p.m(U)p.m(U)p.m(G)p.m(U)p.m(C)[sp].m(A)}|CHEM1{[	CAAA UGGG CACU UUCU

	nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGUCA
SSR-0107162	RNA1{p.m(A)[sp].m(A)p.m(U)p.m(G)p.m(G)p.m(G)p.[fl2r](C)p.m(A)p.[fl2r](C)p.[fl2r](U)p.[fl2r](U)p.m(U)p.m(C)p.m(U)p.m(U)p.m(G)p.m(U)p.m(C)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AAUGGGCACUUUCUUGUCUGA
SSR-0107163	RNA1{p.m(A)[sp].m(U)p.m(G)p.m(G)p.m(G)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](U)p.[fl2r](U)p.[fl2r](U)p.m(C)p.m(U)p.m(U)p.m(G)p.m(U)p.m(C)p.m(U)p.m(G)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AUGGGCACUUUCUUGUCUGA
SSR-0107164	RNA1{p.m(U)[sp].m(G)p.m(G)p.m(G)p.m(C)p.m(A)p.[fl2r](C)p.m(U)p.[fl2r](U)p.[fl2r](U)p.[fl2r](C)p.m(U)p.m(U)p.m(G)p.m(U)p.m(C)p.m(U)p.m(G)p.m(A)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGGGCACUUUCUGUCUGAGA
SSR-0107165	RNA1{p.m(U)[sp].m(U)p.m(A)p.m(U)p.m(U)p.m(C)p.[fl2r](C)p.m(A)p.[fl2r](G)p.[fl2r](G)p.[fl2r](U)p.m(U)p.m(G)p.m(G)p.m(C)p.m(U)p.m(G)p.m(A)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UUAUUCCAGGUUGGCUGAUGA
SSR-0107166	RNA1{p.m(A)[sp].m(U)p.m(U)p.m(C)p.m(C)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](U)p.[fl2r](U)p.[fl2r](G)p.m(G)p.m(C)p.m(U)p.m(G)p.m(A)p.m(U)p.m(G)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AUUCCAGGUUGGCUGAUGUGA
SSR-0107167	RNA1{p.m(U)[sp].m(G)p.m(G)p.m(C)p.m(U)p.m(G)p.[fl2r](A)p.m(U)p.[fl2r](G)p.[fl2r](U)p.[fl2r](G)p.m(U)p.m(U)p.m(G)p.m(G)p.m(G)p.m(A)p.m(G)p.m(A)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGGCUGAUGUGUUGGGAGAUA
SSR-0107168	RNA1{p.m(G)[sp].m(A)p.m(G)p.m(A)p.m(U)p.m(G)p.[fl2r](G)p.m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(A)p.m(G)p.m(C)p.m(G)p.m(U)p.m(U)p.m(U)p.m(C)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GAGAUGGGUAAAGCGUUUCUA
SSR-0107169	RNA1{p.m(U)[sp].m(G)p.m(G)p.m(G)p.m(U)p.m(A)p.[fl2r](A)p.m(A)p.[fl2r](G)p.[fl2r](C)p.[fl2r](G)p.m(U)p.m(U)p.m(U)p.m(C)p.m(U)p.m(U)p.m(C)p.m(U)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGGGUAAAGCGUUUCUUCUAA

SSR-0107170	RNA1{p.m(G)[sp].m(G)p.m(U)p.m(A)p.m(A)p.m(A)p.[fl2r](G)p.m(C)p.[fl2r](G)p.[fl2r](U)p.[fl2r](U)p.m(U)p.m(C)p.m(U)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGUAAAGCGUUUCUUCUAAAA
SSR-0107171	RNA1{p.m(A)[sp].m(A)p.m(G)p.m(C)p.m(A)p.m(U)p.[fl2r](G)p.m(A)p.[fl2r](U)p.[fl2r](U)p.[fl2r](U)p.m(C)p.m(C)p.m(U)p.m(G)p.m(C)p.m(C)p.m(C)p.m(U)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AAGCAUGAUUUCCUGCCCUAA
SSR-0107172	RNA1{p.m(G)[sp].m(C)p.m(A)p.m(U)p.m(G)p.m(A)p.[fl2r](U)p.m(U)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(G)p.m(C)p.m(C)p.m(C)p.m(U)p.m(A)p.m(A)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GCAUGAUUUCCUGCCCUAAGA
SSR-0107173	RNA1{p.m(C)[sp].m(A)p.m(U)p.m(G)p.m(A)p.m(U)p.[fl2r](U)p.m(U)p.[fl2r](C)p.[fl2r](C)p.[fl2r](U)p.m(G)p.m(C)p.m(C)p.m(C)p.m(U)p.m(A)p.m(A)p.m(G)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CAUGAUUUCCUGCCCUAAGUA
SSR-0107174	RNA1{p.m(A)[sp].m(U)p.m(G)p.m(A)p.m(U)p.m(U)p.[fl2r](U)p.m(C)p.[fl2r](C)p.[fl2r](U)p.[fl2r](G)p.m(C)p.m(C)p.m(C)p.m(U)p.m(A)p.m(A)p.m(G)p.m(U)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AUGAUUUCCUGCCCUAAGUCA
SSR-0107175	RNA1{p.m(U)[sp].m(G)p.m(A)p.m(U)p.m(U)p.m(U)p.[fl2r](C)p.m(C)p.[fl2r](U)p.[fl2r](G)p.[fl2r](C)p.m(C)p.m(C)p.m(U)p.m(A)p.m(A)p.m(G)p.m(U)p.m(C)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGAUUUCCUGCCCUAAGUCCA
SSR-0107176	RNA1{p.m(U)[sp].m(U)p.m(C)p.m(C)p.m(U)p.m(G)p.[fl2r](C)p.m(C)p.[fl2r](C)p.[fl2r](U)p.[fl2r](A)p.m(A)p.m(G)p.m(U)p.m(C)p.m(C)p.m(U)p.m(G)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UUCCUGCCCUAAGUCCUGUGA
SSR-0107177	RNA1{p.m(C)[sp].m(U)p.m(A)p.m(A)p.m(G)p.m(U)p.[fl2r](C)p.m(C)p.[fl2r](U)p.[fl2r](G)p.[fl2r](U)p.m(G)p.m(A)p.m(G)p.m(A)p.m(A)p.m(G)p.m(A)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUAAGUCCUGUGAGAAGAUGA
SSR-0107178	RNA1{p.m(U)[sp].m(C)p.m(C)p.m(U)p.m(G)p.m(U)p.[fl2r](G)p.m(A)p.[fl2r](G)p.[fl2r](A)p.[fl2r](A)p.m(G)p.m(A)p.m(U)p.	UCCUGUGA

	m(G)p.m(U)p.m(C)p.m(A)p.m(G)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GAAGAUGUCAGGA
SSR-0107179	RNA1{p.m(A)[sp].m(G)p.m(A)p.m(U)p.m(G)p.m(U)p.[fl2r](C)p.m(A)p.[fl2r](G)p.[fl2r](G)p.[fl2r](G)p.m(A)p.m(C)p.m(U)p.m(A)p.m(G)p.m(G)p.m(G)p.m(A)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGAUGUCAGGACUAGGGAG
SSR-0107180	RNA1{p.m(A)[sp].m(U)p.m(G)p.m(U)p.m(C)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](G)p.[fl2r](A)p.[fl2r](C)p.m(U)p.m(A)p.m(G)p.m(G)p.m(G)p.m(A)p.m(G)p.m(G)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AUGUCAGGGACUAGGGAGGGA
SSR-0107181	RNA1{p.m(C)[sp].m(A)p.m(G)p.m(G)p.m(G)p.m(A)p.[fl2r](C)p.m(U)p.[fl2r](A)p.[fl2r](G)p.[fl2r](G)p.m(G)p.m(A)p.m(G)p.m(G)p.m(G)p.m(A)p.m(G)p.m(G)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CAGGGACUAGGGAGGGA
SSR-0107182	RNA1{p.m(G)[sp].m(A)p.m(C)p.m(U)p.m(A)p.m(G)p.[fl2r](G)p.m(G)p.[fl2r](A)p.[fl2r](G)p.[fl2r](G)p.m(G)p.m(A)p.m(G)p.m(G)p.m(G)p.m(A)p.m(G)p.m(G)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GACUAGGGAGGGAGGGA
SSR-0107183	RNA1{p.m(G)[sp].m(G)p.m(C)p.m(A)p.m(G)p.m(A)p.[fl2r](G)p.m(A)p.[fl2r](A)p.[fl2r](A)p.[fl2r](A)p.m(A)p.m(U)p.m(U)p.m(A)p.m(C)p.m(U)p.m(U)p.m(A)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGCAGAGAAAAUUACUUAGA
SSR-0107184	RNA1{p.m(A)[sp].m(G)p.m(A)p.m(G)p.m(A)p.m(A)p.[fl2r](A)p.m(A)p.[fl2r](A)p.[fl2r](U)p.[fl2r](U)p.m(A)p.m(C)p.m(U)p.m(U)p.m(A)p.m(G)p.m(C)p.m(C)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGAGAAAAAUUACUUAGCCUA
SSR-0107185	RNA1{p.m(A)[sp].m(G)p.m(C)p.m(C)p.m(U)p.m(C)p.[fl2r](U)p.m(C)p.[fl2r](C)p.[fl2r](C)p.[fl2r](A)p.m(A)p.m(G)p.m(A)p.m(U)p.m(G)p.m(A)p.m(G)p.m(A)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGCCUCUCCCAAGAUGAGAAA
SSR-0107186	RNA1{p.m(G)[sp].m(C)p.m(C)p.m(U)p.m(C)p.m(U)p.[fl2r](C)p.m(C)p.[fl2r](C)p.[fl2r](A)p.[fl2r](A)p.m(G)p.m(A)p.m(U)p.m(G)p.m(A)p.m(G)p.m(A)p.m(A)p.m(A)[sp].m(A)}|CHEM1{[	GCCUCUCCCAAGA

	nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGAG AAAA
SSR-0107187	RNA1{p.m(C)[sp].m(A)p.m(A)p.m(G)p.m(A)p.m(U)p.[fl2r](G)p.m(A)p.[fl2r](G)p.[fl2r](A)p.[fl2r](A)p.m(A)p.m(G)p.m(U)p.m(C)p.m(C)p.m(U)p.m(C)p.m(A)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CAAG AUGA GAAA GUCC UCAA A
SSR-0107188	RNA1{p.m(G)[sp].m(A)p.m(G)p.m(A)p.m(A)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](C)p.[fl2r](C)p.[fl2r](U)p.m(C)p.m(A)p.m(A)p.m(G)p.m(U)p.m(G)p.m(A)p.m(G)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GAGA AAGU CCUC AAGU GAGG A
SSR-0107189	RNA1{p.m(G)[sp].m(U)p.m(C)p.m(C)p.m(A)p.m(G)p.[fl2r](C)p.m(A)p.[fl2r](G)p.[fl2r](G)p.[fl2r](C)p.m(U)p.m(U)p.m(G)p.m(A)p.m(A)p.m(G)p.m(C)p.m(A)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GUCC AGCA GGCU UGAA GCAG A
SSR-0107190	RNA1{p.m(A)[sp].m(G)p.m(C)p.m(A)p.m(G)p.m(G)p.[fl2r](C)p.m(U)p.[fl2r](U)p.[fl2r](G)p.[fl2r](A)p.m(A)p.m(G)p.m(C)p.m(A)p.m(G)p.m(G)p.m(G)p.m(U)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGCA GGCU UGAA GCAG GGUA A
SSR-0107191	RNA1{p.m(A)[sp].m(G)p.m(G)p.m(C)p.m(U)p.m(U)p.[fl2r](G)p.m(A)p.[fl2r](A)p.[fl2r](G)p.[fl2r](C)p.m(A)p.m(G)p.m(G)p.m(G)p.m(U)p.m(A)p.m(A)p.m(G)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGGC UUGA AGCA GGGU AAGC A
SSR-0107192	RNA1{p.m(G)[sp].m(G)p.m(C)p.m(U)p.m(U)p.m(G)p.[fl2r](A)p.m(A)p.[fl2r](G)p.[fl2r](C)p.[fl2r](A)p.m(G)p.m(G)p.m(G)p.m(U)p.m(A)p.m(A)p.m(G)p.m(C)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGCU UGAA GCAG GGUA AGCA A
SSR-0107193	RNA1{p.m(G)[sp].m(C)p.m(A)p.m(G)p.m(G)p.m(G)p.[fl2r](U)p.m(A)p.[fl2r](A)p.[fl2r](G)p.[fl2r](C)p.m(A)p.m(G)p.m(G)p.m(C)p.m(U)p.m(G)p.m(G)p.m(C)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GCAG GGUA AGCA GGCU GGCC A
SSR-0107194	RNA1{p.m(C)[sp].m(A)p.m(G)p.m(G)p.m(C)p.m(U)p.[fl2r](G)p.m(G)p.[fl2r](C)p.[fl2r](C)p.[fl2r](C)p.m(A)p.m(G)p.m(G)p.m(G)p.m(U)p.m(A)p.m(A)p.m(G)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CAGG CUGG CCCA GGGU AAGG A

SSR-0107195	RNA1{p.m(A)[sp].m(G)p.m(G)p.m(C)p.m(U)p.m(G)p.[fl2r](G)p.m(C)p.[fl2r](C)p.[fl2r](C)p.[fl2r](A)p.m(G)p.m(G)p.m(G)p.m(U)p.m(A)p.m(A)p.m(G)p.m(G)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGGC UGGC CCAG GGUA AGGG A
SSR-0107196	RNA1{p.m(G)[sp].m(G)p.m(C)p.m(C)p.m(C)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](G)p.[fl2r](U)p.[fl2r](A)p.m(A)p.m(G)p.m(G)p.m(G)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGCC CAGG GUAA GGGC UGUU A
SSR-0107197	RNA1{p.m(G)[sp].m(G)p.m(U)p.m(A)p.m(A)p.m(G)p.[fl2r](G)p.m(G)p.[fl2r](C)p.[fl2r](U)p.[fl2r](G)p.m(U)p.m(U)p.m(G)p.m(A)p.m(G)p.m(G)p.m(U)p.m(A)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGUA AGGG CUGU UGAG GUAC A
SSR-0107198	RNA1{p.m(G)[sp].m(G)p.m(G)p.m(A)p.m(A)p.m(G)p.[fl2r](G)p.m(U)p.[fl2r](C)p.[fl2r](A)p.[fl2r](A)p.m(G)p.m(A)p.m(G)p.m(G)p.m(G)p.m(A)p.m(G)p.m(A)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGGA AGGU CAAG AGGG AGAU A
SSR-0107199	RNA1{p.m(A)[sp].m(G)p.m(G)p.m(U)p.m(C)p.m(A)p.[fl2r](A)p.m(G)p.[fl2r](A)p.[fl2r](G)p.[fl2r](G)p.m(G)p.m(A)p.m(G)p.m(A)p.m(U)p.m(G)p.m(G)p.m(G)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGGU CAAG AGGG AGAU GGGC A
SSR-0107200	RNA1{p.m(A)[sp].m(G)p.m(G)p.m(G)p.m(A)p.m(G)p.[fl2r](A)p.m(U)p.[fl2r](G)p.[fl2r](G)p.[fl2r](G)p.m(C)p.m(A)p.m(A)p.m(G)p.m(G)p.m(C)p.m(G)p.m(C)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGGG AGAU GGGC AAGG CGCU A
SSR-0107201	RNA1{p.m(G)[sp].m(G)p.m(G)p.m(A)p.m(G)p.m(A)p.[fl2r](U)p.m(G)p.[fl2r](G)p.[fl2r](G)p.[fl2r](C)p.m(A)p.m(A)p.m(G)p.m(G)p.m(C)p.m(G)p.m(C)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGGA GAUG GGCA AGGC GCUG A
SSR-0107202	RNA1{p.m(G)[sp].m(A)p.m(G)p.m(A)p.m(U)p.m(G)p.[fl2r](G)p.m(G)p.[fl2r](C)p.[fl2r](A)p.[fl2r](A)p.m(G)p.m(G)p.m(C)p.m(G)p.m(C)p.m(U)p.m(G)p.m(A)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GAGA UGGG CAAG GCGC UGAG A
SSR-0107203	RNA1{p.m(A)[sp].m(A)p.m(G)p.m(G)p.m(C)p.m(G)p.[fl2r](C)p.m(U)p.[fl2r](G)p.[fl2r](A)p.[fl2r](G)p.m(G)p.m(G)p.m(A)p.	AAGG CGCU

	m(G)p.m(G)p.m(A)p.m(U)p.m(G)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GAGGGAGGAUGCA
SSR-0107204	RNA1{p.m(A)[sp].m(G)p.m(G)p.m(C)p.m(G)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](A)p.[fl2r](G)p.[fl2r](G)p.m(G)p.m(A)p.m(G)p.m(G)p.m(A)p.m(U)p.m(G)p.m(C)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGGCGCUGAGGGAGGAUGCUA
SSR-0107205	RNA1{p.m(G)[sp].m(G)p.m(C)p.m(G)p.m(C)p.m(U)p.[fl2r](G)p.m(A)p.[fl2r](G)p.[fl2r](G)p.[fl2r](G)p.m(A)p.m(G)p.m(G)p.m(A)p.m(U)p.m(G)p.m(C)p.m(U)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGCGCUGAGGGAGGAUGCUUA
SSR-0107206	RNA1{p.m(G)[sp].m(C)p.m(G)p.m(C)p.m(U)p.m(G)p.[fl2r](A)p.m(G)p.[fl2r](G)p.[fl2r](G)p.[fl2r](A)p.m(G)p.m(G)p.m(A)p.m(U)p.m(G)p.m(C)p.m(U)p.m(U)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GCGCUGAGGGAGGAUGCUUAA
SSR-0107207	RNA1{p.m(C)[sp].m(A)p.m(G)p.m(A)p.m(A)p.m(A)p.[fl2r](C)p.m(A)p.[fl2r](G)p.[fl2r](G)p.[fl2r](A)p.m(G)p.m(U)p.m(C)p.m(A)p.m(G)p.m(G)p.m(A)p.m(A)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CAGAAACAGGAGUCAGGAAAA
SSR-0107208	RNA1{p.m(G)[sp].m(A)p.m(A)p.m(A)p.m(C)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](A)p.[fl2r](G)p.[fl2r](U)p.m(C)p.m(A)p.m(G)p.m(G)p.m(A)p.m(A)p.m(A)p.m(A)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GAAACAGGAGUCAGGAAAUA
SSR-0107209	RNA1{p.m(A)[sp].m(A)p.m(C)p.m(A)p.m(G)p.m(G)p.[fl2r](A)p.m(G)p.[fl2r](U)p.[fl2r](C)p.[fl2r](A)p.m(G)p.m(G)p.m(A)p.m(A)p.m(A)p.m(A)p.m(U)p.m(G)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AACAGGAGUCAGGAAAUGAA
SSR-0107210	RNA1{p.m(A)[sp].m(G)p.m(G)p.m(A)p.m(G)p.m(U)p.[fl2r](C)p.m(A)p.[fl2r](G)p.[fl2r](G)p.[fl2r](A)p.m(A)p.m(A)p.m(A)p.m(U)p.m(G)p.m(A)p.m(G)p.m(G)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGGAGUCAGGAAAUGAGGCA
SSR-0107211	RNA1{p.m(G)[sp].m(A)p.m(G)p.m(U)p.m(C)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](A)p.[fl2r](A)p.[fl2r](A)p.m(A)p.m(U)p.m(G)p.m(A)p.m(G)p.m(G)p.m(C)p.m(A)p.m(C)[sp].m(A)}|CHEM1{[	GAGUCAGGAAAAUGAG

	nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GCAC A
SSR-0107212	RNA1{p.m(A)[sp].m(G)p.m(G)p.m(A)p.m(A)p.m(A)p.[fl2r](A)p.m(U)p.[fl2r](G)p.[fl2r](A)p.[fl2r](G)p.m(G)p.m(C)p.m(A)p.m(C)p.m(U)p.m(A)p.m(A)p.m(G)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGGA AAAU GAGG CACU AAGC A
SSR-0107213	RNA1{p.m(A)[sp].m(A)p.m(A)p.m(U)p.m(G)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](C)p.[fl2r](A)p.[fl2r](C)p.m(U)p.m(A)p.m(A)p.m(G)p.m(C)p.m(C)p.m(U)p.m(A)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AAAU GAGG CACU AAGC CUAA A
SSR-0107214	RNA1{p.m(A)[sp].m(A)p.m(U)p.m(G)p.m(A)p.m(G)p.[fl2r](G)p.m(C)p.[fl2r](A)p.[fl2r](C)p.[fl2r](U)p.m(A)p.m(A)p.m(G)p.m(C)p.m(C)p.m(U)p.m(A)p.m(A)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AAUG AGGC ACUA AGCC UAAG A
SSR-0107215	RNA1{p.m(A)[sp].m(U)p.m(G)p.m(A)p.m(G)p.m(G)p.[fl2r](C)p.m(A)p.[fl2r](C)p.[fl2r](U)p.[fl2r](A)p.m(A)p.m(G)p.m(C)p.m(C)p.m(U)p.m(A)p.m(A)p.m(G)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AUGA GGCA CUAA GCCU AAGA A
SSR-0107216	RNA1{p.m(G)[sp].m(A)p.m(G)p.m(G)p.m(C)p.m(A)p.[fl2r](C)p.m(U)p.[fl2r](A)p.[fl2r](A)p.[fl2r](G)p.m(C)p.m(C)p.m(U)p.m(A)p.m(A)p.m(G)p.m(A)p.m(A)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GAGG CACU AAGC CUAA GAAG A
SSR-0107217	RNA1{p.m(A)[sp].m(G)p.m(G)p.m(C)p.m(A)p.m(C)p.[fl2r](U)p.m(A)p.[fl2r](A)p.[fl2r](G)p.[fl2r](C)p.m(C)p.m(U)p.m(A)p.m(A)p.m(G)p.m(A)p.m(A)p.m(G)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGGC ACUA AGCC UAAG AAGU A
SSR-0107218	RNA1{p.m(G)[sp].m(C)p.m(A)p.m(C)p.m(U)p.m(A)p.[fl2r](A)p.m(G)p.[fl2r](C)p.[fl2r](C)p.[fl2r](U)p.m(A)p.m(A)p.m(G)p.m(A)p.m(A)p.m(G)p.m(U)p.m(U)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GCAC UAAG CCUA AGAA GUUC A
SSR-0107219	RNA1{p.m(C)[sp].m(C)p.m(U)p.m(A)p.m(A)p.m(G)p.[fl2r](A)p.m(A)p.[fl2r](G)p.[fl2r](U)p.[fl2r](U)p.m(C)p.m(C)p.m(C)p.m(U)p.m(G)p.m(G)p.m(U)p.m(U)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CCUA AGAA GUUC CCUG GUUU A

SSR-0107220	RNA1{p.m(A)[sp].m(A)p.m(G)p.m(A)p.m(A)p.m(G)p.[fl2r](U)p.m(U)p.[fl2r](C)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(G)p.m(G)p.m(U)p.m(U)p.m(U)p.m(U)p.m(U)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AAGA AGUU CCCU GGUU UUUC A
SSR-0107221	RNA1{p.m(C)[sp].m(C)p.m(C)p.m(A)p.m(C)p.m(U)p.[fl2r](G)p.m(G)p.[fl2r](G)p.[fl2r](A)p.[fl2r](G)p.m(A)p.m(C)p.m(A)p.m(A)p.m(G)p.m(C)p.m(A)p.m(U)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CCCAC UGGG AGAC AAGC AUUA
SSR-0107222	RNA1{p.m(C)[sp].m(C)p.m(A)p.m(C)p.m(U)p.m(G)p.[fl2r](G)p.m(G)p.[fl2r](A)p.[fl2r](G)p.[fl2r](A)p.m(C)p.m(A)p.m(A)p.m(G)p.m(C)p.m(A)p.m(U)p.m(U)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CCAC UGGG AGAC AAGC AUUU A
SSR-0107223	RNA1{p.m(C)[sp].m(A)p.m(C)p.m(U)p.m(G)p.m(G)p.[fl2r](G)p.m(A)p.[fl2r](G)p.[fl2r](A)p.[fl2r](C)p.m(A)p.m(A)p.m(G)p.m(C)p.m(A)p.m(U)p.m(U)p.m(U)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CACU GGGA GACA AGCA UUUA A
SSR-0107224	RNA1{p.m(U)[sp].m(G)p.m(G)p.m(G)p.m(A)p.m(G)p.[fl2r](A)p.m(C)p.[fl2r](A)p.[fl2r](A)p.[fl2r](G)p.m(C)p.m(A)p.m(U)p.m(U)p.m(U)p.m(A)p.m(U)p.m(A)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGGG AGAC AAGC AUUU AUAC A
SSR-0107225	RNA1{p.m(G)[sp].m(G)p.m(G)p.m(A)p.m(G)p.m(A)p.[fl2r](C)p.m(A)p.[fl2r](A)p.[fl2r](G)p.[fl2r](C)p.m(A)p.m(U)p.m(U)p.m(U)p.m(A)p.m(U)p.m(A)p.m(C)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGGA GACA AGCA UUUA UACU A
SSR-0107226	RNA1{p.m(G)[sp].m(G)p.m(A)p.m(G)p.m(A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.[fl2r](C)p.[fl2r](A)p.m(U)p.m(U)p.m(U)p.m(A)p.m(U)p.m(A)p.m(C)p.m(U)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGAG ACAA GCAU UUAU ACUU A
SSR-0107227	RNA1{p.m(A)[sp].m(C)p.m(U)p.m(U)p.m(U)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](A)p.[fl2r](A)p.[fl2r](U)p.m(A)p.m(A)p.m(A)p.m(A)p.m(A)p.m(G)p.m(G)p.m(A)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	ACUU UCUU AAUA AAAA GGAG A
SSR-0107228	RNA1{p.m(A)[sp].m(A)p.m(G)p.m(G)p.m(A)p.m(G)p.[fl2r](A)p.m(A)p.[fl2r](A)p.[fl2r](G)p.[fl2r](A)p.m(A)p.m(A)p.m(A)p.m(U)p.m(C)p.m(A)p.m(A)p.m(C)p.m(A)[sp].m(A)}|CHEM1{[	AAGG AGAA AGAA

	nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AAUCAACAA
SSR-0107229	RNA1{p.m(G)[sp].m(G)p.m(A)p.m(G)p.m(A)p.m(A)p.[fl2r](A)p.m(G)p.[fl2r](A)p.[fl2r](A)p.[fl2r](A)p.m(A)p.m(U)p.m(C)p.m(A)p.m(A)p.m(C)p.m(A)p.m(A)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGAGAAAGAAAAUCAACAAAA
SSR-0107230	RNA1{p.m(G)[sp].m(A)p.m(A)p.m(A)p.m(G)p.m(A)p.[fl2r](A)p.m(A)p.[fl2r](A)p.[fl2r](U)p.[fl2r](C)p.m(A)p.m(A)p.m(C)p.m(A)p.m(A)p.m(A)p.m(U)p.m(G)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GAAAGAAAAUCAACAAAUGUA
SSR-0107231	RNA1{p.m(A)[sp].m(A)p.m(A)p.m(G)p.m(A)p.m(A)p.[fl2r](A)p.m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](A)p.m(A)p.m(C)p.m(A)p.m(A)p.m(A)p.m(U)p.m(G)p.m(U)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AAAGAAAAUCAACAAUGUGA
SSR-0107232	RNA1{p.m(A)[sp].m(G)p.m(A)p.m(A)p.m(A)p.m(A)p.[fl2r](U)p.m(C)p.[fl2r](A)p.[fl2r](A)p.[fl2r](C)p.m(A)p.m(A)p.m(A)p.m(U)p.m(G)p.m(U)p.m(G)p.m(A)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGAAAAUCAACAAUGUGAGA
SSR-0107233	RNA1{p.m(A)[sp].m(A)p.m(C)p.m(A)p.m(A)p.m(A)p.[fl2r](U)p.m(G)p.[fl2r](U)p.[fl2r](G)p.[fl2r](A)p.m(G)p.m(U)p.m(C)p.m(A)p.m(U)p.m(A)p.m(A)p.m(A)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AACAAAUGUGAGUCAUAAAGA
SSR-0107234	RNA1{p.m(A)[sp].m(C)p.m(A)p.m(A)p.m(A)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.[fl2r](A)p.[fl2r](G)p.m(U)p.m(C)p.m(A)p.m(U)p.m(A)p.m(A)p.m(A)p.m(G)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	ACAAAUGUGAGUCAUAAGAA
SSR-0107235	RNA1{p.m(U)[sp].m(G)p.m(U)p.m(G)p.m(A)p.m(G)p.[fl2r](U)p.m(C)p.[fl2r](A)p.[fl2r](U)p.[fl2r](A)p.m(A)p.m(A)p.m(G)p.m(A)p.m(A)p.m(G)p.m(G)p.m(G)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGUGAGUCAUAAAGAAGGGUA
SSR-0107236	RNA1{p.m(U)[sp].m(G)p.m(A)p.m(G)p.m(U)p.m(C)p.[fl2r](A)p.m(U)p.[fl2r](A)p.[fl2r](A)p.[fl2r](A)p.m(G)p.m(A)p.m(A)p.m(G)p.m(G)p.m(G)p.m(U)p.m(U)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGAGUCAUAAAGAAGG

		GUUA A
SSR-0107237	RNA1{p.m(G)[sp].m(A)p.m(G)p.m(U)p.m(C)p.m(A)p.[fl2r](U)p.m(A)p.[fl2r](A)p.[fl2r](A)p.[fl2r](G)p.m(A)p.m(A)p.m(G)p.m(G)p.m(G)p.m(U)p.m(U)p.m(A)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GAGU CAUA AAGA AGGG UUAG A
SSR-0107238	RNA1{p.m(A)[sp].m(G)p.m(U)p.m(C)p.m(A)p.m(U)p.[fl2r](A)p.m(A)p.[fl2r](A)p.[fl2r](G)p.[fl2r](A)p.m(A)p.m(G)p.m(G)p.m(G)p.m(U)p.m(U)p.m(A)p.m(G)p.m(G)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AGUC AUAA AGAA GGGU UAGG A
SSR-0107239	RNA1{p.m(U)[sp].m(C)p.m(A)p.m(U)p.m(A)p.m(A)p.[fl2r](A)p.m(G)p.[fl2r](A)p.[fl2r](A)p.[fl2r](G)p.m(G)p.m(G)p.m(U)p.m(U)p.m(A)p.m(G)p.m(G)p.m(G)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UCAU AAAG AAGG GUUA GGGU A
SSR-0107240	RNA1{p.m(A)[sp].m(U)p.m(A)p.m(A)p.m(A)p.m(G)p.[fl2r](A)p.m(A)p.[fl2r](G)p.[fl2r](G)p.[fl2r](G)p.m(U)p.m(U)p.m(A)p.m(G)p.m(G)p.m(G)p.m(U)p.m(G)p.m(A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AUAA AGAA GGGU UAGG GUGA A
SSR-0107241	RNA1{p.m(U)[sp].m(A)p.m(A)p.m(A)p.m(G)p.m(A)p.[fl2r](A)p.m(G)p.[fl2r](G)p.[fl2r](G)p.[fl2r](U)p.m(U)p.m(A)p.m(G)p.m(G)p.m(G)p.m(U)p.m(G)p.m(A)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UAAA GAAG GGUU AGGG UGAU A
SSR-0107242	RNA1{p.m(C)[sp].m(A)p.m(A)p.m(C)p.m(A)p.m(G)p.[fl2r](U)p.m(U)p.[fl2r](C)p.[fl2r](U)p.[fl2r](U)p.m(C)p.m(A)p.m(A)p.m(G)p.m(U)p.m(G)p.m(U)p.m(A)p.m(C)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CAAC AGUU CUUC AAGU GUAC A
SSR-0107999	RNA1{p.m(U)[sp].m(C)p.m(C)p.m(U)p.m(U)p.m(C)p.[fl2r](C)p.m(A)p.[fl2r](U)p.[fl2r](U)p.[fl2r](C)p.m(U)p.m(G)p.m(C)p.m(C)p.m(G)p.m(U)p.m(C)p.m(U)p.m(U)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UCCU UCCA UUCU GCCG UCUU A
SSR-0108001	RNA1{p.m(U)[Ssp].m(C)p.m(C)p.m(U)p.m(U)p.m(C)p.[fl2r](C)p.m(A)p.[fl2r](U)p.[fl2r](U)p.[fl2r](C)p.m(U)p.m(G)p.m(C)p.m(C)p.m(G)p.m(U)p.m(C)p.m(U)p.m(U)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UCCU UCCA UUCU GCCG UCUU A

SSR-0108045	RNA1{p.m(A)[Ssp].m(C)p.m(C)p.m(A)p.m(G)p.m(U)p.[fl2r](C)p.m(G)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(C)p.m(A)p.m(G)p.m(A)p.m(A)p.m(U)p.m(A)p.m(A)p.m(C)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	ACCAGUCGUCCCAGAAUAACA
SSR-0108046	RNA1{p.m(U)[Ssp].m(C)p.m(G)p.m(U)p.m(C)p.m(C)p.[fl2r](C)p.m(A)p.[fl2r](G)p.[fl2r](A)p.[fl2r](A)p.m(U)p.m(A)p.m(A)p.m(C)p.m(U)p.m(C)p.m(A)p.m(U)p.m(C)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UCGUCCCAGAAUAACUCAUCA
SSR-0108047	RNA1{p.m(G)[Ssp].m(G)p.m(A)p.m(G)p.m(G)p.m(U)p.[fl2r](C)p.m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](A)p.m(G)p.m(C)p.m(U)p.m(U)p.m(U)p.m(G)p.m(C)p.m(U)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGAGGUCAUCAGCUUUGCUAA
SSR-0108048	RNA1{p.m(C)[Ssp].m(A)p.m(U)p.m(C)p.m(A)p.m(G)p.[fl2r](C)p.m(U)p.[fl2r](U)p.[fl2r](U)p.[fl2r](G)p.m(C)p.m(U)p.m(A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(C)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CAUCAGCUUUGCUACUGUCAA
SSR-0108049	RNA1{p.m(G)[Ssp].m(A)p.m(G)p.m(A)p.m(A)p.m(G)p.[fl2r](U)p.m(C)p.[fl2r](U)p.[fl2r](G)p.[fl2r](G)p.m(U)p.m(G)p.m(U)p.m(C)p.m(C)p.m(U)p.m(G)p.m(A)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GAGAAGUCUGGUGUCCUGAAA
SSR-0108050	RNA1{p.m(G)[Ssp].m(C)p.m(A)p.m(G)p.m(G)p.m(C)p.[fl2r](G)p.m(A)p.[fl2r](G)p.[fl2r](A)p.[fl2r](C)p.m(C)p.m(A)p.m(U)p.m(U)p.m(A)p.m(C)p.m(G)p.m(U)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GCAGGCGAGACCAUUACGUAA
SSR-0108051	RNA1{p.m(U)[Ssp].m(C)p.m(U)p.m(U)p.m(U)p.m(C)p.[fl2r](C)p.m(A)p.[fl2r](U)p.[fl2r](U)p.[fl2r](C)p.m(U)p.m(G)p.m(C)p.m(C)p.m(G)p.m(U)p.m(C)p.m(U)p.m(U)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UCUUUCCAUUCUGCCGUCUUA
SSR-0108052	RNA1{p.m(C)[Ssp].m(U)p.m(G)p.m(G)p.m(A)p.m(U)p.[fl2r](C)p.m(A)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(U)p.m(G)p.m(G)p.m(C)p.m(A)p.m(A)p.m(U)p.m(G)p.m(U)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUGGAUCAUAAUGGCAAUGUA
SSR-0108053	RNA1{p.m(C)[Ssp].m(U)p.m(U)p.m(U)p.m(G)p.m(G)p.[fl2r](A)p.m(G)p.[fl2r](U)p.[fl2r](G)p.[fl2r](A)p.m(A)p.m(G)p.m(A)	CUUUGGAG

	p.m(G)p.m(A)p.m(C)p.m(C)p.m(A)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGAAGAGACCAAA
SSR-0108054	RNA1{p.m(C)[Ssp].m(U)p.m(G)p.m(U)p.m(G)p.m(A)p.[fl2r](C)p.m(U)p.[fl2r](G)p.[fl2r](G)p.[fl2r](A)p.m(G)p.m(G)p.m(C)p.m(A)p.m(U)p.m(C)p.m(A)p.m(G)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUGUGACUGGAGGCAUCAGAA
SSR-0108055	RNA1{p.m(A)[Ssp].m(C)p.m(U)p.m(G)p.m(G)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](C)p.[fl2r](A)p.[fl2r](U)p.m(C)p.m(A)p.m(G)p.m(A)p.m(U)p.m(U)p.m(C)p.m(C)p.m(U)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	ACUGGAGGCAUCAGAUUCCUA
SSR-0108056	RNA1{p.m(C)[Ssp].m(C)p.m(A)p.m(A)p.m(A)p.m(U)p.[fl2r](G)p.m(G)p.[fl2r](G)p.[fl2r](C)p.[fl2r](A)p.m(C)p.m(U)p.m(U)p.m(U)p.m(C)p.m(U)p.m(U)p.m(G)p.m(U)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CCAAAUGGGCACUUUCUUGUA
SSR-0108057	RNA1{p.m(C)[Ssp].m(A)p.m(A)p.m(A)p.m(U)p.m(G)p.[fl2r](G)p.m(G)p.[fl2r](C)p.[fl2r](A)p.[fl2r](C)p.m(U)p.m(U)p.m(U)p.m(C)p.m(U)p.m(U)p.m(G)p.m(U)p.m(C)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CAAAUGGGCACUUUCUGUCA
SSR-0108058	RNA1{p.m(A)[Ssp].m(A)p.m(U)p.m(G)p.m(G)p.m(G)p.[fl2r](C)p.m(A)p.[fl2r](C)p.[fl2r](U)p.[fl2r](U)p.m(U)p.m(C)p.m(U)p.m(U)p.m(G)p.m(U)p.m(C)p.m(U)p.m(G)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AAUGGGCACUUUCUUGUCUGA
SSR-0108059	RNA1{p.m(U)[Ssp].m(G)p.m(G)p.m(G)p.m(C)p.m(A)p.[fl2r](C)p.m(U)p.[fl2r](U)p.[fl2r](U)p.[fl2r](C)p.m(U)p.m(U)p.m(G)p.m(U)p.m(C)p.m(U)p.m(G)p.m(A)p.m(G)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGGGCACUUUCUGUCUGAGA
SSR-0108060	RNA1{p.m(U)[Ssp].m(U)p.m(A)p.m(U)p.m(U)p.m(C)p.[fl2r](C)p.m(A)p.[fl2r](G)p.[fl2r](G)p.[fl2r](U)p.m(U)p.m(G)p.m(G)p.m(C)p.m(U)p.m(G)p.m(A)p.m(U)p.m(G)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UUAUUCCAGGUUGGCUGAUGA
SSR-0108061	RNA1{p.m(G)[Ssp].m(A)p.m(G)p.m(A)p.m(U)p.m(G)p.[fl2r](G)p.m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(A)p.m(G)p.m(C)p.m(G)p.m(U)p.m(U)p.m(U)p.m(C)p.m(U)[Ssp].m(A)}|CHEM	GAGAUGGGUAAAGCGU

	1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UUCUA
SSR-0108062	RNA1{p.m(U)[Ssp].m(G)p.m(G)p.m(G)p.m(U)p.m(A)p.[fl2r](A)p.m(A)p.[fl2r](G)p.[fl2r](C)p.[fl2r](G)p.m(U)p.m(U)p.m(U)p.m(C)p.m(U)p.m(U)p.m(C)p.m(U)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGGGUAAAGCGUUUCUUCUAA
SSR-0108063	RNA1{p.m(G)[Ssp].m(G)p.m(U)p.m(A)p.m(A)p.m(A)p.[fl2r](G)p.m(C)p.[fl2r](G)p.[fl2r](U)p.[fl2r](U)p.m(U)p.m(C)p.m(U)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGUAAAGCGUUUCUUCUAAAA
SSR-0108064	RNA1{p.m(C)[Ssp].m(A)p.m(A)p.m(G)p.m(A)p.m(U)p.[fl2r](G)p.m(A)p.[fl2r](G)p.[fl2r](A)p.[fl2r](A)p.m(A)p.m(G)p.m(U)p.m(C)p.m(C)p.m(U)p.m(C)p.m(A)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CAAGAUGAGAAAGUCCUCAAA
SSR-0108065	RNA1{p.m(G)[Ssp].m(A)p.m(A)p.m(A)p.m(C)p.m(A)p.[fl2r](G)p.m(G)p.[fl2r](A)p.[fl2r](G)p.[fl2r](U)p.m(C)p.m(A)p.m(G)p.m(G)p.m(A)p.m(A)p.m(A)p.m(A)p.m(U)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GAAACAGGAGUCAGGAAAAUA
SSR-0108066	RNA1{p.m(C)[Ssp].m(C)p.m(A)p.m(C)p.m(U)p.m(G)p.[fl2r](G)p.m(G)p.[fl2r](A)p.[fl2r](G)p.[fl2r](A)p.m(C)p.m(A)p.m(A)p.m(G)p.m(C)p.m(A)p.m(U)p.m(U)p.m(U)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CCACUGGGAGACAAGCAUUUA
SSR-0108067	RNA1{p.m(C)[Ssp].m(A)p.m(C)p.m(U)p.m(G)p.m(G)p.[fl2r](G)p.m(A)p.[fl2r](G)p.[fl2r](A)p.[fl2r](C)p.m(A)p.m(A)p.m(G)p.m(C)p.m(A)p.m(U)p.m(U)p.m(U)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CACUGGGAGACAAGCAUUUAA
SSR-0108068	RNA1{p.m(U)[Ssp].m(G)p.m(G)p.m(G)p.m(A)p.m(G)p.[fl2r](A)p.m(C)p.[fl2r](A)p.[fl2r](A)p.[fl2r](G)p.m(C)p.m(A)p.m(U)p.m(U)p.m(U)p.m(A)p.m(U)p.m(A)p.m(C)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGGGAGACAAGCAUUUAUACA
SSR-0108069	RNA1{p.m(G)[Ssp].m(G)p.m(A)p.m(G)p.m(A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.[fl2r](C)p.[fl2r](A)p.m(U)p.m(U)p.m(U)p.m(A)p.m(U)p.m(A)p.m(C)p.m(U)p.m(U)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGAGACAAGCAUUUAUACUUA

SSR-0108070	RNA1{p.m(G)[Ssp].m(G)p.m(A)p.m(G)p.m(A)p.m(A)p.[fl2r](A)p.m(G)p.[fl2r](A)p.[fl2r](A)p.[fl2r](A)p.m(A)p.m(U)p.m(C)p.m(A)p.m(A)p.m(C)p.m(A)p.m(A)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GGAGAAAGAAAAUCAACAAAA
SSR-0108071	RNA1{p.m(G)[Ssp].m(A)p.m(A)p.m(A)p.m(G)p.m(A)p.[fl2r](A)p.m(A)p.[fl2r](A)p.[fl2r](U)p.[fl2r](C)p.m(A)p.m(A)p.m(C)p.m(A)p.m(A)p.m(A)p.m(U)p.m(G)p.m(U)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	GAAAGAAAAUCAACAAAUGUA
SSR-0108072	RNA1{p.m(A)[Ssp].m(C)p.m(A)p.m(A)p.m(A)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.[fl2r](A)p.[fl2r](G)p.m(U)p.m(C)p.m(A)p.m(U)p.m(A)p.m(A)p.m(A)p.m(G)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	ACAAAUGUGAGUCAUAAAGAA
SSR-0108073	RNA1{p.m(C)[Ssp].m(A)p.m(A)p.m(C)p.m(A)p.m(G)p.[fl2r](U)p.m(U)p.[fl2r](C)p.[fl2r](U)p.[fl2r](U)p.m(C)p.m(A)p.m(A)p.m(G)p.m(U)p.m(G)p.m(U)p.m(A)p.m(C)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CAACAGUUCUUCAAGUGUACA
SSR-0108074	RNA1{p.m(C)[Ssp].m(C)p.m(A)p.m(G)p.m(A)p.m(A)p.[fl2r](U)p.m(A)p.[fl2r](A)p.[fl2r](C)p.[fl2r](U)p.m(C)p.m(A)p.m(U)p.m(C)p.m(C)p.m(U)p.m(C)p.m(C)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CCAGAAUAACUCAUCCUCCAA
SSR-0108075	RNA1{p.m(C)[Ssp].m(U)p.m(G)p.m(U)p.m(C)p.m(A)p.[fl2r](C)p.m(A)p.[fl2r](G)p.[fl2r](A)p.[fl2r](C)p.m(U)p.m(C)p.m(C)p.m(A)p.m(C)p.m(U)p.m(U)p.m(C)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUGUCACAGACUCCACUUCAA
SSR-0108076	RNA1{p.m(U)[Ssp].m(G)p.m(U)p.m(C)p.m(A)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](A)p.[fl2r](C)p.[fl2r](U)p.m(C)p.m(C)p.m(A)p.m(C)p.m(U)p.m(U)p.m(C)p.m(A)p.m(G)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UGUCACAGACUCCACUUCAGA
SSR-0108077	RNA1{p.m(C)[Ssp].m(U)p.m(U)p.m(U)p.m(G)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](G)p.[fl2r](A)p.[fl2r](G)p.m(G)p.m(A)p.m(U)p.m(C)p.m(U)p.m(U)p.m(C)p.m(C)p.m(G)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CUUUGCUUGAGGAUCUUCCGA
SSR-0108078	RNA1{p.m(G)[Ssp].m(A)p.m(C)p.m(A)p.m(A)p.m(G)p.[fl2r](C)p.m(A)p.[fl2r](U)p.[fl2r](U)p.[fl2r](U)p.m(A)p.m(U)p.m(A)	GACAAGCA

	p.m(C)p.m(U)p.m(U)p.m(U)p.m(C)p.m(U)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UUUA UACU UUCU A
SSR-0108079	RNA1{p.m(A)[Ssp].m(C)p.m(A)p.m(A)p.m(G)p.m(C)p.[fl2r](A)p.m(U)p.[fl2r](U)p.[fl2r](U)p.[fl2r](A)p.m(U)p.m(A)p.m(C)p.m(U)p.m(U)p.m(U)p.m(C)p.m(U)p.m(U)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	ACAA GCAU UUAU ACUU UCUU A

Notes:

Such notation language is described in Zhang, T. et. al. *Chem. Inf. Model.* 2012, 52, 10, 2796–2806 and Milton, J. et al. *J. Chem. Inf. Model.* 2017, 57, 6, 1233–1239. Description, Base Sequence and Stereochemistry/Linkage, due to their length, may be divided into multiple lines in Table 1. Unless otherwise specified, all oligonucleotides in Table 1 are single-stranded. As appreciated by those skilled in the art, nucleoside units are unmodified and contain unmodified nucleobases and 2'-deoxy sugars unless otherwise indicated (e.g., with r, m, etc.); linkages, unless otherwise indicated, are natural phosphate linkages; and acidic/basic groups may independently exist in their salt forms. If a sugar is not specified, the sugar is a natural DNA sugar; and if an internucleotidic linkage is not specified, the internucleotidic linkage is a natural phosphate linkage. Moieties and modifications:

m: 2'-OMe;

f or fl2r: 2'-F;

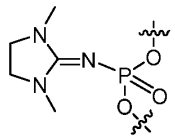
O, PO, or p: phosphodiester (phosphate). It can a linkage or be an end group (or a component thereof), e.g., a linkage between a linker and an oligonucleotide chain, an internucleotidic linkage (a natural phosphate linkage), etc. Phosphodiesters are typically indicated with "O" in the Stereochemistry/Linkage column and are typically not marked in the Description column (if it is an end group, e.g., a 5'-end group, it is indicated in the Description and typically not in Stereochemistry/Linkage); if no linkage is indicated in the Description column, it is typically a phosphodiester unless otherwise indicated. Note that a phosphate linkage between a linker (e.g., L001) and an oligonucleotide chain may not be marked in the Description column, but may be indicated with "O" in the Stereochemistry/Linkage column;

*, PS: Phosphorothioate. It can be an end group (if it is an end group, e.g., a 5'-end group, it is indicated in the Description and typically not in Stereochemistry/Linkage), or a linkage, e.g., a linkage between linker (e.g., L001) and an oligonucleotide chain, an internucleotidic linkage (a phosphorothioate internucleotidic linkage), etc.;

R, *R*p, or Rsp: Phosphorothioate in the *R*p configuration. Note that * R in Description indicates a single phosphorothioate linkage in the *R*p configuration;

S, *S*p or Ssp: Phosphorothioate in the *S*p configuration. Note that * S in Description indicates a single phosphorothioate linkage in the *S*p configuration;

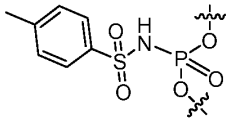
X: stereorandom phosphorothioate or phosphoryl guanidine;

n001:  ;

nX: stereorandom n001;

nR or n001R or [n001R]: n001 in Rp configuration;

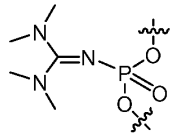
nS or n001S or [n001S]: n001 in Sp configuration;

n002:  ;

nX: stereorandom n002;

nR or n002R: n002 in Rp configuration;

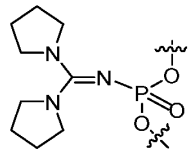
nS or n002S: n002 in Sp configuration;

n003:  ;

nX: stereorandom n003;

nR or n003R: n003 in Rp configuration;

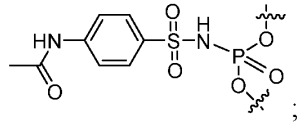
nS or n003S: n003 in Sp configuration;

n004:  ;

nX: stereorandom n004;

nR or n004R: n004 in Rp configuration;

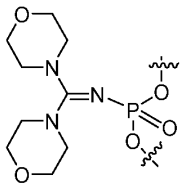
nS or n004S: n004 in Sp configuration;

n006:  ;

nX: stereorandom n006;

nR or n006R: n006 in Rp configuration;

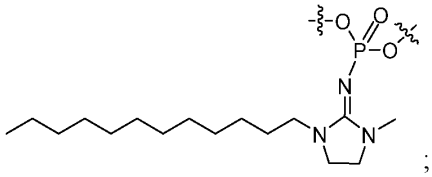
nS or n006S: n006 in Sp configuration;

n008:  ;

nX: stereorandom n008;

nR or n008R: n008 in Rp configuration;

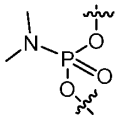
nS or n008S: n008 in Sp configuration;

n009:  ;

nX: stereorandom n009;

nR or n009R: n009 in Rp configuration;

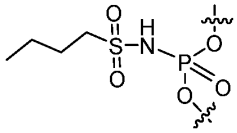
nS or n009S: n009 in Sp configuration;

n012:  ;

nX: stereorandom n012;

nR or n012R: n012 in Rp configuration;

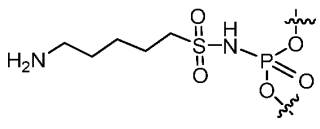
nS or n012S: n012 in Sp configuration;

n020:  ;

nX: stereorandom n020;

nR or n020R: n020 in Rp configuration;

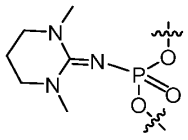
nS or n020S: n020 in Sp configuration;

n021:  ;

nX: stereorandom n021;

nR or n021R: n021 in Rp configuration;

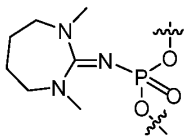
nS or n021S: n021 in Sp configuration;

n025:  ;

nX: stereorandom n025;

nR or n025R: n025 in Rp configuration;

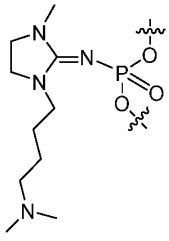
nS or n025S: n025 in Sp configuration;

n026:  ;

nX: stereorandom n026;

nR or n026R: n026 in Rp configuration;

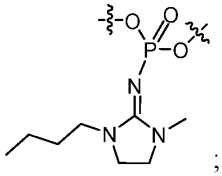
nS or n026S: n026 in Sp configuration;

n029:  ;

nX: stereorandom n029;

nR or n029R: n029 in Rp configuration;

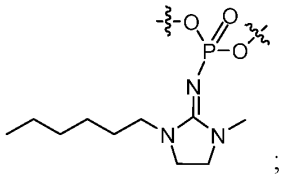
nS or n029S: n029 in Sp configuration;

n030:  ;

nX: stereorandom n030;

nR or n030R: n030 in Rp configuration;

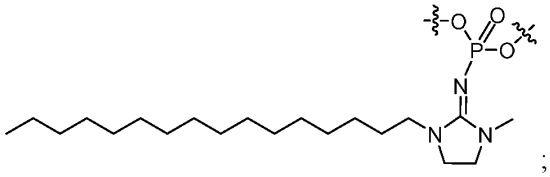
nS or n030S: n030 in Sp configuration;

n031:  ;

nX: stereorandom n031;

nR or n031R: n031 in Rp configuration;

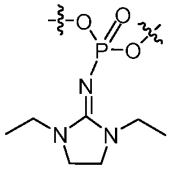
nS or n031S: n031 in Sp configuration;

n033:  ;

nX: stereorandom n033;

nR or n033R: n033in Rp configuration;

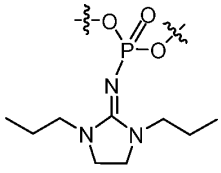
nS or n033S: n033 in Sp configuration;

n034:  ;

nX: stereorandom n034;

nR or n034R: n034in Rp configuration;

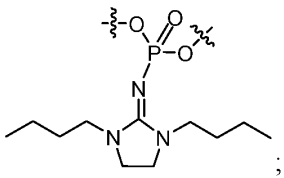
nS or n034S: n034 in Sp configuration;

n035:  ;

nX: stereorandom n035;

nR or n035R: n035in Rp configuration;

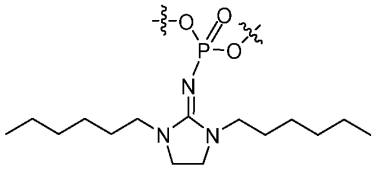
nS or n035S: n035 in Sp configuration;

n036:  ;

nX: stereorandom n036;

nR or n036R: n036in Rp configuration;

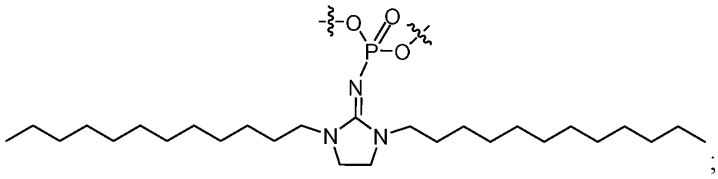
nS or n036S: n036 in Sp configuration;

n037:  ;

nX: stereorandom n037;

nR or n037R: n037in Rp configuration;

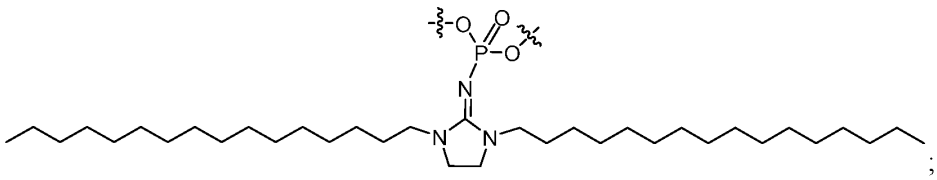
nS or n037S: n037 in Sp configuration;

n039:  ;

nX: stereorandom n039;

nR or n039R: n039 in Rp configuration;

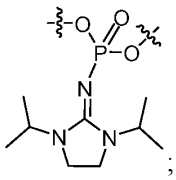
nS or n039S: n039 in Sp configuration;

n040:  ;

nX: stereorandom n040;

nR or n040R: n040in Rp configuration;

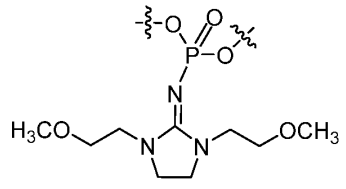
nS or n040S: n040 in Sp configuration;

n041:  ;

nX: stereorandom n041;

nR or n041R: n041in Rp configuration;

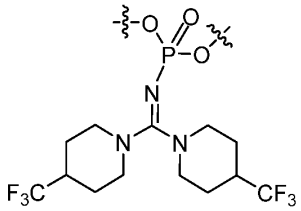
nS or n041S: n041 in Sp configuration;

n043: 

nX: stereorandom n043;

nR or n043R: n043 in Rp configuration;

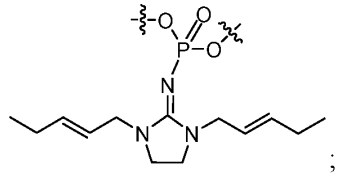
nS or n043S: n043 in Sp configuration;

n045: 

nX: stereorandom n045;

nR or n045R: n045 in Rp configuration;

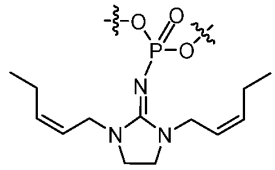
nS or n045S: n045 in Sp configuration;

n046:  ;

nX: stereorandom n046;

nR or n046R: n046in Rp configuration;

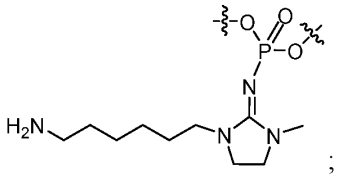
nS or n046S: n046 in Sp configuration;

n047:  ;

nX: stereorandom n047;

nR or n047R: n047in Rp configuration;

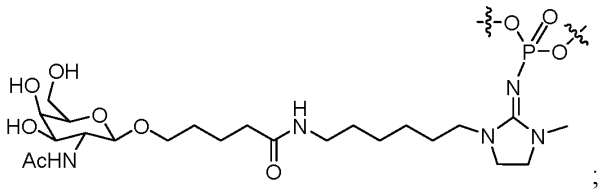
nS or n047S: n047 in Sp configuration;

n051:  ;

nX: stereorandom n051;

nR or n051R: n051in Rp configuration;

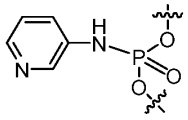
nS or n051S: n051 in Sp configuration;

n052:  ;

nX: stereorandom n052;

nR or n052R: n052in Rp configuration;

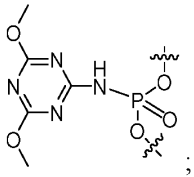
nS or n052S: n052 in Sp configuration;

n054:  ;

nX: stereorandom n054;

nR or n054R: n054 in Rp configuration;

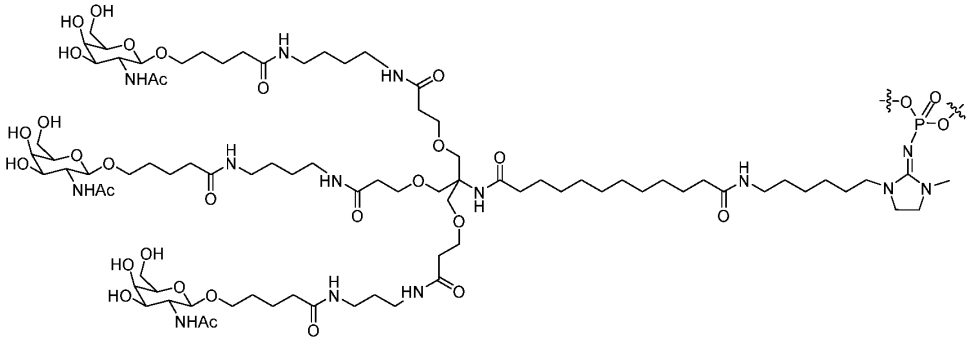
nS or n054S: n054 in Sp configuration;

n055:  ;

nX: stereorandom n055;

nR or n055R: n055 in Rp configuration;

nS or n055S: n055 in Sp configuration;

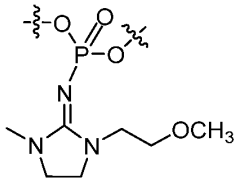


n057:

nX: stereorandom n057;

nR or n057R: n057 in Rp configuration;

nS or n057S: n057 in Sp configuration;

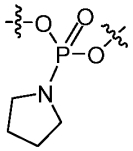


n058:

nX: stereorandom n058;

nR or n058R: n058 in Rp configuration;

nS or n058S: n058 in Sp configuration;

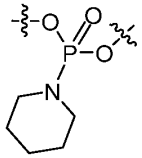


n060:

nX: stereorandom n060;

nR or n060R: n060 in Rp configuration;

nS or n060S: n060 in Sp configuration;

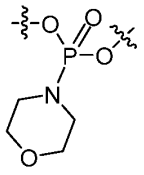


n061:

nX: stereorandom n061;

nR or n061R: n061 in Rp configuration;

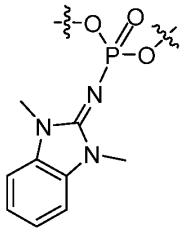
nS or n061S: n061 in Sp configuration;

n062: 

nX: stereorandom n062;

nR or n062R: n062 in Rp configuration;

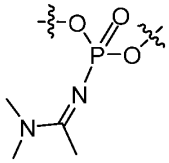
nS or n062S: n062 in Sp configuration;

n065: 

nX: stereorandom n065;

nR or n065R: n065 in Rp configuration;

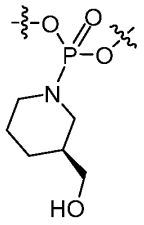
nS or n065S: n065 in Sp configuration;

n066: 

nX: stereorandom n066;

nR or n066R: n066 in Rp configuration;

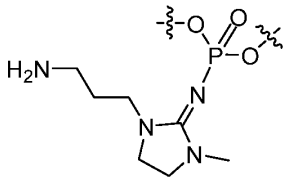
nS or n066S: n066 in Sp configuration;

n068: 

nX: stereorandom n068;

nR or n068R: n068 in Rp configuration;

nS or n068S: n068 in Sp configuration;

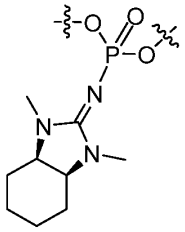


n069:

nX: stereorandom n069;

nR or n069R: n069 in Rp configuration;

nS or n069S: n069 in Sp configuration;

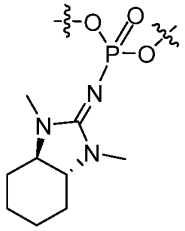


n070:

nX: stereorandom n070;

nR or n070R: n070 in Rp configuration;

nS or n070S: n070 in Sp configuration;

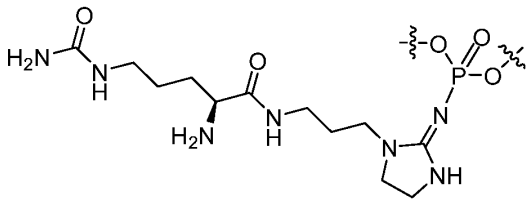


n071:

nX: stereorandom n071;

nR or n071R: n071 in Rp configuration;

nS or n071S: n071 in Sp configuration;

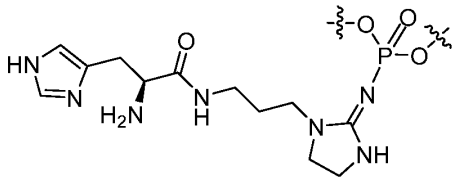


n072:

nX: stereorandom n072;

nR or n072R: n072 in Rp configuration;

nS or n072S: n072 in Sp configuration;

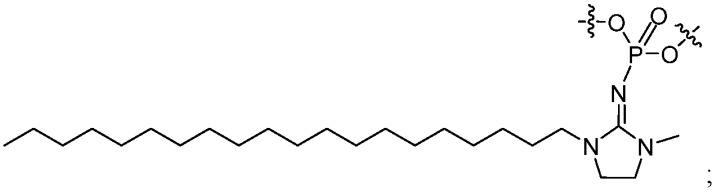


n073:

nX: stereorandom n073;

nR or n073R: n073 in Rp configuration;

nS or n073S: n073 in Sp configuration;

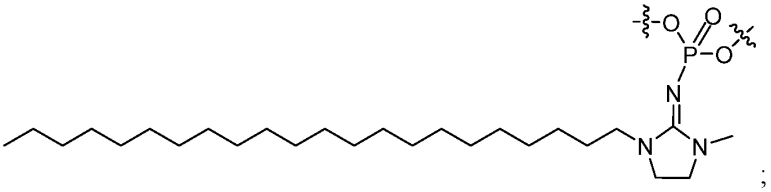


;

nX: stereorandom n076;

nR or n076R: n076in Rp configuration;

nS or n076S: n076 in Sp configuration;



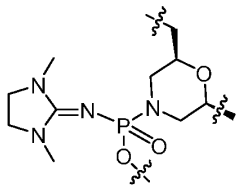
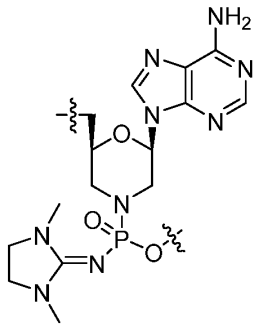
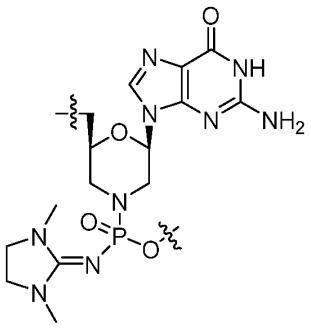
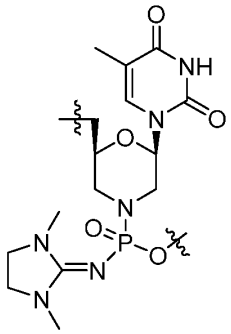
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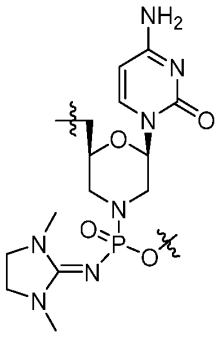
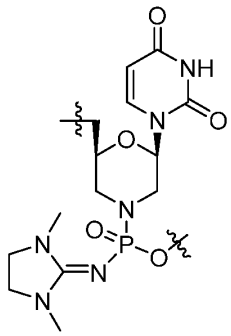
nX: stereorandom n077;

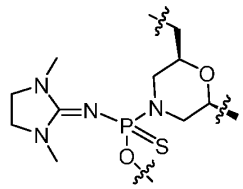
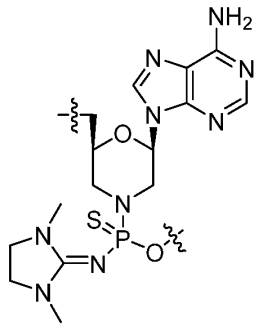
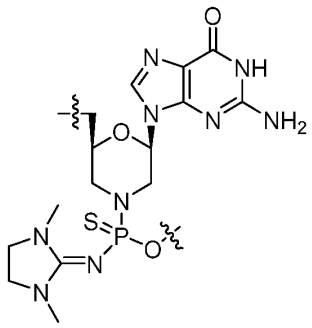
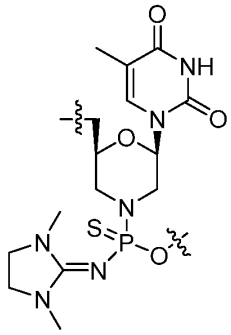
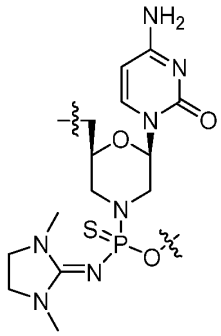
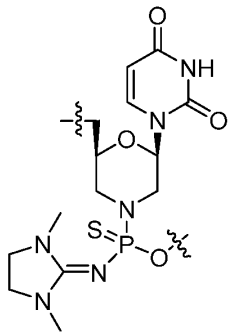
nR or n077R: n077in Rp configuration;

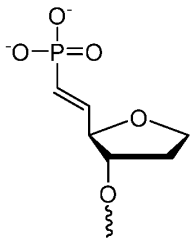
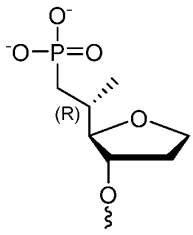
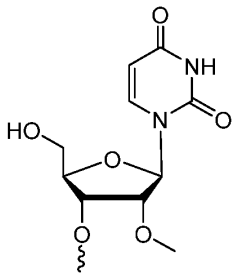
nS or n077S: n077 in Sp configuration;

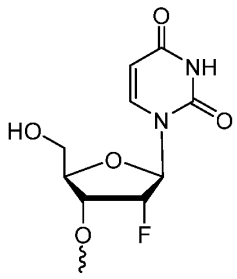
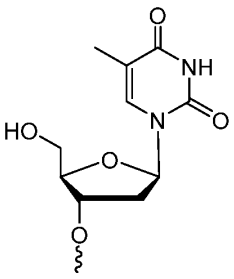
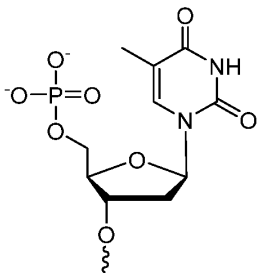
X: stereorandom phosphorothioate or phosphoryl guanidine;

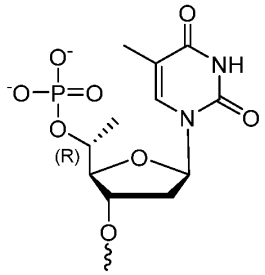
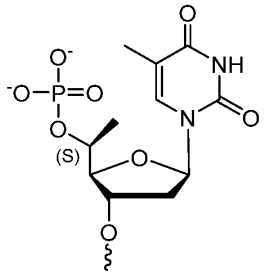
sm01n001:  (e.g., Asm01n001:  ; Gsm01n001:  ; Tsm01n001:  ;

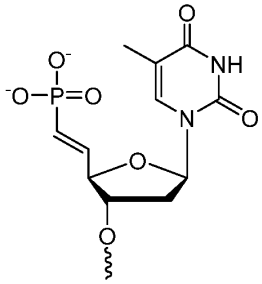
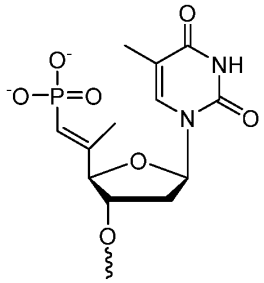
Csm01n001:  Usm01n001: );

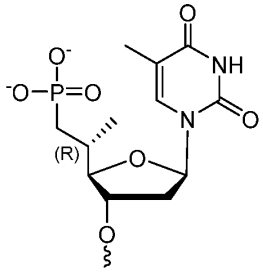
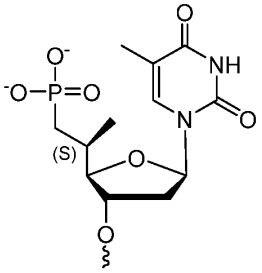
sm01*n001:  (e.g., Asm01*n001:  ; Gsm01*n001:  ; Tsm01*n001:  ; Csm01*n001:  Usm01*n001: );

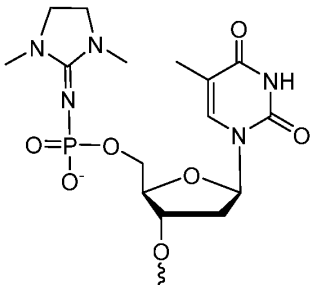
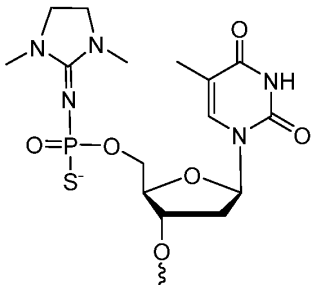
5 L026  ; L027  ; mU  ;

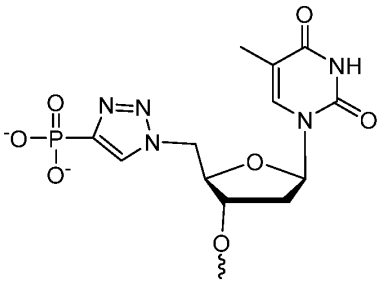
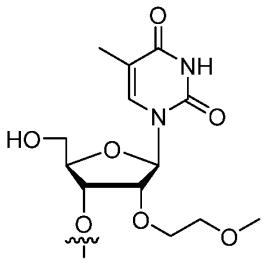
fU  ; dT  ; POdT or PO4-dT  ;

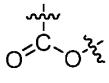
PO5MRdT  ; PO5MSdT  ;

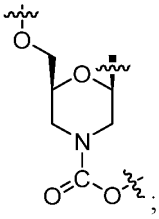
VPdT  ; 5mvpdT  ;

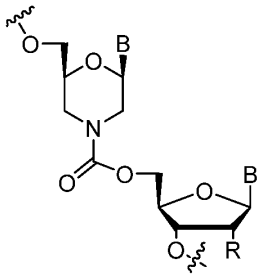
5 5mrpdT or p[Rm5d5m]T  ; 5mspdT  ;

PNdT  ; SPNdT  ;

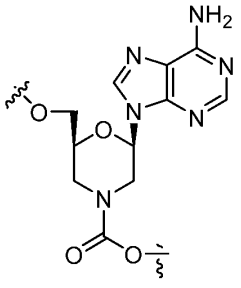
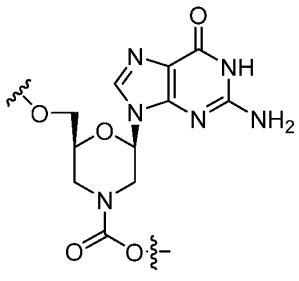
5ptzdT  ; Teo  ;

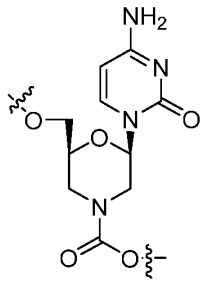
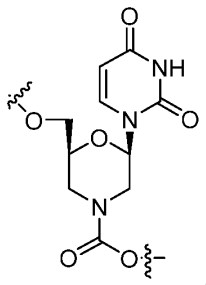
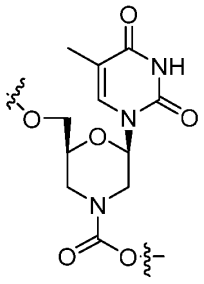
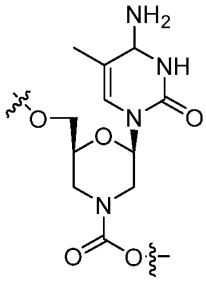
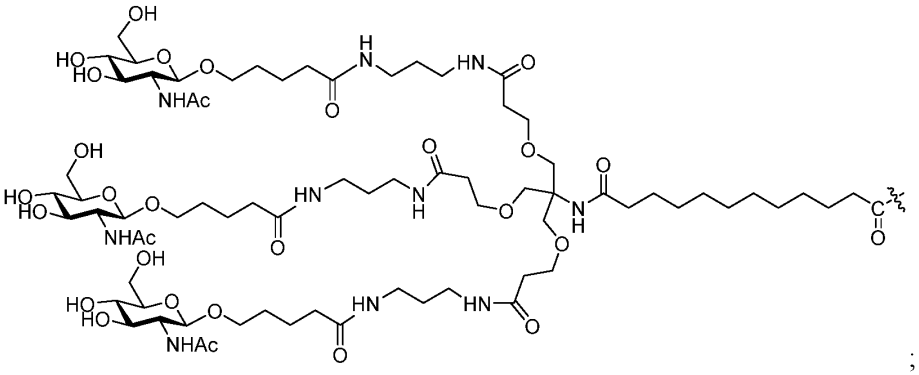
n013:  , wherein −C(O)− is bonded to nitrogen;

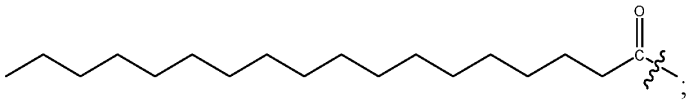
sm01n013:  ;

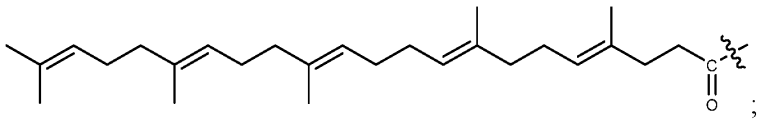


i.e. morpholine carbamate internucleotidic linkage (sm01n013)

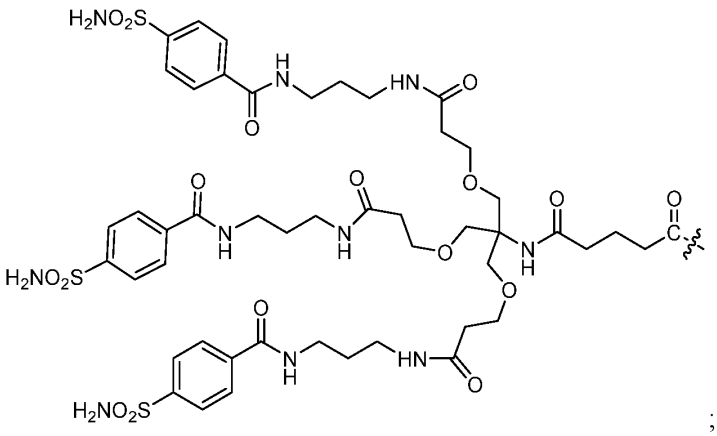
; Asm01n013  ; Gsm01n013:  ;

Csm01n013:  ; Usm01n013:  ; Tsm01n013:  ; m5Csm01n013:  ; Mod001:  ;

Mod015:  ;

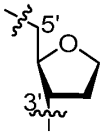
Mod020:  ;

Mod029:



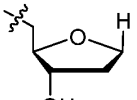
;

L001 : –NH–$(CH_2)_6$– linker (C6 linker, C6 amine linker or C6 amino linker), connected to Mod (e.g., Mod001) through –NH–, and, in the case of, for example, WV-38061, the 5'-end of the oligonucleotide chain through a phosphate linkage (O or PO). For example, in WV-38061, L001 is connected to Mod001 through –NH– (forming an amide group –C(O)–NH–), and is connected to the oligonucleotide chain through a phosphate linkage (O).



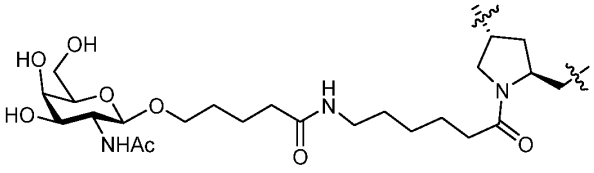
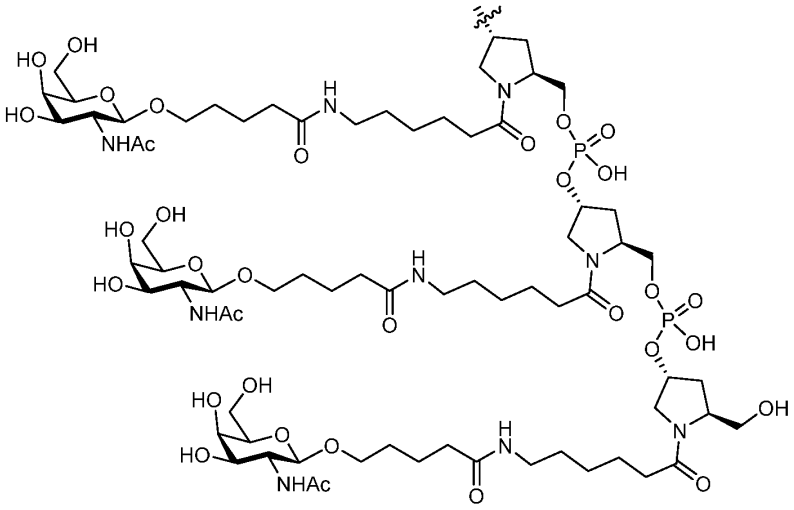
L010: . In some embodiments, when L010 is present in the middle of an oligonucleotide, it is bonded to internucleotidic linkages as other sugars (e.g., DNA sugars), e.g., its 5'-carbon is connected to another unit (e.g., 3' of a sugar) and its 3'-carbon is connected to another unit (e.g., a 5'-carbon of a carbon) independently, e.g., via a linkage (e.g., a phosphate linkage (O or PO) or a phosphorothioate linkage (can be either not chirally controlled or chirally controlled (*S*p or *R*p)));

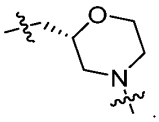
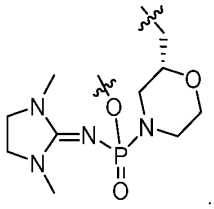
L012:–$CH_2CH_2OCH_2CH_2OCH_2CH_2$–. When L012 is present in the middle of an oligonucleotide, each of its two ends is independently bonded to an internucleotidic linkage (e.g., a phosphate linkage (O or PO) or a phosphorothioate linkage (can be either not chirally controlled or chirally controlled (*S*p or *R*p)));



L022: , wherein L022 is connected to the rest of a molecule through a phosphate unless indicated otherwise;

L023: HO–$(CH_2)_6$–, wherein CH_2 is connected to the rest of a molecule through a phosphate unless indicated otherwise. For example, in WV-42644 (wherein the **O** in OnRnRnRnRSSSSSSSSSSSSSSSSSSnRSSSSSnRSSnR indicates a phosphate linkage connecting L023 to the rest of the molecule);

L025:  , wherein the $-CH_2-$ connection site is utilized as a C5 connection site of a sugar (e.g., a DNA sugar) and is connected to another unit (e.g., 3' of a sugar), and the connection site on the ring is utilized as a C3 connection site and is connected to another unit (e.g., a 5'-carbon of a carbon), each of which is independently, e.g., via a linkage (e.g., a phosphate linkage (O or PO) or a phosphorothioate linkage (can be either not chirally controlled or chirally controlled (*S*p or *R*p))). When L025 is at a5'-end without any modifications, its $-CH_2-$ connection site is bonded to $-OH$. For example, L025L025L025− in various oligonucleotides has the structure of  (may exist as various salt forms) and is connected to 5'-carbon of an oligonucleotide chain via a linkage as indicated (e.g., a phosphate linkage (O or PO) or a phosphorothioate linkage (can be either not chirally controlled or chirally controlled (*S*p or *R*p)));

L016:  . wherein L016 is connected to the rest of a molecule through a phosphate unless indicated otherwise; L016 is utilized with n001 to form L016n001, which has the structure of  .

Double Stranded Oligonucleotide Lengths

As appreciated by those skilled in the art, ds oligonucleotides targeting INHBE can be of various lengths to provide desired properties and/or activities for various uses. Many technologies for assessing, selecting and/or optimizing oligonucleotide length are available in the art and can be utilized in accordance with the present disclosure. As demonstrated herein, in many embodiments, ds oligonucleotides targeting INHBE are of suitable lengths to hybridize with their targets and reduce levels of their targets and/or an encoded product thereof. In some embodiments, an oligonucleotide is long enough to recognize a target nucleic acid (e.g., a INHBE mRNA). In some embodiments, an oligonucleotide is sufficiently long to distinguish between a target nucleic acid and other nucleic acids (e.g., a nucleic acid having a base sequence which is not INHBE) to reduce off-target effects. In some embodiments, a ds oligonucleotide targeting INHBE is sufficiently short to reduce complexity of manufacture or production and to reduce cost of products.

In some embodiments, the base sequence of an oligonucleotide is about 10-500 nucleobases in length. In some embodiments, a base sequence is about 10-500 nucleobases in length. In some embodiments, a base sequence is about 10-50 nucleobases in length. In some embodiments, a base sequence is about 15-50 nucleobases in length. In some embodiments, a base sequence is from about 15 to about 30 nucleobases in length. In some embodiments, a base sequence is from about 10 to about 25 nucleobases in length. In some embodiments, a base sequence is from about 15 to about 22 nucleobases in length. In some embodiments, a base sequence is about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleobases in length. In some embodiments, a base sequence is about 18 nucleobases in length. In some embodiments, a base sequence is about 19 nucleobases in length. In some embodiments, a base sequence is about 20 nucleobases in length. In some embodiments, a base sequence is about 21 nucleobases in length. In some embodiments, a base sequence is about 22 nucleobases in length. In some embodiments, a base sequence is about 23 nucleobases in length. In some embodiments, a base sequence is about 24 nucleobases in length. In some embodiments, a base sequence is about 25 nucleobases in length. In some embodiments, each nucleobase is optionally substituted A, T, C, G, U, or an optionally substituted tautomer of A, T, C, G, or U.

Double Stranded Oligonucleotide Internucleotidic Linkages

In some embodiments, ds oligonucleotides targeting INHBE comprise base

modifications, sugar modifications, and/or internucleotidic linkage modifications. Various internucleotidic linkages can be utilized in accordance with the present disclosure to link units comprising nucleobases, e.g., nucleosides. In some embodiments, ds oligonucleotides targeting INHBE comprise both one or more modified internucleotidic linkages and one or more natural phosphate linkages. As widely known by those skilled in the art, natural phosphate linkages are widely found in natural DNA and RNA molecules; they have the structure of −OP(O)(OH)O−, connect sugars in the nucleosides in DNA and RNA, and may be in various salt forms, for example, at physiological pH (about 7.4), natural phosphate linkages are predominantly exist in salt forms with the anion being $-OP(O)(O^-)O-$. A modified internucleotidic linkage, or a non-natural phosphate linkage, is an internucleotidic linkage that is not natural phosphate linkage or a salt form thereof. Modified internucleotidic linkages, depending on their structures, may also be in their salt forms. For example, as appreciated by those skilled in the art, phosphorothioate internucleotidic linkages which have the structure of −OP(O)(SH)O− may be in various salt forms, e.g., at physiological pH (about 7.4) with the anion being $-OP(O)(S^-)O-$.

In some embodiments, an oligonucleotide comprises an internucleotidic linkage which is a modified internucleotidic linkage, e.g., phosphorothioate, phosphorodithioate, methylphosphonate, phosphoroamidate, thiophosphate, 3'-thiophosphate, or 5'-thiophosphate.

In some embodiments, a modified internucleotidic linkage is a chiral internucleotidic linkage which comprises a chiral linkage phosphorus. In some embodiments, a chiral internucleotidic linkage is a phosphorothioate linkage. In some embodiments, a chiral internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, a chiral internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, a chiral internucleotidic linkage is chirally controlled with respect to its chiral linkage phosphorus. In some embodiments, a chiral internucleotidic linkage is stereochemically pure with respect to its chiral linkage phosphorus. In some embodiments, a chiral internucleotidic linkage is not chirally controlled. In some embodiments, a pattern of backbone chiral centers comprises or consists of positions and linkage phosphorus configurations of chirally controlled internucleotidic linkages (*R*p or *S*p) and positions of achiral internucleotidic linkages (e.g., natural phosphate linkages).

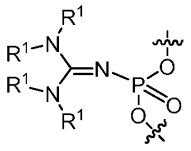
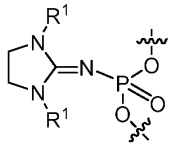
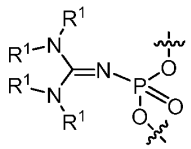
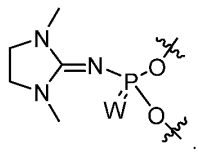
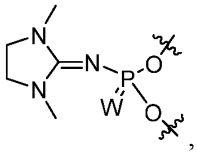
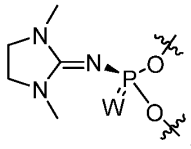
In certain embodiments, an internucleotidic linkage comprises a P-modification, wherein a P-modification is a modification at a linkage phosphorus. In certain embodiments, a modified internucleotidic linkage is a moiety which does not comprise a phosphorus but

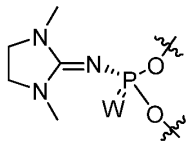
serves to link two sugars or two moieties that each independently comprises a nucleobase, e.g., as in peptide nucleic acid (PNA).

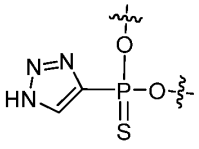
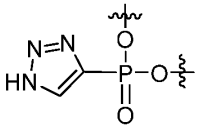
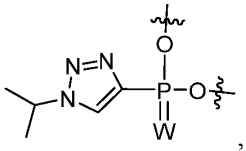
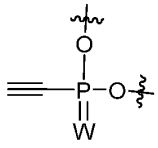
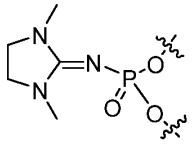
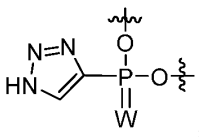
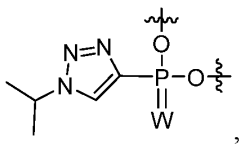
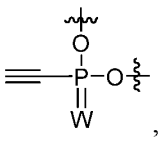
In certain embodiments, a ds oligonucleotide comprises a modified internucleotidic linkage, e.g., those having the structure of Formula **I**, **I-a**, **I-b**, or **I-c** and described herein and/or in: WO 2018/022473, WO 2018/098264, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, and/or WO 2019/032612, the internucleotidic linkages (e.g., those of Formula **I**, **I-a**, **I-b**, **I-c**, etc.) of each of which are independently incorporated herein by reference. In certain embodiments, a modified internucleotidic linkage is a chiral internucleotidic linkage. In certain embodiments, a modified internucleotidic linkage is a phosphorothioate internucleotidic linkage.

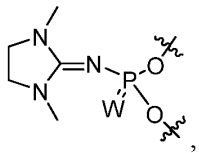
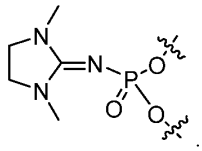
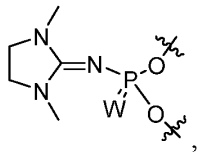
In certain embodiments, a modified internucleotidic linkage is a non-negatively charged internucleotidic linkage. In certain embodiments, provided ds oligonucleotides comprise one or more non-negatively charged internucleotidic linkages. In certain embodiments, a non-negatively charged internucleotidic linkage is a positively charged internucleotidic linkage. In certain embodiments, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage. In certain embodiments, the present disclosure provides ds oligonucleotides comprising one or more neutral internucleotidic linkages. In certain embodiments, a non-negatively charged internucleotidic linkage has the structure of Formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc., or a salt form thereof, as described herein and/or in US 9394333, US 9744183, US 9605019, US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/022473, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO2019/032612, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, and/or WO 2019/032612, the non-negatively charged internucleotidic linkages (e.g., those of Formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc., or a suitable salt form thereof) of each of which are independently incorporated herein by reference.

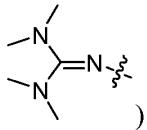
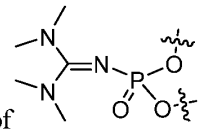
In certain embodiments, a non-negatively charged internucleotidic linkage can improve the delivery and/or activities (e.g., adenosine editing activity).

In certain embodiments, a modified internucleotidic linkage (e.g., a non-negatively charged internucleotidic linkage) comprises optionally substituted triazolyl. In certain embodiments, a modified internucleotidic linkage (e.g., a non-negatively charged internucleotidic linkage) comprises optionally substituted alkynyl. In certain embodiments, a modified internucleotidic linkage comprises a triazole or alkyne moiety. In certain embodiments, a triazole moiety, e.g., a triazolyl group, is optionally substituted. In certain embodiments, a triazole moiety, e.g., a triazolyl group) is substituted. In certain embodiments, a triazole moiety is unsubstituted. In certain embodiments, a modified internucleotidic linkage comprises an optionally substituted cyclic guanidine moiety. In certain embodiments, a modified internucleotidic linkage has the structure of  and is optionally chirally controlled, wherein R^1 is −L−R', wherein L is L^B as described herein, and R' is as described herein. In certain embodiments, each R^1 is independently R'. In certain embodiments, each R' is independently R. In certain embodiments, two R^1 are R and are taken together to form a ring as described herein. In certain embodiments, two R^1 on two different nitrogen atoms are R and are taken together to form a ring as described herein. In certain embodiments, R^1 is independently optionally substituted C_{1-6} aliphatic as described herein. In certain embodiments, R^1 is methyl. In certain embodiments, two R' on the same nitrogen atom are R and are taken together to form a ring as described herein. In certain embodiments, a modified internucleotidic linkage has the structure of  and is optionally chirally controlled. In certain embodiments,  is  . In certain embodiments, a modified internucleotidic linkage comprises an optionally substituted cyclic guanidine moiety and has the structure of:  ,  , or

 , wherein W is O or S. In certain embodiments, W is O. In certain embodiments, W is S. In certain embodiments, a non-negatively charged internucleotidic linkage is stereochemically controlled.

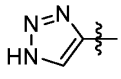
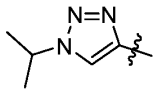
In certain embodiments, a non-negatively charged internucleotidic linkage or a neutral internucleotidic linkage is an internucleotidic linkage comprising a triazole moiety. In some embodiments, an internucleotidic linkage comprising a triazole moiety (e.g., an optionally substituted triazolyl group) has the structure of  . In some embodiments, an internucleotidic linkage comprising a triazole moiety has the structure of  . In some embodiments, an internucleotidic linkage comprising a triazole moiety has the formula of  , where W is O or S. In some embodiments, an internucleotidic linkage comprising an alkyne moiety (e.g., an optionally substituted alkynyl group) has the formula of  , wherein W is O or S. In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage, a neutral internucleotidic linkage, comprises a cyclic guanidine moiety. In some embodiments, an internucleotidic linkage comprising a cyclic guanidine moiety has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage, or a neutral internucleotidic linkage, is or comprising a structure selected from  ,  ,  , or

 , wherein W is O or S. In certain embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage, a neutral internucleotidic linkage, comprises a cyclic guanidine moiety. In certain embodiments, an internucleotidic linkage comprising a cyclic guanidine moiety has the structure of  . In certain embodiments, a non-negatively charged internucleotidic linkage, or a neutral internucleotidic linkage, is or comprising a structure  , wherein W is O or S.

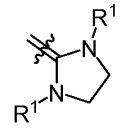
In certain embodiments, an internucleotidic linkage comprises a Tmg group (). In certain embodiments, an internucleotidic linkage comprises a Tmg group and has the structure of  (the "Tmg internucleotidic linkage"). In certain embodiments, neutral internucleotidic linkages include internucleotidic linkages of PNA and PMO, and a Tmg internucleotidic linkage.

In certain embodiments, a non-negatively charged internucleotidic linkage has the structure of Formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc., or a salt form thereof. In certain embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 3-20 membered heterocyclyl or heteroaryl group having 1-10 heteroatoms. In certain embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 3-20 membered heterocyclyl or heteroaryl group having 1-10 heteroatoms, wherein at least one heteroatom is nitrogen. In certain embodiments, such a heterocyclyl or heteroaryl group is of a 5-membered ring. In certain embodiments, such a heterocyclyl or heteroaryl group is of a 6-membered ring.

In certain embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-20 membered heteroaryl group having 1-10 heteroatoms. In certain embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-20 membered heteroaryl group having 1-10 heteroatoms, wherein at least one heteroatom is nitrogen. In certain embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-6 membered heteroaryl group having 1-4 heteroatoms, wherein at least one heteroatom is nitrogen. In certain embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-membered heteroaryl group having 1-4 heteroatoms, wherein at least one heteroatom is nitrogen. In certain embodiments, a heteroaryl group is directly bonded to a linkage phosphorus.

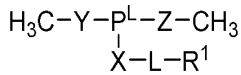
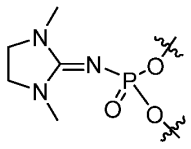
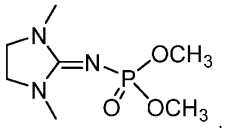
In certain embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-20 membered heterocyclyl group having 1-10 heteroatoms. In certain embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-20 membered heterocyclyl group having 1-10 heteroatoms, wherein at least one heteroatom is nitrogen. In certain embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-6 membered heterocyclyl group having 1-4 heteroatoms, wherein at least one heteroatom is nitrogen. In certain embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-membered heterocyclyl group having 1-4 heteroatoms, wherein at least one heteroatom is nitrogen. In certain embodiments, at least two heteroatoms are nitrogen. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted triazolyl group. In some embodiments, a non-negatively charged internucleotidic linkage comprises an unsubstituted triazolyl group, e.g.,  . In some embodiments, a non-negatively charged internucleotidic linkage comprises a substituted triazolyl group, e.g.,  .

In certain embodiments, a heterocyclyl group is directly bonded to a linkage phosphorus. In certain embodiments, a heterocyclyl group is bonded to a linkage phosphorus through a linker, e.g., =N– when the heterocyclyl group is part of a guanidine moiety who directed bonded to a linkage phosphorus through its =N–. In certain embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted  group.

In certain embodiments, a non-negatively charged internucleotidic linkage comprises an substituted  group. In certain embodiments, a non-negatively charged internucleotidic linkage comprises a  group, wherein each R^1 is independently −L−R. In certain embodiments, each R^1 is independently optionally substituted C_{1-6} alkyl. In certain embodiments, each R^1 is independently methyl.

In certain embodiments, a modified internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage, comprises a triazole or alkyne moiety, each of which is optionally substituted. In certain embodiments, a modified internucleotidic linkage comprises a triazole moiety. In certain embodiments, a modified internucleotidic linkage comprises a unsubstituted triazole moiety. In certain embodiments, a modified internucleotidic linkage comprises a substituted triazole moiety. In certain embodiments, a modified internucleotidic linkage comprises an alkyl moiety. In certain embodiments, a modified internucleotidic linkage comprises an optionally substituted alkynyl group. In certain embodiments, a modified internucleotidic linkage comprises an unsubstituted alkynyl group. In certain embodiments, a modified internucleotidic linkage comprises a substituted alkynyl group. In certain embodiments, an alkynyl group is directly bonded to a linkage phosphorus.

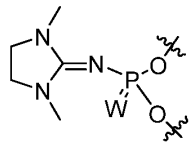
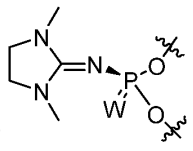
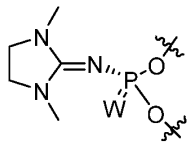
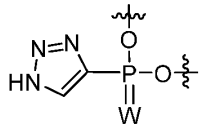
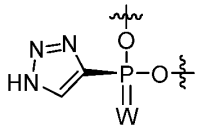
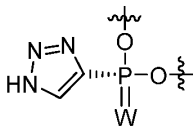
In certain embodiments, a ds oligonucleotide comprises different types of internucleotidic phosphorus linkages. In certain embodiments, a chirally controlled oligonucleotide comprises at least one natural phosphate linkage and at least one modified (non-natural) internucleotidic linkage. In certain embodiments, a ds oligonucleotide comprises at least one natural phosphate linkage and at least one phosphorothioate. In certain embodiments, a ds oligonucleotide comprises at least one non-negatively charged internucleotidic linkage. In certain embodiments, a ds oligonucleotide comprises at least one natural phosphate linkage and at least one non-negatively charged internucleotidic linkage. In certain embodiments, a ds oligonucleotide comprises at least one phosphorothioate internucleotidic linkage and at least one non-negatively charged internucleotidic linkage. In certain embodiments, a ds oligonucleotide comprises at least one phosphorothioate internucleotidic linkage, at least one natural phosphate linkage, and at least one non-negatively charged internucleotidic linkage. In certain embodiments, ds oligonucleotides comprise one

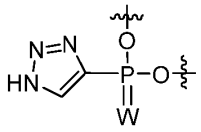
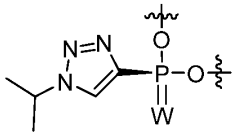
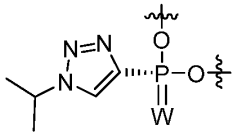
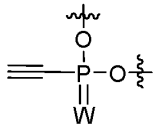
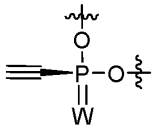
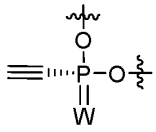
or more, e.g., 1-50, 1-40, 1-30, 1-20, 1-15, 1-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more non-negatively charged internucleotidic linkages. In certain embodiments, a non-negatively charged internucleotidic linkage is not negatively charged in that at a given pH in an aqueous solution less than 50%, 40%, 40%, 30%, 20%, 10%, 5%, or 1% of the internucleotidic linkage exists in a negatively charged salt form. In certain embodiments, a pH is about pH 7.4. In certain embodiments, a pH is about 4-9. In certain embodiments, the percentage is less than 10%. In certain embodiments, the percentage is less than 5%. In certain embodiments, the percentage is less than 1%. In certain embodiments, an internucleotidic linkage is a non-negatively charged internucleotidic linkage in that the neutral form of the internucleotidic linkage has no pKa that is no more than about 1, 2, 3, 4, 5, 6, or 7 in water. In certain embodiments, no pKa is 7 or less. In certain embodiments, no pKa is 6 or less. In certain embodiments, no pKa is 5 or less. In certain embodiments, no pKa is 4 or less. In certain embodiments, no pKa is 3 or less. In certain embodiments, no pKa is 2 or less. In certain embodiments, no pKa is 1 or less. In certain embodiments, pKa of the neutral form of an internucleotidic linkage can be represented by pKa of the neutral form of a compound having the structure of CH_3–the internucleotidic linkage–CH_3. For example, pKa of the neutral form of an internucleotidic linkage having the structure of Formula I may be represented by the pKa of the neutral form of a compound having the structure of  (wherein each of X, Y, Z is independently –O–, –S–, –N(R')–; L is L^B, and R^1 is –L–R'), pKa of  can be represented by pKa  . In certain embodiments, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage. In certain embodiments, a non-negatively charged internucleotidic linkage is a positively-charged internucleotidic linkage. In certain embodiments, a non-negatively charged internucleotidic linkage comprises a guanidine moiety. In certain embodiments, a non-negatively charged internucleotidic linkage comprises a heteroaryl base moiety. In certain embodiments, a non-negatively charged internucleotidic linkage comprises a triazole moiety. In certain embodiments, a non-negatively charged internucleotidic linkage comprises an alkynyl moiety.

In certain embodiments, a neutral or non-negatively charged internucleotidic linkage has the structure of any neutral or non-negatively charged internucleotidic linkage described in any of: US 9394333, US 9744183, US 9605019, US 9982257, US 20170037399, US

20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/022473, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO2019/032612, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, and/or WO 2019/032612,2607, WO2019032612, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, and/or WO 2019/032612, each neutral or non-negatively charged internucleotidic linkage of each of which is hereby incorporated by reference.

In certain embodiments, each R' is independently optionally substituted C_{1-6} aliphatic. In certain embodiments, each R' is independently optionally substituted C_{1-6} alkyl. In certain embodiments, each R' is independently $-CH_3$. In certain embodiments, each R^s is $-H$.

In certain embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In certain embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In certain embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-

negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage has the structure of  . In some embodiments, W is O. In some embodiments, W is S. In some embodiments, a neutral internucleotidic linkage is a non-negatively charged internucleotidic linkage described above.

In certain embodiments, provided ds oligonucleotides comprise 1 or more internucleotidic linkages of Formula **I, I-a, I-b, I-c, I-n-1, I-n-2, I-n-3, I-n-4, II, II-a-1, II-a-2, II-b-1, II-b-2, II-c-1, II-c-2, II-d-1,** or **II-d-2**, which are described in US 9394333, US 9744183, US 9605019, US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/022473, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO2019/032612, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, and/or WO 2019/032612,2607, WO2019032612, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, and/or WO 2019/032612, the Formula **I, I-a, I-b, I-c, I-n-1, I-n-2, I-n-3, I-n-4, II, II-a-1, II-**

a-2, II-b-1, II-b-2, II-c-1, II-c-2, II-d-1, or **II-d-2**, or salt forms thereof, each of which are independently incorporated herein by reference.

In certain embodiments, a ds oligonucleotide comprises a neutral internucleotidic linkage and a chirally controlled internucleotidic linkage. In certain embodiments, a ds oligonucleotide comprises a neutral internucleotidic linkage and a chirally controlled internucleotidic linkage which is not the neutral internucleotidic linkage. In certain embodiments, a ds oligonucleotide comprises a neutral internucleotidic linkage and a chirally controlled phosphorothioate internucleotidic linkage. In certain embodiments, the present disclosure provides a ds oligonucleotide comprising one or more non-negatively charged internucleotidic linkages and one or more phosphorothioate internucleotidic linkages, wherein each phosphorothioate internucleotidic linkage in the oligonucleotide is independently a chirally controlled internucleotidic linkage. In certain embodiments, the present disclosure provides a ds oligonucleotide comprising one or more neutral internucleotidic linkages and one or more phosphorothioate internucleotidic linkage, wherein each phosphorothioate internucleotidic linkage in the ds oligonucleotide is independently a chirally controlled internucleotidic linkage. In certain embodiments, a ds oligonucleotide comprises at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more chirally controlled phosphorothioate internucleotidic linkages. In certain embodiments, non-negatively charged internucleotidic linkage is chirally controlled. In certain embodiments, non-negatively charged internucleotidic linkage is not chirally controlled. In certain embodiments, a neutral internucleotidic linkage is chirally controlled. In certain embodiments, a neutral internucleotidic linkage is not chirally controlled.

Without wishing to be bound by any particular theory, the present disclosure notes that a neutral internucleotidic linkage can be more hydrophobic than a phosphorothioate internucleotidic linkage (PS), which can be more hydrophobic than a natural phosphate linkage (PO). Typically, unlike a PS or PO, a neutral internucleotidic linkage bears less charge. Without wishing to be bound by any particular theory, the present disclosure notes that incorporation of one or more neutral internucleotidic linkages into a ds oligonucleotide may increase the ds oligonucleotides' ability to be taken up by a cell and/or to escape from endosomes. Without wishing to be bound by any particular theory, the present disclosure notes that incorporation of one or more neutral internucleotidic linkages can be utilized to modulate melting temperature of duplexes formed between a ds oligonucleotide and its target nucleic acid.

Without wishing to be bound by any particular theory, the present disclosure notes that incorporation of one or more non-negatively charged internucleotidic linkages, e.g., neutral internucleotidic linkages, into a ds oligonucleotide may be able to increase the ds oligonucleotide's ability to mediate a function such as target adenosine editing.

As appreciated by those skilled in the art, internucleotidic linkages such as natural phosphate linkages and those of Formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or salt forms thereof typically connect two nucleosides (which can either be natural or modified) as described in US 9394333, US 9744183, US 9605019, US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/022473, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO2019032612, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, and/or WO 2019/032612, the Formula **I**, **I-a**, **I-b**, **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, or salt forms thereof, each of which are independently incorporated herein by reference. A typical connection, as in natural DNA and RNA, is that an internucleotidic linkage forms bonds with two sugars (which can be either unmodified or modified as described herein). In many embodiments, as exemplified herein an internucleotidic linkage forms bonds through its oxygen atoms or heteroatoms (e.g., Y and Z in various formulae) with one optionally modified ribose or deoxyribose at its 5' carbon, and the other optionally modified ribose or deoxyribose at its 3' carbon. In certain embodiments, each nucleoside units connected by an internucleotidic linkage independently comprises a nucleobase which is independently an optionally substituted A, T, C, G, or U, or a substituted tautomer of A, T, C, G or U, or a nucleobase comprising an optionally substituted heterocyclyl and/or a heteroaryl ring having at least one nitrogen atom.

In some embodiments, a linkage has the structure of or comprises $-Y-P^L(-X-R^L)-Z-$, or a salt form thereof, wherein:

P^L is P, P(=W), P–>B($-L^L-R^L$)$_3$, or P^N;

W is O, N($-L^L-R^L$), S or Se;

P^N is $P=N-C(-L^L-R')(=L^N-R')$ or $P=N-L^L-R^L$;

L^N is $=N-L^{L1}-$, $=CH-L^{L1}-$ wherein CH is optionally substituted, or $=N^+(R')(Q^-)-L^{L1}-$;

Q^- is an anion;

each of X, Y and Z is independently –O–, –S–, $-L^{L}-N(-L^{L}-R^{L})-L^{L}-$, $-L^{L}-N=C(-L^{L}-R^{L})-L^{L}-$, or L^{L};

each R^{L} is independently $-L^{L}-N(R')_2$, $-L^{L}-R'$, $-N=C(-L^{L}-R')_2$, $-L^{L}-N(R')C(NR')N(R')_2$, $-L^{L}-N(R')C(O)N(R')_2$, a carbohydrate, or one or more additional chemical moieties optionally connected through a linker;

each of L^{L1} and L^{L} is independently L;

$-Cy^{IL}-$ is $-Cy-$;

each L is independently a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms, $-C(R')_2-$, −Cy−, −O−, −S−, −S−S−, −N(R')−, −C(O)−, −C(S)−, −C(NR')−, −C(NR')N(R')−, −N(R')C(NR')N(R')−, −C(O)N(R')−, −N(R')C(O)N(R')−, −N(R')C(O)O−, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, −C(O)S−, −C(O)O−, −P(O)(OR')−, −P(O)(SR')−, −P(O)(R')−, −P(O)(NR')−, −P(S)(OR')−, −P(S)(SR')−, −P(S)(R')−, −P(S)(NR')−, −P(R')−, −P(OR')−, −P(SR')−, −P(NR')−, $-P(OR')[B(R')_3]-$, −OP(O)(OR')O−, −OP(O)(SR')O−, −OP(O)(R')O−, −OP(O)(NR')O−, −OP(OR')O−, −OP(SR')O−, −OP(NR')O−, −OP(R')O−, $-OP(OR')[B(R')_3]O-$, and $-[C(R')_2C(R')_2O]n-$, wherein n is 1-50, and one or more nitrogen or carbon atoms are optionally and independently replaced with Cy^{L};

each −Cy− is independently an optionally substituted bivalent 3-30 membered, monocyclic, bicyclic or polycyclic ring having 0-10 heteroatoms;

each Cy^{L} is independently an optionally substituted trivalent or tetravalent, 3-30 membered, monocyclic, bicyclic or polycyclic ring having 0-10 heteroatoms;

each R' is independently −R, −C(O)R, $-C(O)N(R)_2$, −C(O)OR, or $-S(O)_2R$;

each R is independently −H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms, 5-30 membered heteroaryl having 1-10 heteroatoms, and 3-30 membered heterocyclyl having 1-10 heteroatoms, or

two R groups are optionally and independently taken together to form a covalent bond, or:

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms; or

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms.

In some embodiments, an internucleotidic linkage has the structure of $-O-P^L(-X-R^L)-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-O-P(=W)(-X-R^L)-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-O-P(=W)[-N(-L^L-R^L)-R^L]-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-O-P(=W)(-NH-L^L-R^L)-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-O-P(=W)[-N(R')_2]-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-O-P(=W)(-NHR')-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-O-P(=W)(-NHSO_2R)-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-O-P(=W)[-N=C(-L^L-R')_2]-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-O-P(=W)[-N=C[N(R')_2]_2]-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-OP(=W)(-N=C(R'')_2)-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-OP(=W)(-N(R'')_2)-O-$, wherein each variable is independently as described herein. In some embodiments, W is O. In some embodiments, W is S. In some embodiments, such an internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, such an internucleotidic linkage is a neutral internucleotidic linkage.

In some embodiments, an internucleotidic linkage has the structure of $-P^L(-X-R^L)-Z-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-P^L(-X-R^L)-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-P(=W)(-X-R^L)-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-P(=W)[-N(-L^L-R^L)-R^L]-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-P(=W)(-NH-L^L-R^L)-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-P(=W)[-N(R')_2]-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-P(=W)(-NHR')-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-P(=W)(-NHSO_2R)-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-P(=W)[-N=C(-L^L-R')_2]-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-P(=W)[-N=C[N(R')_2]_2]-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-P(=W)(-N=C(R'')_2)-O-$, wherein each variable is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-P(=W)(-N(R'')_2)-O-$, wherein each variable is independently as described herein. In some embodiments, W is O. In some embodiments, W is S. In some embodiments, such an internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, such an internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, P of such an internucleotidic linkage is bonded to N of a sugar.

In some embodiments, a linkage is a phosphoryl guanidine internucleotidic linkage. In some embodiments, a linkage is a thio-phosphoryl guanidine internucleotidic linkage.

In some embodiments, one or more methylene units are optionally and independently replaced with a moiety as described herein. In some embodiments, L or L^L is or comprises $-SO_2-$. In some embodiments, L or L^L is or comprises $-SO_2N(R')-$. In some embodiments, L or L^L is or comprises $-C(O)-$. In some embodiments, L or L^L is or comprises $-C(O)O-$. In some embodiments, L or L^L is or comprises $-C(O)N(R')-$. In some embodiments, L or L^L is or comprises $-P(=W)(R')-$. In some embodiments, L or L^L is or comprises $-P(=O)(R')-$. In

some embodiments, L or L^L is or comprises −P(=S)(R')−. In some embodiments, L or L^L is or comprises −P(R')−. In some embodiments, L or L^L is or comprises −P(=W)(OR')−. In some embodiments, L or L^L is or comprises −P(=O)(OR')−. In some embodiments, L or L^L is or comprises −P(=S)(OR')−. In some embodiments, L or L^L is or comprises −P(OR')−.

In some embodiments, $-X-R^L$ is $-N(R')SO_2R^L$. In some embodiments, $-X-R^L$ is $-N(R')C(O)R^L$. In some embodiments, $-X-R^L$ is $-N(R')P(=O)(R')R^L$.

In some embodiments, a linkage, e.g., a non-negatively charged internucleotidic linkage or neutral internucleotidic linkage, has the structure of or comprises −P(=W)(−N=C(R")$_2$)−, −P(=W)(−N(R')SO_2R")−, −P(=W)(−N(R')C(O)R")−, −P(=W)(−N(R")$_2$)−, −P(=W)(−N(R')P(O)(R")$_2$)−, −OP(=W)(−N=C(R")$_2$)O−, −OP(=W)(−N(R')SO_2R")O−, −OP(=W)(−N(R')C(O)R")O−, −OP(=W)(−N(R")$_2$)O−, −OP(=W)(−N(R')P(O)(R")$_2$)O−, −P(=W)(−N=C(R")$_2$)O−, −P(=W)(−N(R')SO_2R")O−, −P(=W)(−N(R')C(O)R")O−, −P(=W)(−N(R")$_2$)O−, or −P(=W)(−N(R')P(O)(R")$_2$)O−, or a salt form thereof, wherein:

W is O or S;

each R" is independently R', −OR', −P(=W)(R')$_2$, or −N(R')$_2$;

each R' is independently −R, −C(O)R, −C(O)N(R)$_2$, −C(O)OR, or −$S(O)_2$R;

each R is independently −H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms, 5-30 membered heteroaryl having 1-10 heteroatoms, and 3-30 membered heterocyclyl having 1-10 heteroatoms, or

two R groups are optionally and independently taken together to form a covalent bond, or:

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms; or

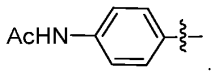
two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms.

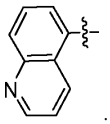
In some embodiments, W is O. In some embodiments, an internucleotidic linkage has the structure of −P(=O)(−N=C(R”)$_2$)−, −P(=O)(−N(R’)SO$_2$R”)−, −P(=O)(−N(R’)C(O)R”)−, −P(=O)(−N(R”)$_2$)−, −P(=O)(−N(R’)P(O)(R”)$_2$)−, −OP(=O)(−N=C(R”)$_2$)O−, −OP(=O)(−N(R’)SO$_2$R”)O−, −OP(=O)(−N(R’)C(O)R”)O−, −OP(=O)(−N(R”)$_2$)O−, −OP(=O)(−N(R’)P(O)(R”)$_2$)O−, −P(=O)(−N=C(R”)$_2$)O−, −P(=O)(−N(R’)SO$_2$R”)O−, −P(=O)(−N(R’)C(O)R”)O−, −P(=O)(−N(R”)$_2$)O−, or −P(=O)(−N(R’)P(O)(R”)$_2$)O−, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −P(=O)(−N=C(R”)$_2$)− −P(=O)(−N(R”)$_2$)−, −OP(=O)(−N=C(R”)$_2$)−O−, −OP(=O)(−N(R”)$_2$)−O−, −P(=O)(−N=C(R”)$_2$)−O− or −P(=O)(−N(R”)$_2$)−O− or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −OP(=O)(−N=C(R”)$_2$)−O− or −OP(=O)(−N(R”)$_2$)−O−, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −OP(=O)(−N=C(R”)$_2$)−O−, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −OP(=O)(−N(R”)$_2$)−O−, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −OP(=O)(−N(R’)SO$_2$R”)O−, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −OP(=O)(−N(R’)C(O)R”)O−, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −OP(=O)(−N(R’)P(O)(R”)$_2$)O−, or a salt form thereof. In some embodiments, a internucleotidic linkage is n001.

In some embodiments, W is S. In some embodiments, an internucleotidic linkage has the structure of −P(=S)(−N=C(R”)$_2$)−, −P(=S)(−N(R’)SO$_2$R”)−, −P(=S)(−N(R’)C(O)R”)−, −P(=S)(−N(R”)$_2$)−, −P(=S)(−N(R’)P(O)(R”)$_2$)−, −OP(=S)(−N=C(R”)$_2$)O−, −OP(=S)(−N(R’)SO$_2$R”)O−, −OP(=S)(−N(R’)C(O)R”)O−, −OP(=S)(−N(R”)$_2$)O−, −OP(=S)(−N(R’)P(O)(R”)$_2$)O−, −P(=S)(−N=C(R”)$_2$)O−, −P(=S)(−N(R’)SO$_2$R”)O−, −P(=S)(−N(R’)C(O)R”)O−, −P(=S)(−N(R”)$_2$)O−, or −P(=S)(−N(R’)P(O)(R”)$_2$)O−, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −P(=S)(−N=C(R”)$_2$)− −P(=S)(−N(R”)$_2$)−, −OP(=S)(−N=C(R”)$_2$)−O−, −OP(=S)(−N(R”)$_2$)−O−, −P(=S)(−N=C(R”)$_2$)−O− or −P(=S)(−N(R”)$_2$)−O− or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −OP(=S)(−N=C(R”)$_2$)−O− or −OP(=S)(−N(R”)$_2$)−O−, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −OP(=S)(−N=C(R”)$_2$)−O−, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −OP(=S)(−N(R”)$_2$)−O−, or a salt form thereof. In some embodiments, an internucleotidic

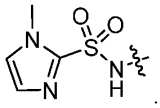
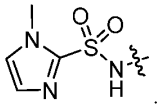
linkage has the structure of −OP(=S)(−N(R')SO_2R")O−, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −OP(=S)(−N(R')C(O)R")O−, or a salt form thereof. In some embodiments, an internucleotidic linkage has the structure of −OP(=S)(−N(R')P(O)(R")$_2$)O−, or a salt form thereof. In some embodiments, a internucleotidic linkage is *n001.

In some embodiments, an internucleotidic linkage has the structure of −P(=O)(−N(R')SO_2R")−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=S)(−N(R')SO_2R")−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=O)(−N(R')SO_2R")O−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=S)(−N(R')SO_2R")O−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −OP(=O)(−N(R')SO_2R")O−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −OP(=S)(−N(R')SO_2R")O−, wherein R" is as described herein. In some embodiments, R', e.g., of −N(R')−, is hydrogen or optionally substituted C_{1-6} aliphatic. In some embodiments, R' is C_{1-6} alkyl. In some embodiments, R' is hydrogen. In some embodiments, R", e.g., in −SO_2R", is R' as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=O)(−NHSO_2R")−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=S)(−NHSO_2R")−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=O)(−NHSO_2R")O−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=S)(−NHSO_2R")O−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −OP(=O)(−NHSO_2R")O−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −OP(=S)(−NHSO_2R")O−, wherein R" is as described herein. In some embodiments, −X−R^L is −N(R')SO_2R^L, wherein each of R' and R^L is independently as described herein. In some embodiments, R^L is R". In some embodiments, R^L is R'. In some embodiments, −X−R^L is −N(R')SO_2R", wherein R' is as described herein. In some embodiments, −X−R^L is −N(R')SO_2R', wherein R' is as described herein. In some embodiments, −X−R^L is −NHSO_2R', wherein R' is as described herein. In some embodiments, R' is R as described herein. In some embodiments, R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R' is optionally substituted C_{1-6} alkyl. In some embodiments, R' is optionally substituted phenyl.

In some embodiments, R' is optionally substituted heteroaryl. In some embodiments, R", e.g., in $-SO_2R$", is R. In some embodiments, R is an optionally substituted group selected from C_{1-6} aliphatic, aryl, heterocyclyl, and heteroaryl. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is optionally substituted C_{1-6} alkenyl. In some embodiments, R is optionally substituted C_{1-6} alkynyl. In some embodiments, R is optionally substituted methyl. In some embodiments, $-X-R^L$ is $-NHSO_2CH_3$. In some embodiments, R is $-CF_3$. In some embodiments, R is methyl. In some embodiments, R is optionally substituted ethyl. In some embodiments, R is ethyl. In some embodiments, R is $-CH_2CHF_2$. In some embodiments, R is $-CH_2CH_2OCH_3$. In some embodiments, R is optionally substituted propyl. In some embodiments, R is optionally substituted butyl. In some embodiments, R is n-butyl. In some embodiments, R is $-(CH_2)_6NH_2$. In some embodiments, R is an optionally substituted linear C_{2-20} aliphatic. In some embodiments, R is optionally substituted linear C_{2-20} alkyl. In some embodiments, R is linear C_{2-20} alkyl. In some embodiments, R is optionally substituted C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} aliphatic. In some embodiments, R is optionally substituted C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} alkyl. In some embodiments, R is optionally substituted linear C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} alkyl. In some embodiments, R is linear C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} alkyl. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is phenyl. In some embodiments, R is p-methylphenyl. In some embodiments, R is 4-dimethylaminophenyl. In some embodiments, R is 3-pyridinyl. In some embodiments, R is 

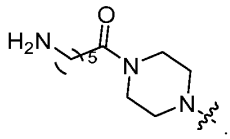
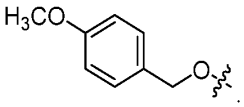
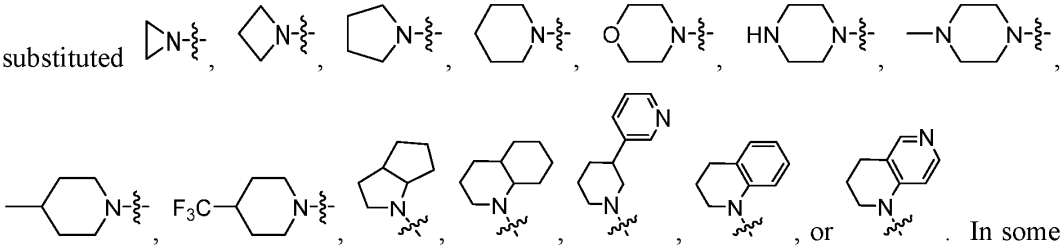
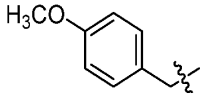
. In some embodiments, R is 

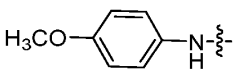
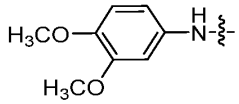
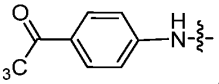
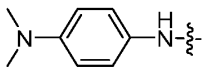
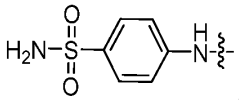
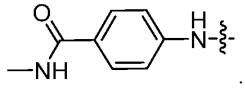
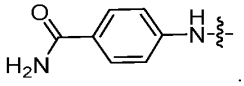
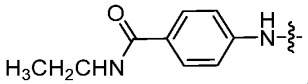
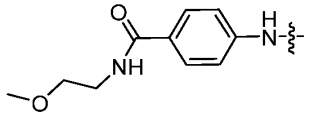
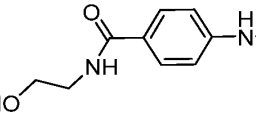
. In some embodiments, R is benzyl. In some embodiments, R is optionally substituted heteroaryl. In some embodiments, R is optionally substituted 1,3-diazolyl. In some embodiments, R is optionally substituted 2-(1,3)-diazolyl. In some embodiments, R is optionally substituted 1-methyl-2-(1,3)-diazolyl. In some embodiments, R is isopropyl. In some embodiments, R" is $-N(R')_2$. In some embodiments, R" is $-N(CH_3)_2$. In some embodiments, R", e.g., in $-SO_2R$", is $-OR'$, wherein R' is as described herein. In some embodiments, R' is R as described herein. In some embodiments, R" is $-OCH_3$. In some embodiments, a linkage is $-OP(=O)(-NHSO_2R)O-$, wherein R is as described herein. In some embodiments, R is optionally substituted linear alkyl as described herein. In some embodiments, R is linear alkyl

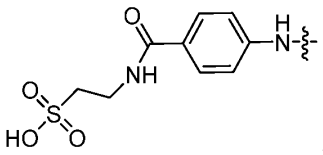
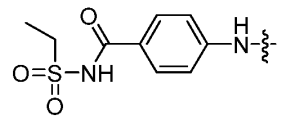
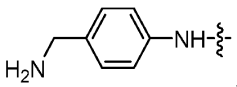
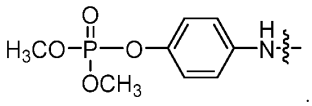
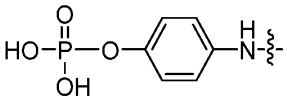
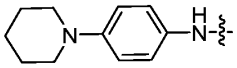
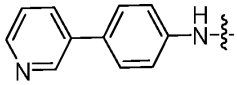
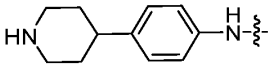
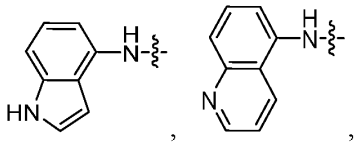
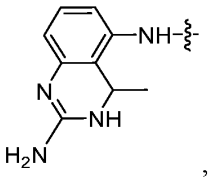
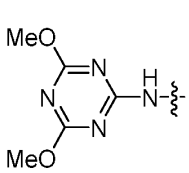
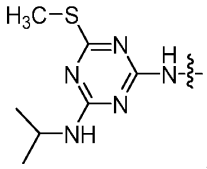
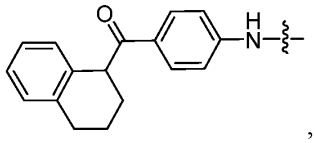
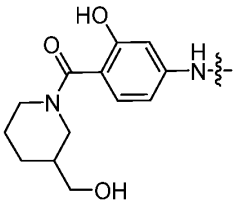
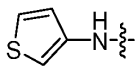
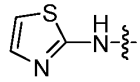
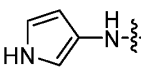
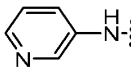
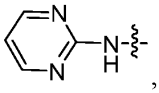
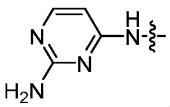
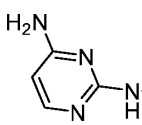
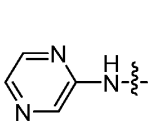
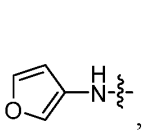
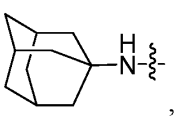
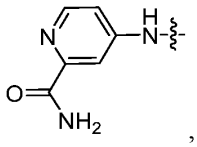
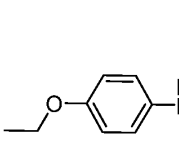
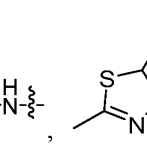
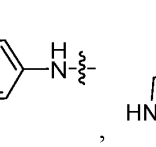
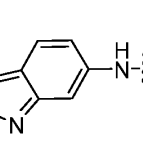
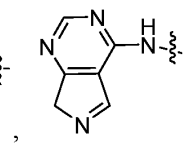
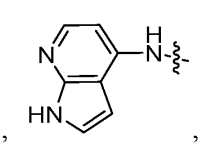
as described herein. In some embodiments, a linkage is −OP(=O)(−$NHSO_2CH_3$)O−. In some embodiments, a linkage is −OP(=O)(−$NHSO_2CH_2CH_3$)O−. In some embodiments, a linkage is −OP(=O)(−$NHSO_2CH_2CH_2OCH_3$)O−. In some embodiments, a linkage is −OP(=O)(−$NHSO_2CH_2Ph$)O−. In some embodiments, a linkage is −OP(=O)(−$NHSO_2CH_2CHF_2$)O−. In some embodiments, a linkage is −OP(=O)(−$NHSO_2$(4-methylphenyl))O−. In some embodiments, −X−R^L is  . In some embodiments, a linkage is −OP(=O)(−X−R^L)O−, wherein −X−R^L is  . In some embodiments, a linkage is −OP(=O)(−$NHSO_2CH(CH_3)_2$)O−. In some embodiments, a linkage is −OP(=O)(−$NHSO_2N(CH_3)_2$)O−.

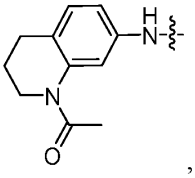
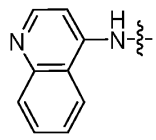
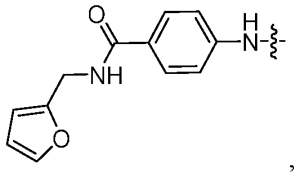
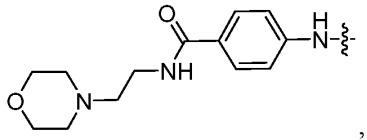
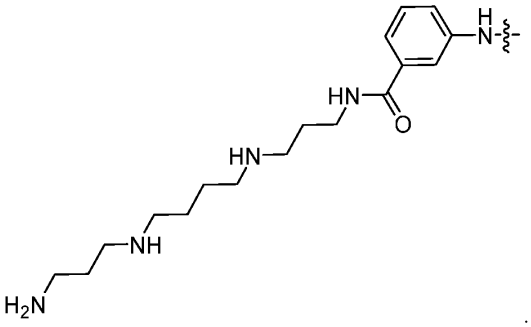
In some embodiments, an internucleotidic linkage has the structure of −P(=O)(−N(R')C(O)R")−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=S)(−N(R')C(O)R")−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=O)(−N(R')C(O)R")O−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=S)(−N(R')C(O)R")O−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −OP(=O)(−N(R')C(O)R")O−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −OP(=S)(−N(R')C(O)R")O−, wherein R" is as described herein. In some embodiments, R', e.g., of −N(R')−, is hydrogen or optionally substituted C_{1-6} aliphatic. In some embodiments, R' is C_{1-6} alkyl. In some embodiments, R' is hydrogen. In some embodiments, R", e.g., in −C(O)R", is R' as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=O)(−NHC(O)R")−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=S)(−NHC(O)R")−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=O)(−NHC(O)R")O−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=S)(−NHC(O)R")O−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −OP(=O)(−NHC(O)R")O−, wherein R" is as described herein. In some embodiments, an internucleotidic linkage has the structure of −OP(=S)(−NHC(O)R")O−, wherein R" is as described herein. In some embodiments, −X−R^L

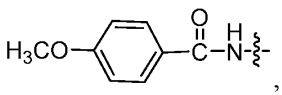
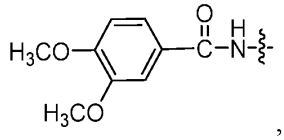
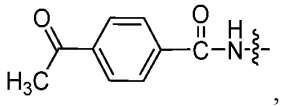
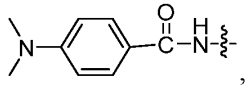
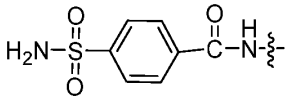
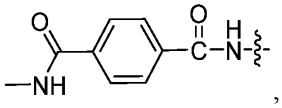
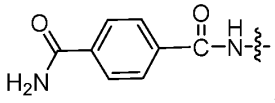
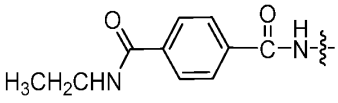
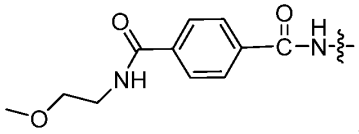
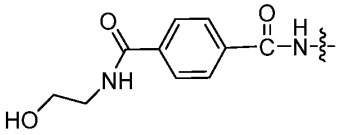
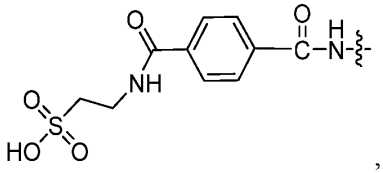
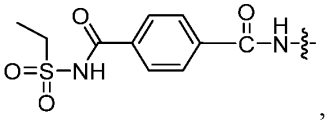
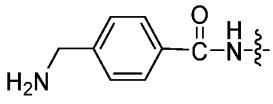
is $-N(R')COR^L$, wherein R^L is as described herein. In some embodiments, $-X-R^L$ is $-N(R')COR''$, wherein R'' is as described herein. In some embodiments, $-X-R^L$ is $-N(R')COR'$, wherein R' is as described herein. In some embodiments, $-X-R^L$ is $-NHCOR'$, wherein R' is as described herein. In some embodiments, R' is R as described herein. In some embodiments, R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R' is optionally substituted C_{1-6} alkyl. In some embodiments, R' is optionally substituted phenyl. In some embodiments, R' is optionally substituted heteroaryl. In some embodiments, R'', e.g., in $-C(O)R''$, is R. In some embodiments, R is an optionally substituted group selected from C_{1-6} aliphatic, aryl, heterocyclyl, and heteroaryl. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is optionally substituted C_{1-6} alkenyl. In some embodiments, R is optionally substituted C_{1-6} alkynyl. In some embodiments, R is methyl. In some embodiments, $-X-R^L$ is $-NHC(O)CH_3$. In some embodiments, R is optionally substituted methyl. In some embodiments, R is $-CF_3$. In some embodiments, R is optionally substituted ethyl. In some embodiments, R is ethyl. In some embodiments, R is $-CH_2CHF_2$. In some embodiments, R is $-CH_2CH_2OCH_3$. In some embodiments, R is optionally substituted C_{1-20} (e.g., C_{1-6}, C_{2-6}, C_{3-6}, C_{1-10}, C_{2-10}, C_{3-10}, C_{2-20}, C_{3-20}, C_{10-20}, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) aliphatic. In some embodiments, R is optionally substituted C_{1-20} (e.g., C_{1-6}, C_{2-6}, C_{3-6}, C_{1-10}, C_{2-10}, C_{3-10}, C_{2-20}, C_{3-20}, C_{10-20}, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) alkyl. In some embodiments, R is an optionally substituted linear C_{2-20} aliphatic. In some embodiments, R is optionally substituted linear C_{2-20} alkyl. In some embodiments, R is linear C_{2-20} alkyl. In some embodiments, R is optionally substituted C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} aliphatic. In some embodiments, R is optionally substituted C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} alkyl. In some embodiments, R is optionally substituted linear C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} alkyl. In some embodiments, R is linear C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} alkyl. In some embodiments, R is optionally substituted aryl. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is p-methylphenyl. In some embodiments, R is benzyl. In some embodiments, R is optionally substituted heteroaryl. In some embodiments, R is optionally substituted 1,3-diazolyl. In some embodiments, R is optionally substituted 2-(1,3)-diazolyl. In some embodiments, R is optionally substituted 1-methyl-2-(1,3)-diazolyl. In some embodiments, R^L is $-(CH_2)_5NH_2$. In

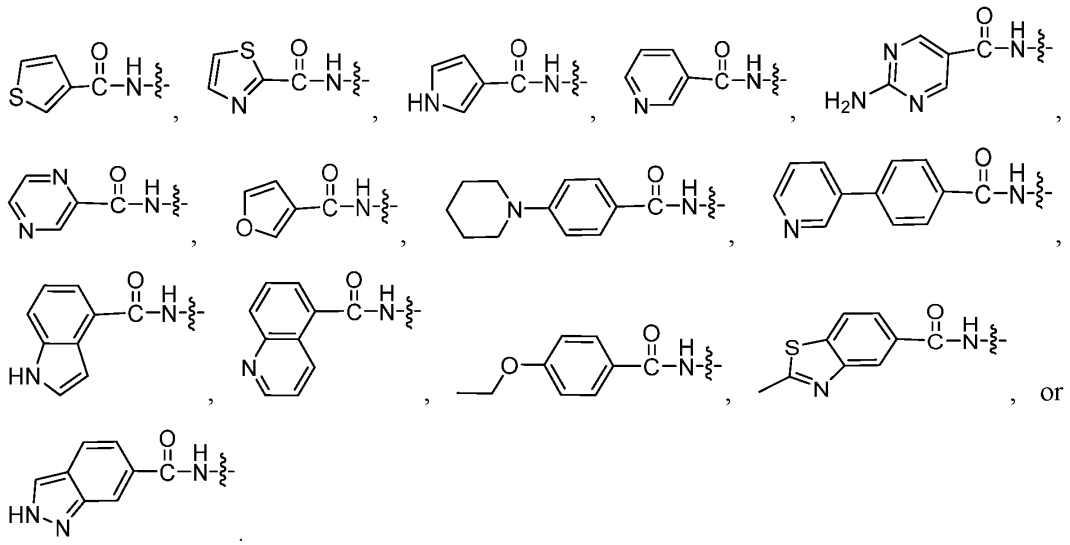
some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R" is $-N(R')_2$. In some embodiments, R" is $-N(CH_3)_2$. In some embodiments, $-X-R^L$ is $-N(R')CON(R^L)_2$, wherein each of R' and R^L is independently as described herein. In some embodiments, $-X-R^L$ is $-NHCON(R^L)_2$, wherein R^L is as described herein. In some embodiments, two R' or two R^L are taken together with the nitrogen atom to which they are attached to form a ring as described herein, e.g., optionally substituted  . In some embodiments, R", e.g., in $-C(O)R$", is $-OR'$, wherein R' is as described herein. In some embodiments, R' is R as described herein. In some embodiments, is optionally substituted C_{1-6} aliphatic. In some embodiments, is optionally substituted C_{1-6} alkyl. In some embodiments, R" is $-OCH_3$. In some embodiments, $-X-R^L$ is $-N(R')C(O)OR^L$, wherein each of R' and R^L is independently as described herein. In some embodiments, R is  . In some embodiments, $-X-R^L$ is $-NHC(O)OCH_3$. In some embodiments, $-X-R^L$ is $-NHC(O)N(CH_3)_2$. In some embodiments, a linkage is $-OP(O)(NHC(O)CH_3)O-$. In some embodiments, a linkage is $-OP(O)(NHC(O)OCH_3)O-$. In some embodiments, a linkage is $-OP(O)(NHC(O)(p\text{-methylphenyl}))O-$. In some embodiments, a linkage is $-OP(O)(NHC(O)N(CH_3)_2)O-$. In some embodiments, $-X-R^L$ is $-N(R')R^L$, wherein each of R' and R^L is independently as described herein. In some embodiments, $-X-R^L$ is $-N(R')R^L$, wherein each of R' and R^L is independently not hydrogen. In some embodiments, $-X-R^L$ is $-NHR^L$, wherein R^L is as described herein. In some embodiments, R^L is not hydrogen. In some embodiments, R^L is optionally substituted aryl or heteroaryl. In some embodiments, R^L is optionally substituted aryl. In some embodiments, R^L is optionally substituted phenyl. In some embodiments, $-X-R^L$ is $-N(R')_2$, wherein each R' is independently as described herein. In some embodiments, $-X-R^L$ is $-NHR'$, wherein R' is as described herein. In some

embodiments, $-X-R^L$ is $-NHR$, wherein R is as described herein. In some embodiments, $-X-R^L$ is R^L, wherein R^L is as described herein. In some embodiments, R^L is $-N(R')_2$, wherein each R' is independently as described herein. In some embodiments, R^L is $-NHR'$, wherein R' is as described herein. In some embodiments, R^L is $-NHR$, wherein R is as described herein. In some embodiments, R^L is $-N(R')_2$, wherein each R' is independently as described herein. In some embodiments, none of R' in $-N(R')_2$ is hydrogen. In some embodiments, R^L is $-N(R')_2$, wherein each R' is independently C_{1-6} aliphatic. In some embodiments, R^L is $-L-R'$, wherein each of L and R' is independently as described herein. In some embodiments, R^L is $-L-R$, wherein each of L and R is independently as described herein. In some embodiments, R^L is $-N(R')-Cy-N(R')-R'$. In some embodiments, R^L is $-N(R')-Cy-C(O)-R'$. In some embodiments, R^L is $-N(R')-Cy-O-R'$. In some embodiments, R^L is $-N(R')-Cy-SO_2-R'$. In some embodiments, R^L is $-N(R')-Cy-SO_2-N(R')_2$. In some embodiments, R^L is $-N(R')-Cy-C(O)-N(R')_2$. In some embodiments, R^L is $-N(R')-Cy-OP(O)(R'')_2$. In some embodiments, $-Cy-$ is an optionally substituted bivalent aryl group. In some embodiments, $-Cy-$ is optionally substituted phenylene. In some embodiments, $-Cy-$ is optionally substituted 1,4-phenylene. In some embodiments, $-Cy-$ is 1,4-phenylene. In some embodiments, R^L is $-N(CH_3)_2$. In some embodiments, R^L is $-N(i\text{-}Pr)_2$. In some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is . In some embodiments, R^L is . In some embodiments, R^L is . In some embodiments, R^L is . In some

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, or

. In some embodiments, $-X-R^L$ is $-N(R')-C(O)-Cy-R^L$. In some embodiments, $-X-R^L$ is R^L. In some embodiments, R^L is $-N(R')-C(O)-Cy-O-R'$. In some embodiments, R^L is $-N(R')-C(O)-Cy-R'$. In some embodiments, R^L is $-N(R')-C(O)-Cy-C(O)-R'$. In some embodiments, R^L is $-N(R')-C(O)-Cy-N(R')_2$. In some embodiments, R^L is $-N(R')-C(O)-Cy-SO_2-N(R')_2$. In some embodiments, R^L is $-N(R')-C(O)-Cy-C(O)-N(R')_2$. In some embodiments, R^L is $-N(R')-C(O)-Cy-C(O)-N(R')-SO_2-R'$. In some embodiments, R' is R as described herein.

In some embodiments, R^L is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,



As described herein, in some embodiments, one or more methylene units of L, or a variable which comprises or is L, are independently replaced with −O−, −N(R')−, −C(O)−, −C(O)N(R')−, $-SO_2-$, $-SO_2N(R')-$, or −Cy−. In some embodiments, a methylene unit is replaced with −Cy−. In some embodiments, −Cy− is an optionally substituted bivalent aryl group. In some embodiments, −Cy− is optionally substituted phenylene. In some embodiments, −Cy− is optionally substituted 1,4-phenylene. In some embodiments, −Cy− is an optionally substituted bivalent 5-20 (e.g. 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) membered heteroaryl group having 1-10 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) heteroatoms. In some embodiments, −Cy− is monocyclic. In some embodiments, −Cy− is bicyclic. In some embodiments, −Cy− is polycyclic. In some embodiments, each monocyclic unit in −Cy− is independently 3-10 (e.g., 3, 4, 5, 6, 7, 8, 9, or 10) membered, and is independently saturated, partially saturated, or aromatic. In some embodiments, −Cy− is an optionally substituted 3-20 (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) membered monocyclic, bicyclic or polycyclic aliphatic group. In some embodiments, −Cy− is an optionally substituted 3-20 (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) membered monocyclic, bicyclic or polycyclic heteroaliphatic group having 1-10 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) heteroatoms.

In some embodiments, an internucleotidic linkage has the structure of $-P(=O)(-N(R')P(O)(R'')_2)-$, wherein each R" is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of $-P(=S)(-N(R')P(O)(R'')_2)-$, wherein each R" is independently as described herein. In some embodiments, an

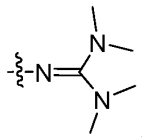
internucleotidic linkage has the structure of −P(=O)(−N(R')P(O)(R")$_2$)O−, wherein each R" is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=S)(−N(R')P(O)(R")$_2$)O−, wherein each R" is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −OP(=O)(−N(R')P(O)(R")$_2$)O−, wherein each R" is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −OP(=S)(−N(R')P(O)(R")$_2$)O−, wherein each R" is independently as described herein. In some embodiments, R', e.g., of −N(R')−, is hydrogen or optionally substituted C_{1-6} aliphatic. In some embodiments, R' is C_{1-6} alkyl. In some embodiments, R' is hydrogen. In some embodiments, R", e.g., in −P(O)(R")$_2$, is R' as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=O)(−NHP(O)(R")$_2$)−, wherein each R" is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=S)(−NHP(O)(R")$_2$)−, wherein each R" is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=O)(−NHP(O)(R")$_2$)O−, wherein each R" is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −P(=S)(−NHP(O)(R")$_2$)O−, wherein each R" is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −OP(=O)(−NHP(O)(R")$_2$)O−, wherein each R" is independently as described herein. In some embodiments, an internucleotidic linkage has the structure of −OP(=S)(−NHP(O)(R")$_2$)O−, wherein each R" is independently as described herein. In some embodiments, an occurrence of R", e.g., in −P(O)(R")$_2$, is R. In some embodiments, R is an optionally substituted group selected from C_{1-6} aliphatic, aryl, heterocyclyl, and heteroaryl. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is optionally substituted C_{1-6} alkenyl. In some embodiments, R is optionally substituted C_{1-6} alkynyl. In some embodiments, R is methyl. In some embodiments, R is optionally substituted methyl. In some embodiments, R is $-CF_3$. In some embodiments, R is optionally substituted ethyl. In some embodiments, R is ethyl. In some embodiments, R is $-CH_2CHF_2$. In some embodiments, R is $-CH_2CH_2OCH_3$. In some embodiments, R is optionally substituted C_{1-20} (e.g., C_{1-6}, C_{2-6}, C_{3-6}, C_{1-10}, C_{2-10}, C_{3-10}, C_{2-20}, C_{3-20}, C_{10-20}, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) aliphatic. In some embodiments, R is optionally substituted C_{1-20} (e.g., C_{1-6}, C_{2-6}, C_{3-6}, C_{1-10}, C_{2-10}, C_{3-10}, C_{2-20}, C_{3-20}, C_{10-20}, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, etc.) alkyl. In some embodiments, R is an optionally substituted linear C_{2-20} aliphatic. In some embodiments, R is optionally substituted linear C_{2-}

$_{20}$ alkyl. In some embodiments, R is linear C_{2-20} alkyl. In some embodiments, R is isopropyl. In some embodiments, R is optionally substituted C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} aliphatic. In some embodiments, R is optionally substituted C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} alkyl. In some embodiments, R is optionally substituted linear C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} alkyl. In some embodiments, R is linear C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} alkyl. In some embodiments, each R" is independently R as described herein, for example, in some embodiments, each R" is methyl. In some embodiments, R" is optionally substituted aryl. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is p-methylphenyl. In some embodiments, R is benzyl. In some embodiments, R is optionally substituted heteroaryl. In some embodiments, R is optionally substituted 1,3-diazolyl. In some embodiments, R is optionally substituted 2-(1,3)-diazolyl. In some embodiments, R is optionally substituted 1-methyl-2-(1,3)-diazolyl. In some embodiments, an occurrence of R" is $-N(R')_2$. In some embodiments, R" is $-N(CH_3)_2$. In some embodiments, an occurrence of R", e.g., in $-P(O)(R")_2$, is $-OR'$, wherein R' is as described herein. In some embodiments, R' is R as described herein. In some embodiments, is optionally substituted C_{1-6} aliphatic. In some embodiments, is optionally substituted C_{1-6} alkyl. In some embodiments, R" is $-OCH_3$. In some embodiments, each R" is $-OR'$ as described herein. In some embodiments, each R" is $-OCH_3$. In some embodiments, each R" is $-OH$. In some embodiments, a linkage is $-OP(O)(NHP(O)(OH)_2)O-$. In some embodiments, a linkage is $-OP(O)(NHP(O)(OCH_3)_2)O-$. In some embodiments, a linkage is $-OP(O)(NHP(O)(CH_3)_2)O-$.

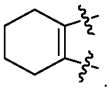
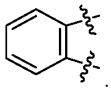
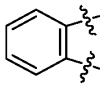
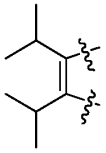
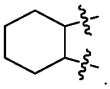
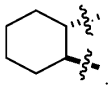
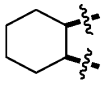
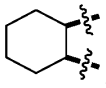
In some embodiments, $-N(R")_2$ is $-N(R')_2$. In some embodiments, $-N(R")_2$ is $-NHR$. In some embodiments, $-N(R")_2$ is $-NHC(O)R$. In some embodiments, $-N(R")_2$ is $-NHC(O)OR$. In some embodiments, $-N(R")_2$ is $-NHS(O)_2R$.

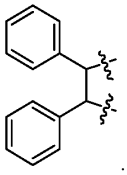
In some embodiments, an internucleotidic linkage is a phosphoryl guanidine internucleotidic linkage. In some embodiments, an internucleotidic linkage comprises $-X-R^L$ as described herein. In some embodiments, $-X-R^L$ is $-N=C(-L^L-R^L)_2$. In some embodiments, $-X-R^L$ is $-N=C[N(R^L)_2]_2$. In some embodiments, $-X-R^L$ is $-N=C[NR'R^L]_2$. In some embodiments, $-X-R^L$ is $-N=C[N(R')_2]_2$. In some embodiments, $-X-R^L$ is $-N=C[N(R^L)_2](CHR^{L1}R^{L2})$, wherein each of R^{L1} and R^{L2} is independently as described herein. In some embodiments, $-X-R^L$ is $-N=C(NR'R^L)(CHR^{L1}R^{L2})$, wherein each of R^{L1} and R^{L2} is

independently as described herein. In some embodiments, $-X-R^L$ is $-N=C(NR'R^L)(CR'R^{L1}R^{L2})$, wherein each of R^{L1} and R^{L2} is independently as described herein. In some embodiments, $-X-R^L$ is $-N=C[N(R')_2](CHR'R^{L2})$. In some embodiments, $-X-R^L$ is $-N=C[N(R^L)_2](R^L)$. In some embodiments, $-X-R^L$ is $-N=C(NR'R^L)(R^L)$. In some embodiments, $-X-R^L$ is $-N=C(NR'R^L)(R')$. In some embodiments, $-X-R^L$ is $-N=C[N(R')_2](R')$. In some embodiments, $-X-R^L$ is $-N=C(NR'R^{L1})(NR'R^{L2})$, wherein each R^{L1} and R^{L2} is independently R^L, and each R' and R^L is independently as described herein. In some embodiments, $-X-R^L$ is $-N=C(NR'R^{L1})(NR'R^{L2})$, wherein variable is independently as described herein. In some embodiments, $-X-R^L$ is $-N=C(NR'R^{L1})(CHR'R^{L2})$, wherein variable is independently as described herein. In some embodiments, $-X-R^L$ is $-N=C(NR'R^{L1})(R')$, wherein variable is independently as described herein. In some embodiments, each R' is independently R. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is methyl. In some embodiments, $-X-R^L$ is

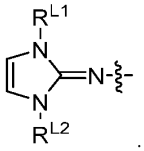


. In some embodiments, two groups selected from R', R^L, R^{L1}, R^{L2}, etc. (in some embodiments, on the same atom (e.g., $-N(R')_2$, or $-NR'R^L$, or $-N(R^L)^2$, wherein R' and R^L can independently be R as described herein), etc.), or on different atoms (e.g., the two **R'** in $-N=C(N\mathbf{R'}R^L)(C\mathbf{R'}R^{L1}R^{L2})$ or $-N=C(N\mathbf{R'}R^{L1})(N\mathbf{R'}R^{L2})$; can also be two other variables that can be R, e.g., R^L, R^{L1}, R^{L2}, etc.)) are independently R and are taken together with their intervening atoms to form a ring as described herein. In some embodiments, two of R, R', R^L, R^{L1}, or R^{L2} on the same atom, e.g., of $-N(R')_2$, $-N(R^L)_2$, $-NR'R^L$, $-NR'R^{L1}$, $-NR'R^{L2}$, $-CR'R^{L1}R^{L2}$, etc., are taken together to form a ring as described herein. In some embodiments, two R', R^L, R^{L1}, or R^{L2} on two different atoms, e.g., the two **R'** in $-N=C(N\mathbf{R'}R^L)(C\mathbf{R'}R^{L1}R^{L2})$, $-N=C(N\mathbf{R'}R^{L1})(N\mathbf{R'}R^{L2})$, etc. are taken together to form a ring as described herein. In some embodiments, a formed ring is an optionally substituted 3-20 (e.g., 3-15, 3-12, 3-10, 3-9, 3-8, 3-7, 3-6, 4-15, 4-12, 4-10, 4-9, 4-8, 4-7, 4-6, 5-15, 5-12, 5-10, 5-9, 5-8, 5-7, 5-6, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc.) monocyclic, bicyclic or tricyclic ring having 0-5 additional heteroatoms. In some embodiments, a formed ring is monocyclic as described herein. In some embodiments, a formed ring is an optionally substituted 5-10 membered monocyclic ring. In some embodiments, a formed ring is bicyclic. In some embodiments, a formed ring is polycyclic. In some embodiments, two groups that are or can be R (e.g., the two **R'** in $-N=C(N\mathbf{R'}R^L)(C\mathbf{R'}R^{L1}R^{L2})$ or $-N=C(N\mathbf{R'}R^{L1})(N\mathbf{R'}R^{L2})$, the two **R'**

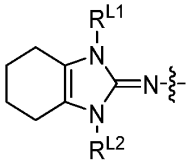
in −N=C(N**R'**R^{L})(C**R'**$R^{L1}R^{L2}$), −N=C(N**R'**R^{L1})(N**R'**R^{L2}), etc.) are taken together to form an optionally substituted bivalent hydrocarbon chain, e.g., an optionally substituted C_{1-20} aliphatic chain, optionally substituted −(CH_2)n− wherein n is 1-20 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20). In some embodiments, a hydrocarbon chain is saturated. In some embodiments, a hydrocarbon chain is partially unsaturated. In some embodiments, a hydrocarbon chain is unsaturated. In some embodiments, two groups that are or can be R (e.g., the two **R'** in −N=C(N**R'**R^{L})(C**R'**$R^{L1}R^{L2}$) or −N=C(N**R'**R^{L1})(N**R'**R^{L2}), the two **R'** in −N=C(N**R'**R^{L})(C**R'**$R^{L1}R^{L2}$), −N=C(N**R'**R^{L1})(N**R'**R^{L2}), etc.) are taken together to form an optionally substituted bivalent heteroaliphatic chain, e.g., an optionally substituted C_{1-20} heteroaliphatic chain having 1-10 heteroatoms. In some embodiments, a heteroaliphatic chain is saturated. In some embodiments, a heteroaliphatic chain is partially unsaturated. In some embodiments, a heteroaliphatic chain is unsaturated. In some embodiments, a chain is optionally substituted −(CH_2)−. In some embodiments, a chain is optionally substituted −$(CH_2)_2$−. In some embodiments, a chain is optionally substituted −(CH_2)−. In some embodiments, a chain is optionally substituted −$(CH_2)_2$−. In some embodiments, a chain is optionally substituted −$(CH_2)_3$−. In some embodiments, a chain is optionally substituted −$(CH_2)_4$−. In some embodiments, a chain is optionally substituted −$(CH_2)_5$−. In some embodiments, a chain is optionally substituted −$(CH_2)_6$−. In some embodiments, a chain is optionally substituted −CH=CH−. In some embodiments, a chain is optionally substituted  . In some embodiments, a chain is optionally substituted  . In some embodiments, a chain is optionally substituted  . In some embodiments, a chain is optionally substituted  . In some embodiments, a chain is optionally substituted  . In some embodiments, a chain is optionally substituted  . In some embodiments, a chain is optionally substituted  . In some embodiments, a chain is optionally substituted  . In some embodiments, a chain is optionally substituted



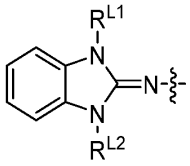
. In some embodiments, two of R, R', R^L, R^{L1}, R^{L2}, etc. on different atoms are taken together to form a ring as described herein. For examples, in some embodiments, $-X-R^L$ is



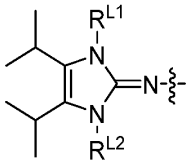
. In some embodiments, $-X-R^L$ is



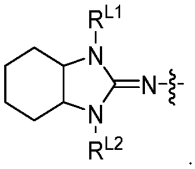
. In some embodiments, $-X-R^L$ is



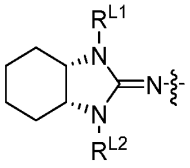
. In some embodiments, $-X-R^L$ is



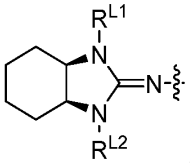
. In some embodiments, $-X-R^L$ is



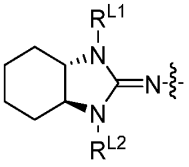
. In some embodiments, $-X-R^L$ is



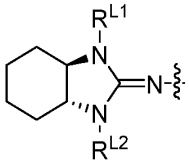
. In some embodiments, $-X-R^L$ is



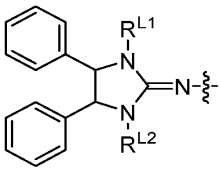
. In some embodiments, $-X-R^L$ is



. In some embodiments, $-X-R^L$ is



. In some embodiments, $-X-R^L$ is

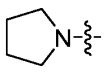


. In some embodiments, $-N(R')_2$, $-N(R)_2$, $-N(R^L)_2$, $-NR'R^L$, $-NR'R^{L1}$, $-NR'R^{L2}$, $-NR^{L1}R^{L2}$, etc. is a formed ring. In some embodiments, a ring is optionally substituted

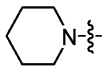
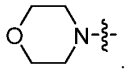
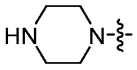
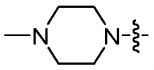
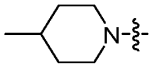
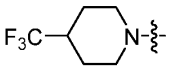
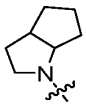
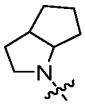
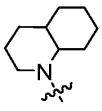
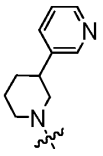
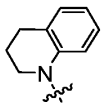
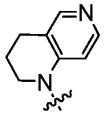
. In some embodiments, a ring is optionally substituted



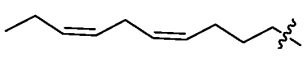
. In some embodiments, a ring is optionally substituted

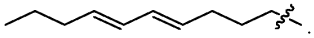
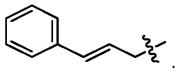
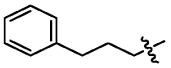
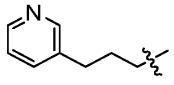
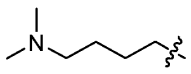
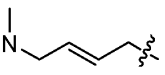
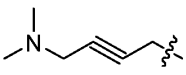


. In some embodiments, a ring

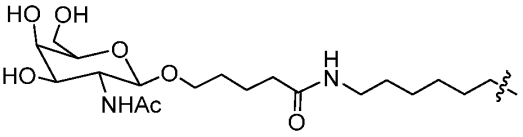
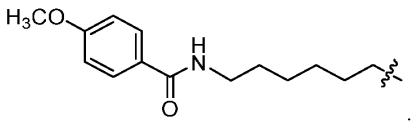
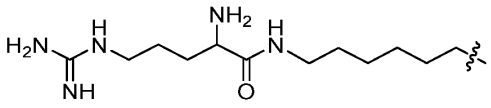
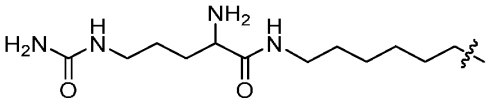
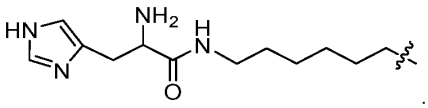
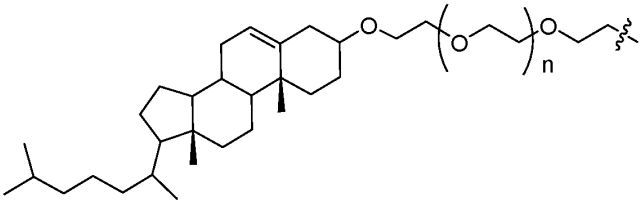
is optionally substituted  . In some embodiments, a ring is optionally substituted  . In some embodiments, a ring is optionally substituted  . In some embodiments, a ring is optionally substituted  . In some embodiments, a ring is optionally substituted  . In some embodiments, a ring is optionally substituted  . In some embodiments, a ring is optionally substituted  . In some embodiments, a ring is optionally substituted  . In some embodiments, a ring is optionally substituted  . In some embodiments, a ring is optionally substituted  . In some embodiments, a ring is optionally substituted  . In some embodiments, a ring is optionally substituted  .

In some embodiments, R^{L1} and R^{L2} are the same. In some embodiments, R^{L1} and R^{L2} are different. In some embodiments, each of R^{L1} and R^{L2} is independently R^L as described herein, e.g., below.

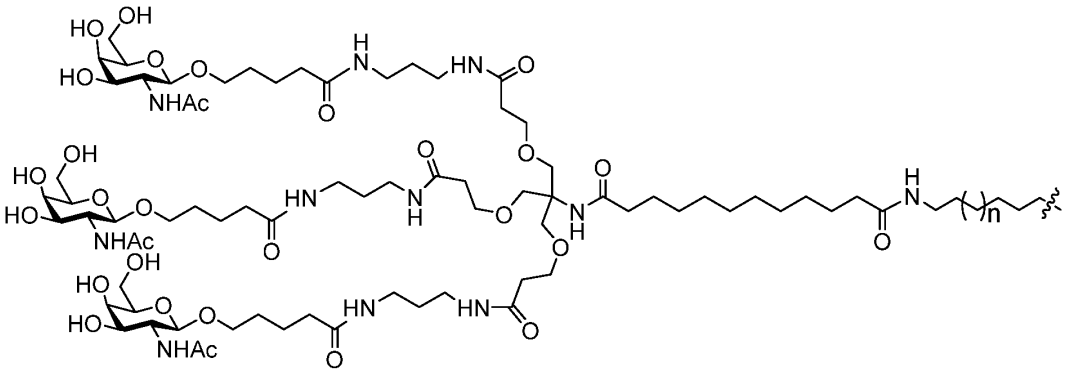
In some embodiments, R^L is optionally substituted C_{1-30} aliphatic. In some embodiments, R^L is optionally substituted C_{1-30} alkyl. In some embodiments, R^L is linear. In some embodiments, R^L is optionally substituted linear C_{1-30} alkyl. In some embodiments, R^L is optionally substituted C_{1-6} alkyl. In some embodiments, R^L is methyl. In some embodiments, R^L is ethyl. In some embodiments, R^L is n-propyl. In some embodiments, R^L is isopropyl. In some embodiments, R^L is n-butyl. In some embodiments, R^L is tert-butyl. In some embodiments, R^L is (E)−CH_2−CH=CH−CH_2−CH_3. In some embodiments, R^L is (Z)−CH_2−CH=CH−CH_2−CH_3. In some embodiments, R^L is  . In

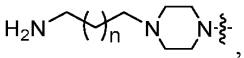
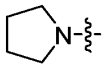
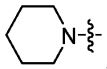
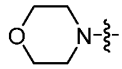
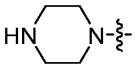
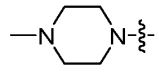
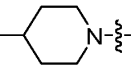
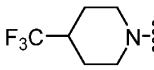
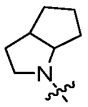
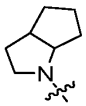
some embodiments, R^L is  . In some embodiments, R^L is $CH_3(CH_2)_2C{\equiv}CC{\equiv}C(CH_2)_3-$. In some embodiments, R^L is $CH_3(CH_2)_5C{\equiv}C-$. In some embodiments, R^L optionally substituted aryl. In some embodiments, R^L is optionally substituted phenyl. In some embodiments, R^L is phenyl substituted with one or more halogen. In some embodiments, R^L is phenyl optionally substituted with halogen, $-N(R')$, or $-N(R')C(O)R'$. In some embodiments, R^L is phenyl optionally substituted with $-Cl$, $-Br$, $-F$, $-N(Me)_2$, or $-NHCOCH_3$. In some embodiments, R^L is $-L^L-R'$, wherein L^L is an optionally substituted C_{1-20} saturated, partially unsaturated or unsaturated hydrocarbon chain. In some embodiments, such a hydrocarbon chain is linear. In some embodiments, such a hydrocarbon chain is unsubstituted. In some embodiments, L^L is $(E)-CH_2-CH=CH-$. In some embodiments, L^L is $-CH_2-C{\equiv}C-CH_2-$. In some embodiments, L^L is $-(CH_2)_3-$. In some embodiments, L^L is $-(CH_2)_4-$. In some embodiments, L^L is $-(CH_2)_n-$, wherein n is 1-30 (e.g., 1-20, 5-30, 6-30, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30, etc.). In some embodiments, R' is optionally substituted aryl as described herein. In some embodiments, R' is optionally substituted phenyl. In some embodiments, R' is phenyl. In some embodiments, R' is optionally substituted heteroaryl as described herein. In some embodiments, R' is 2'-pyridinyl. In some embodiments, R' is 3'-pyridinyl. In some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is $-L^L-N(R')_2$, wherein each variable is independently as described herein. In some embodiments, each R' is independently C_{1-6} aliphatic as described herein. In some embodiments, $-N(R')_2$ is $-N(CH_3)_2$. In some embodiments, $-N(R')_2$ is $-NH_2$. In some embodiments, R^L is $-(CH_2)_n-N(R')_2$, wherein n is 1-30 (e.g., 1-20, 5-30, 6-30, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30, etc.). In some embodiments, R^L is $-(CH_2CH_2O)_n-CH_2CH_2-N(R')_2$, wherein n is 1-30 (e.g., 1-20, 5-30, 6-30, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30, etc.). In some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is $-(CH_2)_n-NH_2$. In some embodiments, R^L is $-(CH_2CH_2O)_n-CH_2CH_2-NH_2$. In some embodiments, R^L is $-(CH_2CH_2O)_n-CH_2CH_2-R'$, wherein n is 1-30 (e.g., 1-20, 5-30, 6-30, 1,

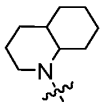
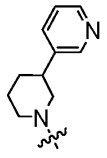
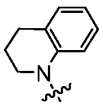
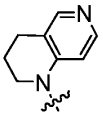
2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30, etc.). In some embodiments, R^L is $-(CH_2CH_2O)_n-CH_2CH_2CH_3$, wherein n is 1-30 (e.g., 1-20, 5-30, 6-30, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30, etc.). In some embodiments, R^L is $-(CH_2CH_2O)_n-CH_2CH_2OH$, wherein n is 1-30 (e.g., 1-20, 5-30, 6-30, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30, etc.). In some embodiments, R^L is or comprises a carbohydrate moiety, e.g., GalNAc. In some embodiments, R^L is $-L^L-$GalNAc.

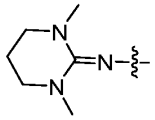
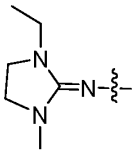
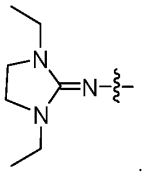
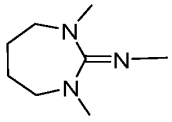
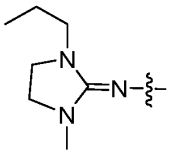
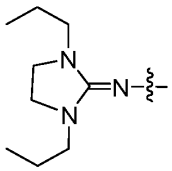
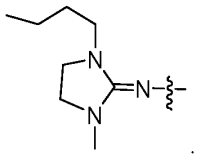
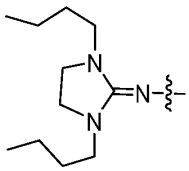
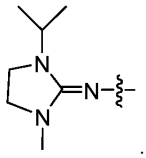
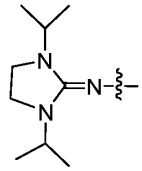
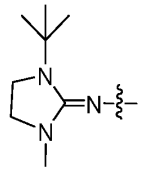
In some embodiments, R^L is  . In some embodiments, one or more methylene units of L^L are independently replaced with $-Cy-$ (e.g., optionally substituted 1,4-phenylene, a 3-30 membered bivalent optionally substituted monocyclic, bicyclic, or polycyclic cycloaliphatic ring, etc.), $-O-$, $-N(R')-$ (e.g., $-NH$), $-C(O)-$, $-C(O)N(R')-$ (e.g., $-C(O)NH-$), $-C(NR')-$ (e.g., $-C(NH)-$), $-N(R')C(O)(N(R')-$ (e.g., $-NHC(O)NH-$), $-N(R')C(NR')(N(R')-$ (e.g., $-NHC(NH)NH-$), $-(CH_2CH_2O)_n-$, etc. For example, in some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is  . In some embodiments, R^L is 

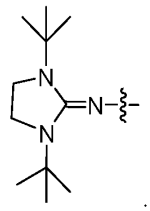
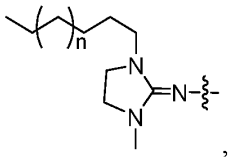
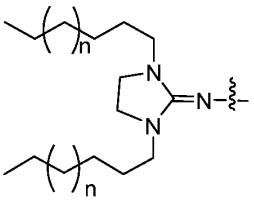
wherein n is 0-20. In some embodiments, R^L is or comprises one or more additional chemical moieties (e.g., carbohydrate moieties, GalNAc moieties, etc.) optionally substituted connected through a linker (which can be bivalent or polyvalent). For example, in some embodiments, R^L is

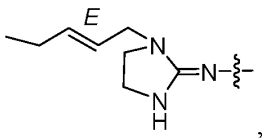
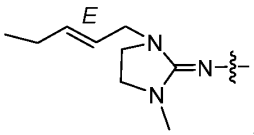
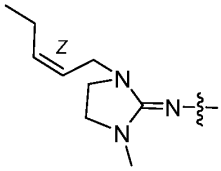
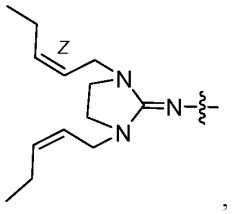


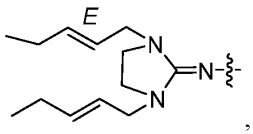
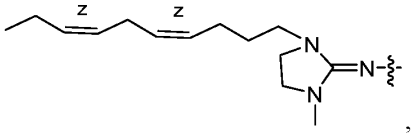
, wherein n is 0-20. In some embodiments, R^L is  , wherein n is 0-20. In some embodiments, R^L is R' as described herein. As described herein, many variable can independently be R'. In some embodiments, R' is R as described herein. As described herein, various variables can independently be R. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is methyl. In some embodiments, R is optionally substituted cycloaliphatic. In some embodiments, R is optionally substituted cycloalkyl. In some embodiments, R is optionally substituted aryl. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is optionally substituted heteroaryl. In some embodiments, R is optionally substituted heterocyclyl. In some embodiments, R is optionally substituted C_{1-20} heterocyclyl having 1-5 heteroatoms, e.g., one of which is nitrogen. In some embodiments, R is optionally substituted  . In some embodiments, R is optionally substituted  . In some embodiments, R is optionally substituted  . In some embodiments, R is optionally substituted  . In some embodiments, R is optionally substituted  . In some embodiments, R is optionally substituted  . In some embodiments, R is optionally substituted  . In some embodiments, R is optionally substituted  . In some embodiments, R is optionally substituted  . In some embodiments, R is optionally substituted  . In some embodiments, R is optionally substituted  In

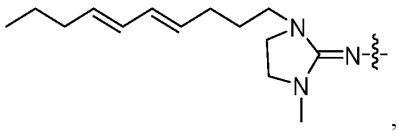
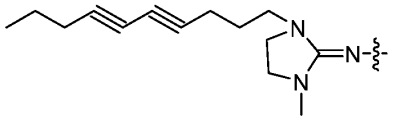
some embodiments, R is optionally substituted  . In some embodiments, R is optionally substituted  . In some embodiments, R is optionally substituted  . In some embodiments, R is optionally substituted  .

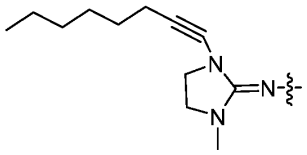
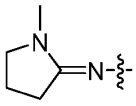
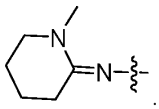
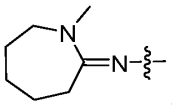
In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is . In some embodiments, $-X-R^L$ is . In some embodiments, $-X-R^L$ is  .

some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  , wherein n is 1-20. In some embodiments, $-X-R^L$ is  , wherein n is 1-20. In some embodiments, $-X-R^L$ is selected from:

 ,  ,  ,  ,

 ,  ,

 ,  and

 . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  .

In some embodiments, R^L is R" as described herein. In some embodiments, R^L is R as described herein.

In some embodiments, R" or R^L is or comprises an additional chemical moiety. In some embodiments, R" or R^L is or comprises an additional chemical moiety, wherein the additional chemical moiety is or comprises a carbohydrate moiety. In some embodiments, R" or R^L is or comprises a GalNAc. In some embodiments, R^L or R" is replaced with, or is utilized to connect to, an additional chemical moiety.

In some embodiments, X is –O–. In some embodiments, X is –S–. In some embodiments, X is $-L^L-N(-L^L-R^L)-L^L-$. In some embodiments, X is $-N(-L^L-R^L)-L^L-$. In some embodiments, X is $-L^L-N(-L^L-R^L)-$. In some embodiments, X is $-N(-L^L-R^L)-$. In some embodiments, X is $-L^L-N=C(-L^L-R^L)-L^L-$. In some embodiments, X is $-N=C(-L^L-R^L)-L^L-$. In some embodiments, X is $-L^L-N=C(-L^L-R^L)-$. In some embodiments, X is $-N=C(-L^L-R^L)-$. In some embodiments, X is L^L. In some embodiments, X is a covalent bond.

In some embodiments, Y is a covalent bond. In some embodiments, Y is −O−. In some embodiments, Y is −N(R')−. In some embodiments, Z is a covalent bond. In some embodiments, Z is −O−. In some embodiments, Z is −N(R')−. In some embodiments, R' is R. In some embodiments, R is −H. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is methyl. In some embodiments, R is ethyl. In some embodiments, R is propyl. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is phenyl.

As described herein, various variables in structures in the present disclosure can be or comprise R. Suitable embodiments for R are described extensively in the present disclosure. As appreciated by those skilled in the art, R embodiments described for a variable that can be R may also be applicable to another variable that can be R. Similarly, embodiments described for a component/moiety (e.g., L) for a variable may also be applicable to other variables that can be or comprise the component/moiety.

In some embodiments, R" is R'. In some embodiments, R" is $-N(R')_2$.

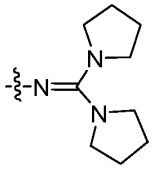
In some embodiments, $-X-R^L$ is −SH. In some embodiments, $-X-R^L$ is −OH.

In some embodiments, $-X-R^L$ is $-N(R')_2$. In some embodiments, each R' is independently optionally substituted C_{1-6} aliphatic. In some embodiments, each R' is independently methyl.

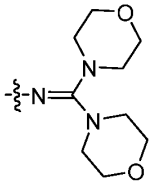
In some embodiments, a non-negatively charged internucleotidic linkage has the structure of $-OP(=O)(-N=C((N(R')_2)_2-O-$. In some embodiments, a R' group of one $N(R')_2$ is R, a R' group of the other $N(R')_2$ is R, and the two R groups are taken together with their

intervening atoms to form an optionally substituted ring, e.g., a 5-membered ring as in n001. In some embodiments, each R' is independently R, wherein each R is independently optionally substituted C_{1-6} aliphatic.

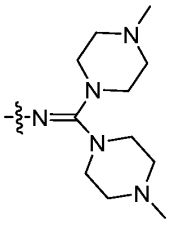
In some embodiments, $-X-R^L$ is $-N=C(-L^L-R')_2$. In some embodiments, $-X-R^L$ is $-N=C(-L^{L1}-L^{L2}-L^{L3}-R')_2$, wherein each L^{L1}, L^{L2} and L^{L3} is independently L", wherein each L" is independently a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-10} aliphatic group and a C_{1-10} heteroaliphatic group having 1-5 heteroatoms, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms, $-C(R')_2-$, $-Cy-$, $-O-$, $-S-$, $-S-S-$, $-N(R')-$, $-C(O)-$, $-C(S)-$, $-C(NR')-$, $-C(O)N(R')-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)O-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, $-C(O)S-$, $-C(O)O-$, $-P(O)(OR')-$, $-P(O)(SR')-$, $-P(O)(R')-$, $-P(O)(NR')-$, $-P(S)(OR')-$, $-P(S)(SR')-$, $-P(S)(R')-$, $-P(S)(NR')-$, $-P(R')-$, $-P(OR')-$, $-P(SR')-$, $-P(NR')-$, $-P(OR')[B(R')_3]-$, $-OP(O)(OR')O-$, $-OP(O)(SR')O-$, $-OP(O)(R')O-$, $-OP(O)(NR')O-$, $-OP(OR')O-$, $-OP(SR')O-$, $-OP(NR')O-$, $-OP(R')O-$, or $-OP(OR')[B(R')_3]O-$, and one or more nitrogen or carbon atoms are optionally and independently replaced with Cy^L. In some embodiments, L^{L2} is $-Cy-$. In some embodiments, L^{L1} is a covalent bond. In some embodiments, L^{L3} is a covalent bond. In some embodiments, $-X-R^L$ is $-N=C(-L^{L1}-Cy-L^{L3}-R')_2$. In some embodiments, $-X-R^L$ is $-N=C(-L^{L1}-Cy-L^{L3}-R')_2$. In some embodiments, $-X-R^L$ is



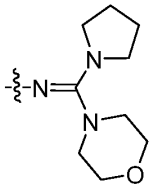
. In some embodiments, $-X-R^L$ is



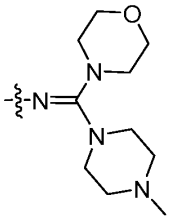
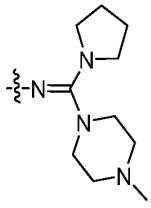
. In some embodiments, $-X-R^L$ is



. In some embodiments, $-X-R^L$ is

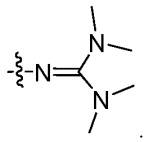


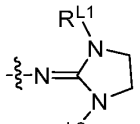
. In some embodiments,

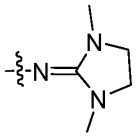
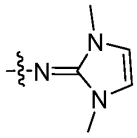
$-X-R^L$ is  . In some embodiments, $-X-R^L$ is  .

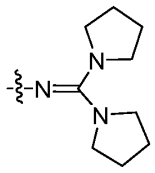
In some embodiments, as utilized in the present disclosure, L is covalent bond. In some embodiments, L is a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms, $-C(R')_2-$, −Cy−, −O−, −S−, −S−S−, −N(R')−, −C(O)−, −C(S)−, −C(NR')−, −C(O)N(R')−, −N(R')C(O)N(R')−, −N(R')C(O)O−, −S(O)−, $-S(O)_2-$, $-S(O)_2N(R')-$, −C(O)S−, −C(O)O−, −P(O)(OR')−, −P(O)(SR')−, −P(O)(R')−, −P(O)(NR')−, −P(S)(OR')−, −P(S)(SR')−, −P(S)(R')−, −P(S)(NR')−, −P(R')−, −P(OR')−, −P(SR')−, −P(NR')−, $-P(OR')[B(R')_3]-$, −OP(O)(OR')O−, −OP(O)(SR')O−, −OP(O)(R')O−, −OP(O)(NR')O−, −OP(OR')O−, −OP(SR')O−, −OP(NR')O−, −OP(R')O−, or $-OP(OR')[B(R')_3]O-$, and one or more nitrogen or carbon atoms are optionally and independently replaced with Cy^L. In some embodiments, L is a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from —C≡C—, $-C(R')_2-$, −Cy−, −O−, −S−, −S−S−, −N(R')−, −C(O)−, −C(S)−, −C(NR')−, −C(O)N(R')−, −N(R')C(O)N(R')−, −N(R')C(O)O−, −S(O)−, $-S(O)_2-$, $-S(O)_2N(R')-$, −C(O)S−, −C(O)O−, −P(O)(OR')−, −P(O)(SR')−, −P(O)(R')−, −P(O)(NR')−, −P(S)(OR')−, −P(S)(SR')−, −P(S)(R')−, −P(S)(NR')−, −P(R')−, −P(OR')−, −P(SR')−, −P(NR')−, $-P(OR')[B(R')_3]-$, −OP(O)(OR')O−, −OP(O)(SR')O−, −OP(O)(R')O−, −OP(O)(NR')O−, −OP(OR')O−, −OP(SR')O−, −OP(NR')O−, −OP(R')O−, or $-OP(OR')[B(R')_3]O-$, and one or more nitrogen or carbon atoms are optionally and independently replaced with Cy^L. In some embodiments, L is a bivalent, optionally substituted, linear or branched group selected from a C_{1-10} aliphatic group and a C_{1-10} heteroaliphatic group having 1-10 heteroatoms, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from —C≡C—, $-C(R')_2-$, −Cy−, −O−, −S−, −S−S−, −N(R')−, −C(O)−, −C(S)−, −C(NR')−, −C(O)N(R')−, −N(R')C(O)N(R')−, −N(R')C(O)O−, −S(O)−, $-S(O)_2-$,

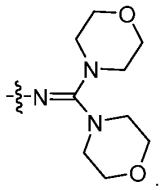
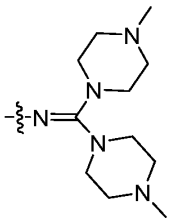
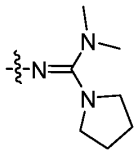
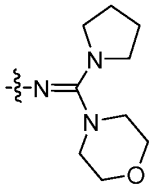
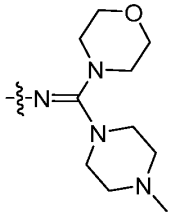
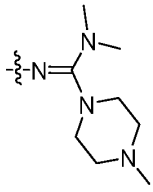
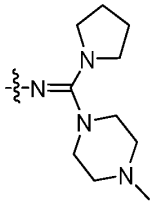
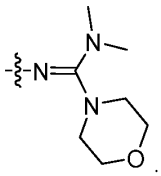
−S(O)$_2$N(R')−, −C(O)S−, −C(O)O−, −P(O)(OR')−, −P(O)(SR')−, −P(O)(R')−, −P(O)(NR')−, −P(S)(OR')−, −P(S)(SR')−, −P(S)(R')−, −P(S)(NR')−, −P(R')−, −P(OR')−, −P(SR')−, −P(NR')−, −P(OR')[B(R')$_3$]−, −OP(O)(OR')O−, −OP(O)(SR')O−, −OP(O)(R')O−, −OP(O)(NR')O−, −OP(OR')O−, −OP(SR')O−, −OP(NR')O−, −OP(R')O−, or −OP(OR')[B(R')$_3$]O−, and one or more nitrogen or carbon atoms are optionally and independently replaced with Cy^L. In some embodiments, one or more methylene units are optionally and independently replaced by an optionally substituted group selected from —C≡C—, −C(R')$_2$−, −Cy−, −O−, −S−, −S−S−, −N(R')−, −C(O)−, −C(S)−, −C(NR')−, −C(O)N(R')−, −N(R')C(O)N(R')−, −N(R')C(O)O−, −S(O)−, −S(O)$_2$−, −S(O)$_2$N(R')−, −C(O)S−, or −C(O)O−.

In some embodiments, an internucleotidic linkage is a phosphoryl guanidine internucleotidic linkage. In some embodiments, −X−R^L is −N=C[N(R')$_2$]$_2$. In some embodiments, each R' is independently R. In some embodiments, R is optionally substituted C$_{1-6}$ aliphatic. In some embodiments, R is methyl. In some embodiments, −X−R^L is  . In some embodiments, one R' on a nitrogen atom is taken with a R' on the other nitrogen to form a ring as described herein.

In some embodiments, −X−R^L is  , wherein R^1 and R^2 are independently R'.

In some embodiments, −X−R^L is  . In some embodiments, −X−R^L is  .

In some embodiments, two R' on the same nitrogen are taken together to form a ring as described herein. In some embodiments, −X−R^L is  . In some embodiments,

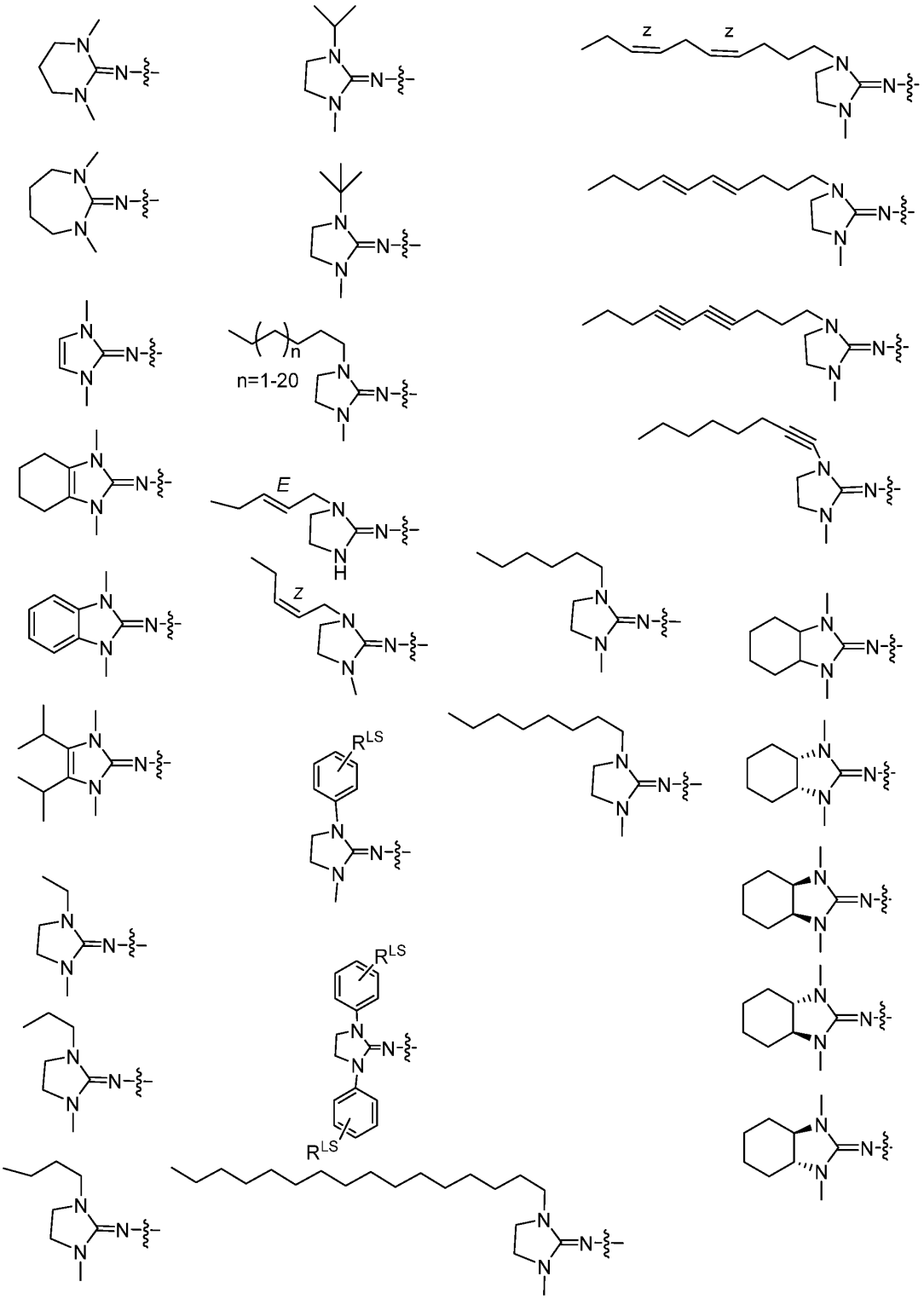
$-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  . In some embodiments, $-X-R^L$ is  .

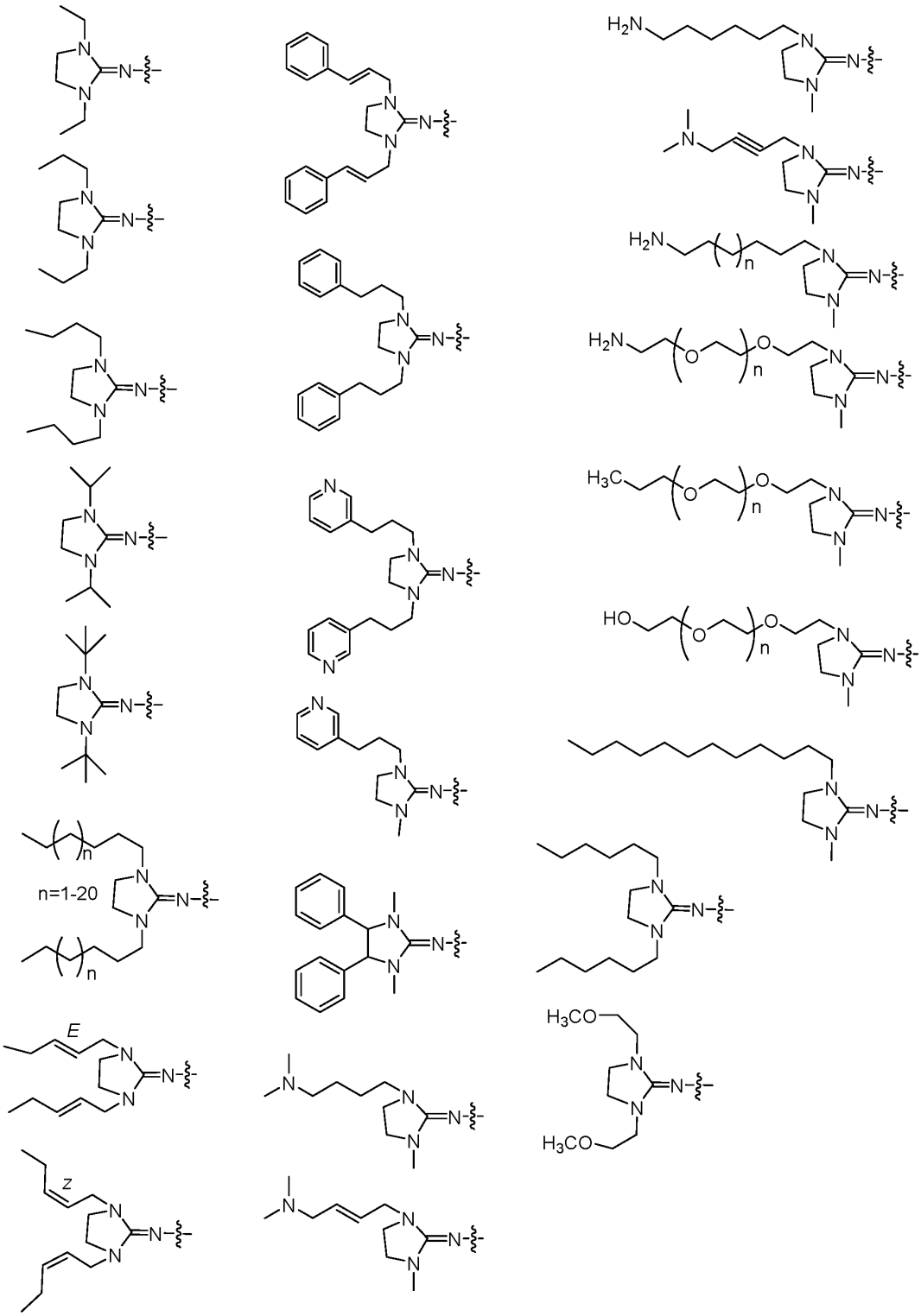
In some embodiments, $-X-R^L$ is R as described herein. In some embodiments, R is not hydrogen. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is methyl.

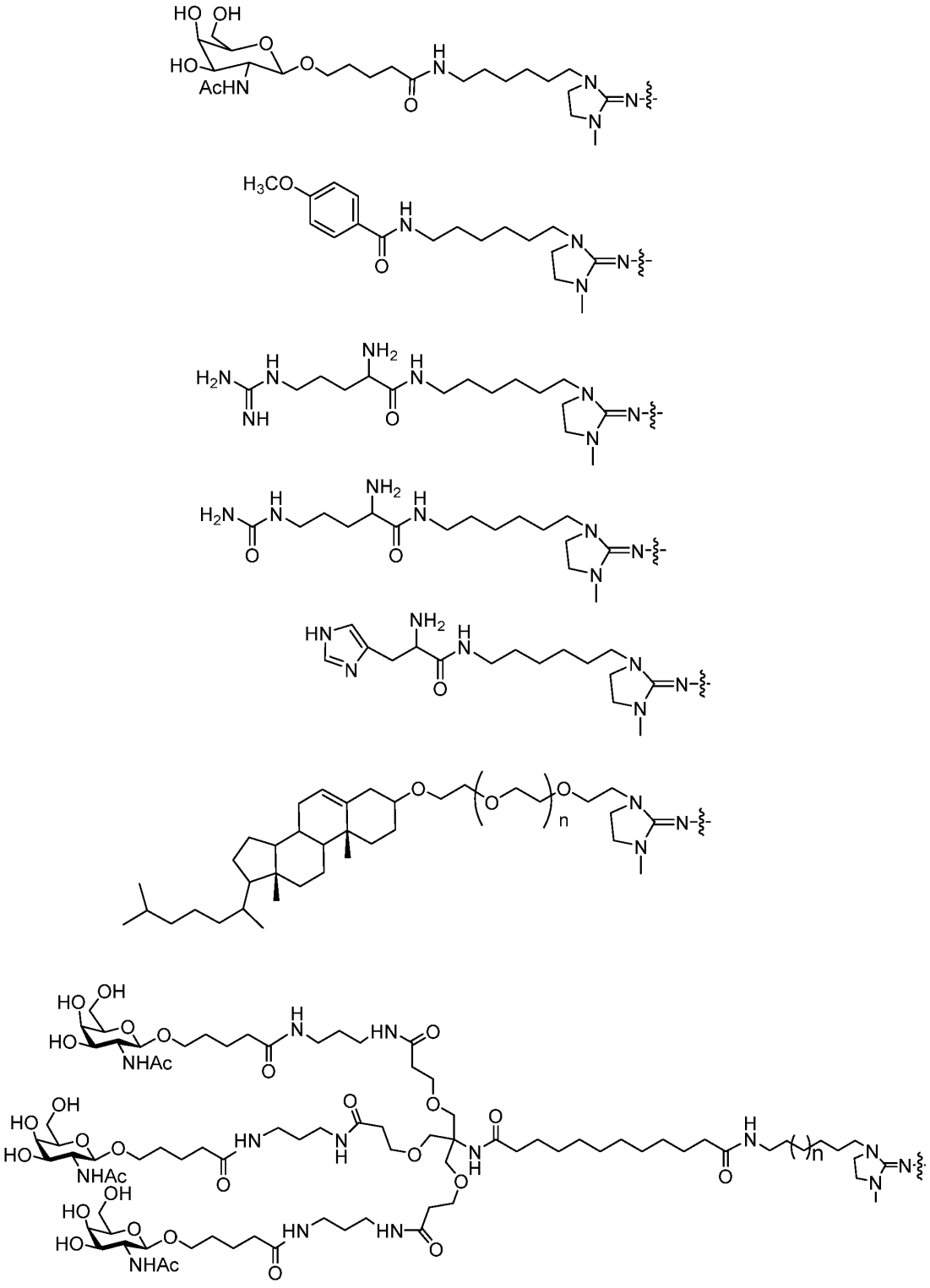
In some embodiments, $-X-R^L$ is selected from Tables below. In some embodiments, X is as described herein. In some embodiments, R^L is as described herein. In some embodiments, a linkage has the structure of $-Y-P^L(-X-R^L)-Z-$, wherein $-X-R^L$ is selected from Tables below, and each other variable is independently as described herein. In some embodiments, a linkage has the structure of or comprises $-P(O)(-X-R^L)-$, wherein $-X-R^L$ is selected from Tables below. In some embodiments, a linkage has the structure of or comprises $-P(S)(-X-R^L)-$, wherein $-X-R^L$ is selected from Tables below. In some embodiments, a linkage has the structure of or comprises $-P(-X-R^L)-$, wherein $-X-R^L$ is selected from Tables below. In some embodiments, a linkage has the structure of or comprises $-O-P(O)(-X-R^L)-O-$, wherein $-X-R^L$ is selected from Tables below. In some embodiments, a linkage has the structure of or comprises $-O-P(S)(-X-R^L)-O-$, wherein $-X-R^L$ is selected

from Tables below. In some embodiments, a linkage has the structure of or comprises −O−P(−X−R^L)−O−, wherein −X−R^L is selected from Tables below. In some embodiments, a linkage has the structure of −O−P(O)(−X−R^L)−O−, wherein −X−R^L is selected from Tables below. In some embodiments, a linkage has the structure of −O−P(S)(−X−R^L)−O−, wherein −X−R^L is selected from Tables below. In some embodiments, a linkage has the structure of −O−P(−X−R^L)−O−, wherein −X−R^L is selected from Tables below. In some embodiments, the Tables below, n is 0-20 or as described herein.

Table L-1. Certain useful moieties bonded to linkage phosphorus (e.g., −X−R^L).


n=1-20
E
Z
Z
Z
R^LS
R^LS
R^LS


n=1-20
E
Z



, wherein each R^{LS} is independently R^{s}. In some embodiments, each R^{LS} is independently −Cl, −Br, −F, $-N(Me)_2$, or $-NHCOCH_3$.

Table L-2. Certain useful moieties bonded to linkage phosphorus (e.g., −X−R^L).

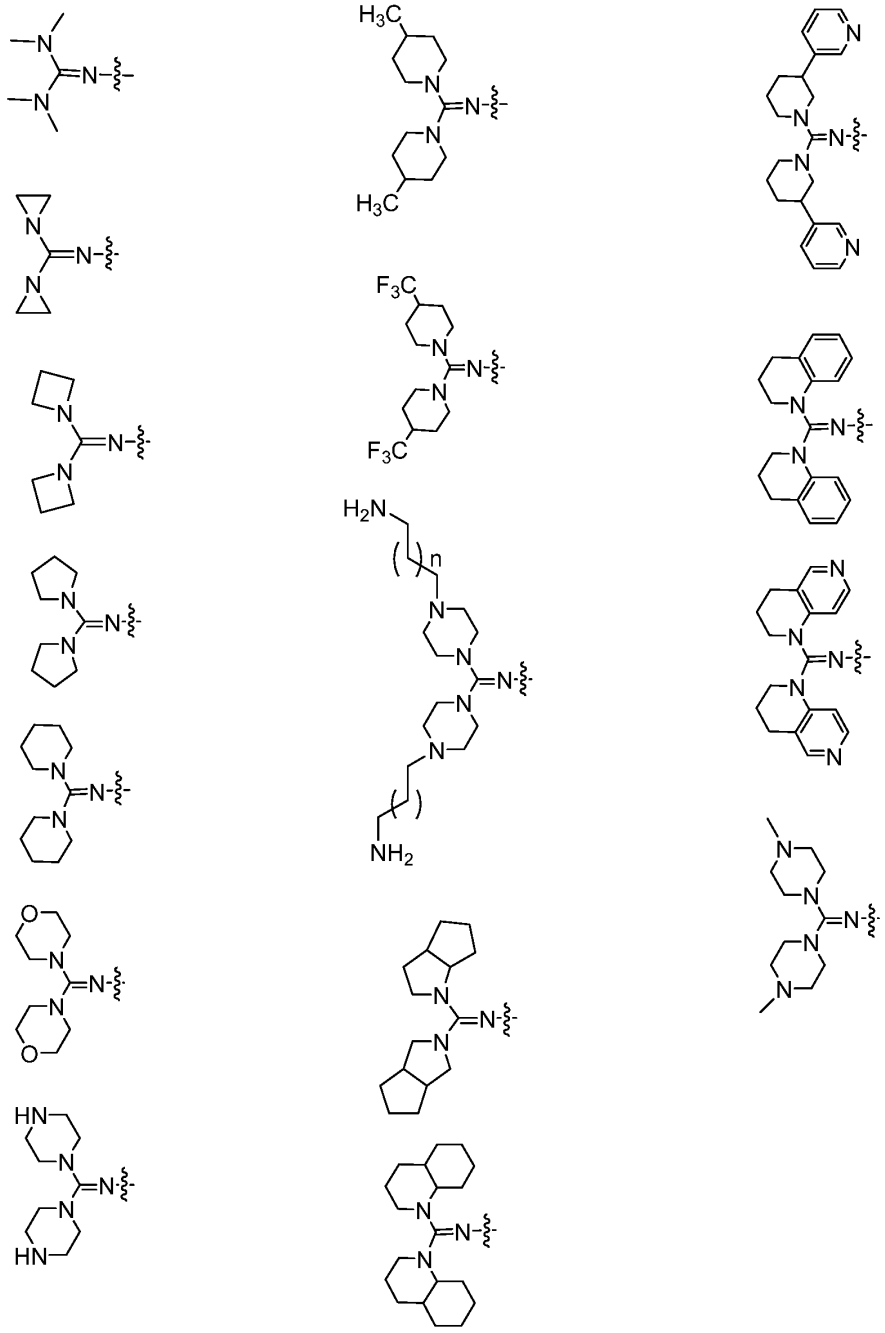


Table L-3. Certain useful moieties bonded to linkage phosphorus (e.g., −X−R^L).

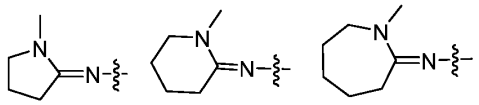
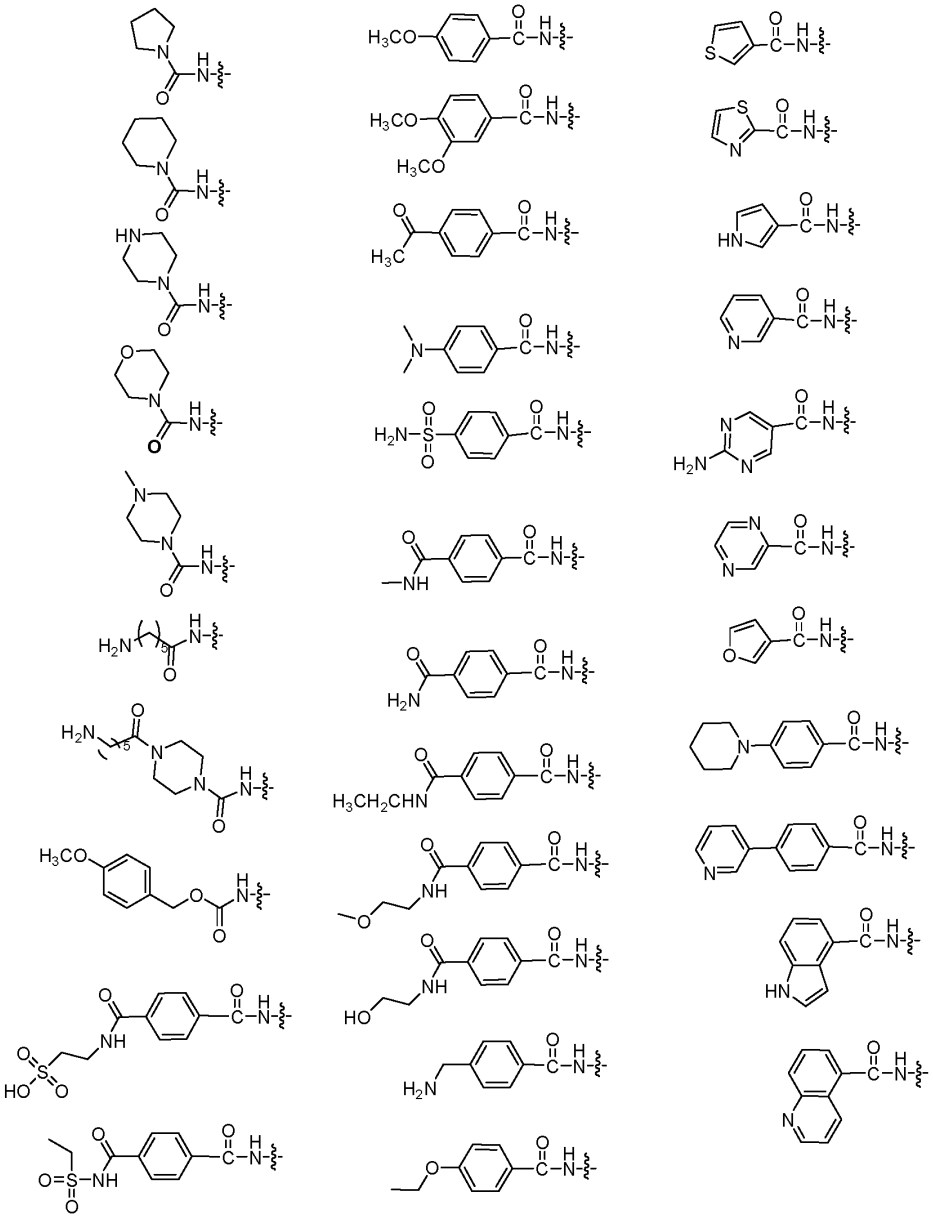


Table L-4. Certain useful moieties bonded to linkage phosphorus (e.g., −X−R^L).



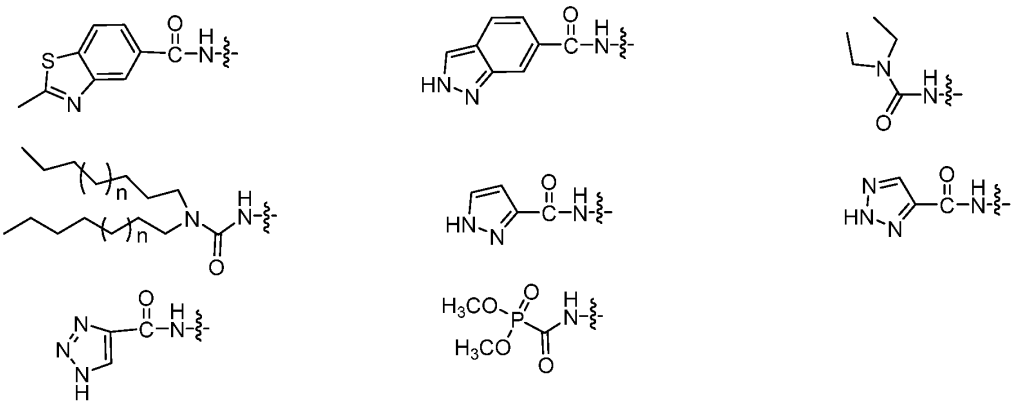
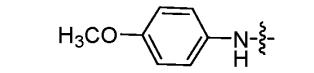
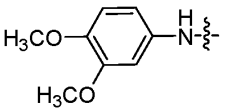
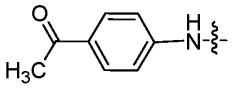
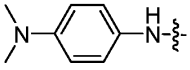
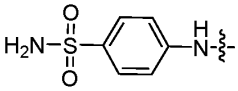
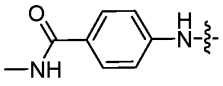
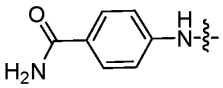
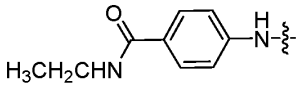
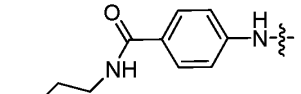
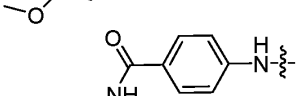
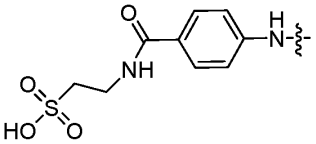
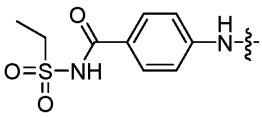
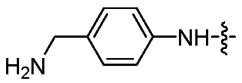
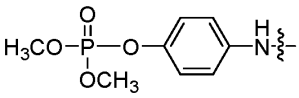
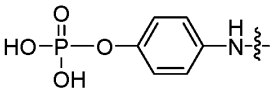
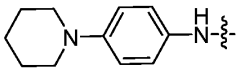
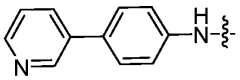
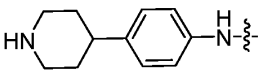
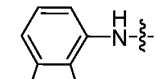
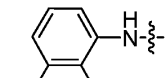
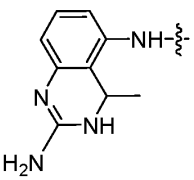
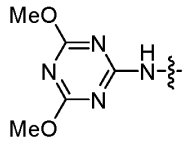
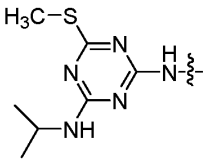
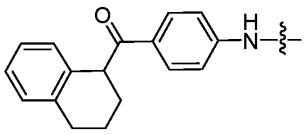
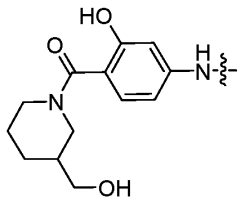
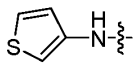
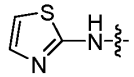
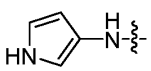
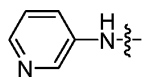
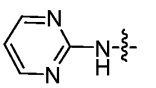
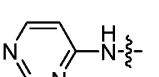
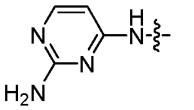


Table L-5. Certain useful moieties bonded to linkage phosphorus (e.g., −X−R^L).

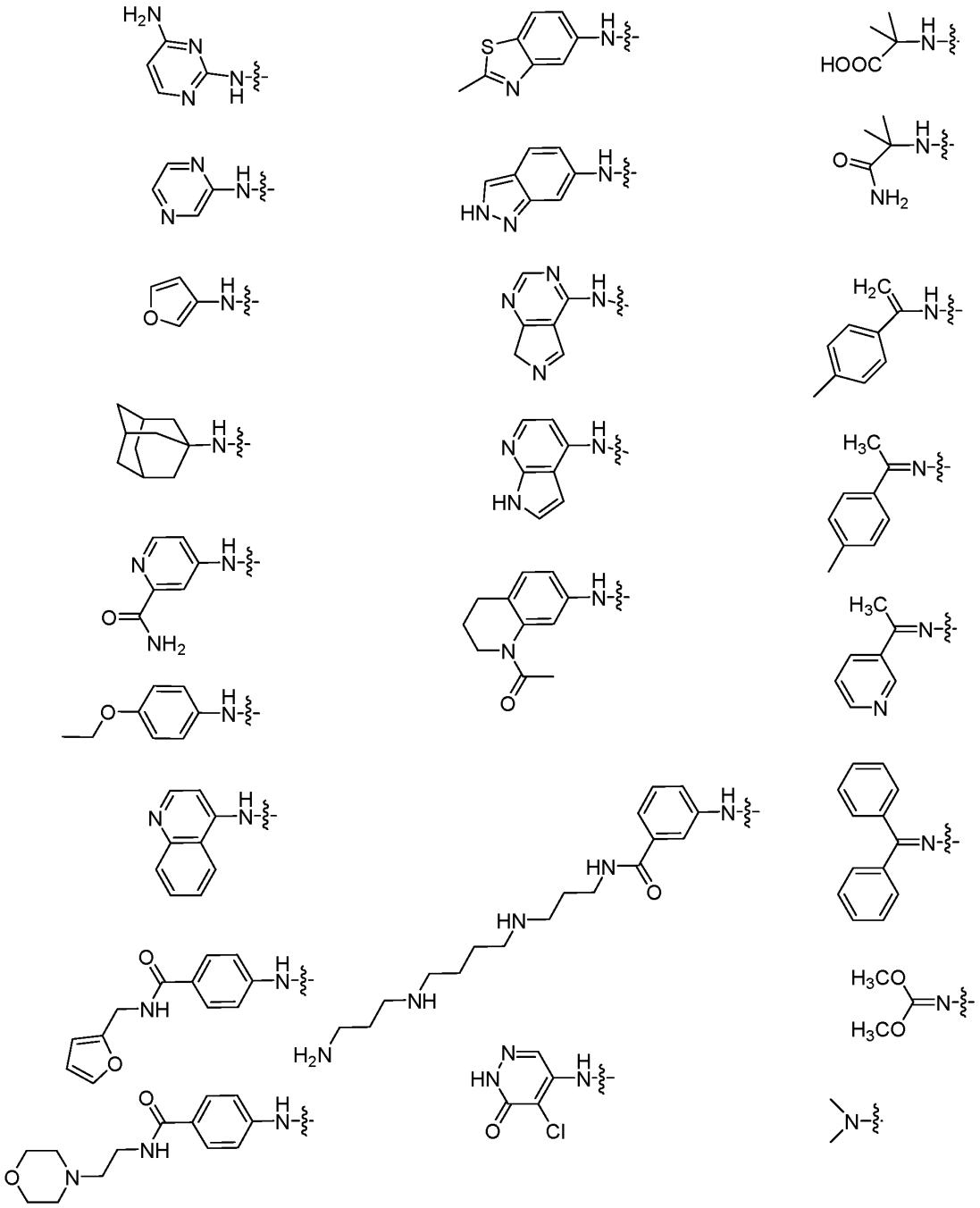
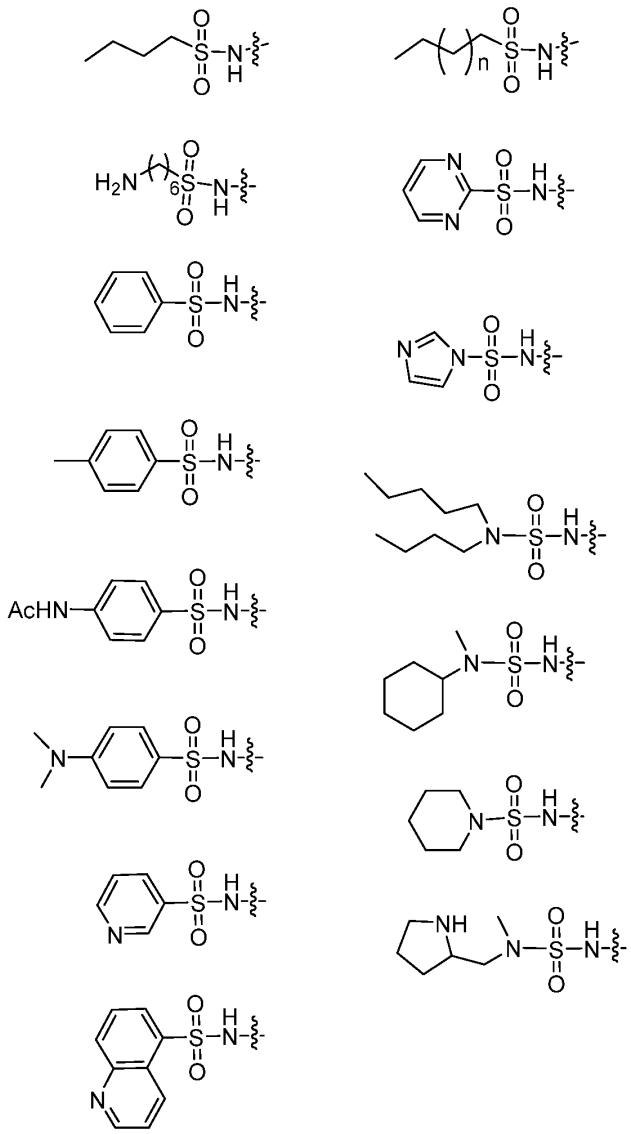
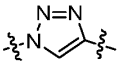
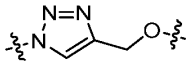


Table L-6. Certain useful moieties bonded to linkage phosphorus (e.g., −X−R^L).



In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage or a neutral internucleotidic linkage, has the structure of $-L^{L1}-Cy^{IL}-L^{L2}-$. In some embodiments, L^{L1} is bonded to a 3'-carbon of a sugar. In some embodiments, L^{L2} is bonded to a 5'-carbon of a sugar. In some embodiments, L^{L1} is $-O-CH_2-$. In some embodiments, L^{L2} is a covalent bond. In some embodiments, L^{L2} is a $-N(R')-$. In some embodiments, L^{L2} is a $-NH-$. In some embodiments, L^{L2} is bonded to a 5'-carbon of a sugar, which 5'-carbon is substituted with =O. In some embodiments, Cy^{IL} is optionally substituted 3-10 membered saturated, partially unsaturated, or aromatic ring having 0-5

heteroatoms. In some embodiments, Cy^{IL} is an optionally substituted triazole ring. In some embodiments, Cy^{IL} is  . In some embodiments, a linkage is  .

In some embodiments, a non-negatively charged internucleotidic linkage has the structure of $-OP(=W)(-N(R')_2)-O-$.

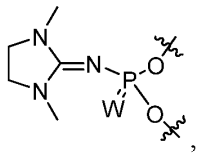
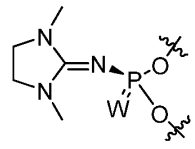
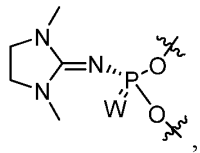
In some embodiments, R' is R. In some embodiments, R' is H. In some embodiments, R' is $-C(O)R$. In some embodiments, R' is $-C(O)OR$. In some embodiments, R' is $-S(O)_2R$.

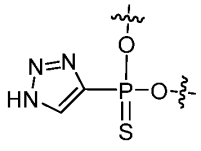
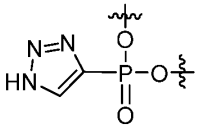
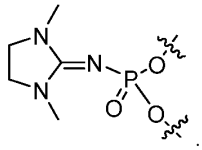
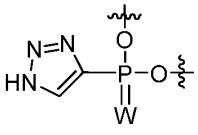
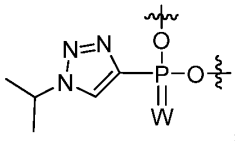
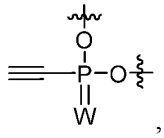
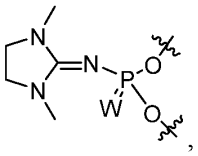
In some embodiments, R" is $-NHR'$. In some embodiments, $-N(R')_2$ is $-NHR'$.

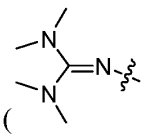
As described herein, some embodiments, R is H. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is methyl. In some embodiments, R is substituted methyl. In some embodiments, R is ethyl. In some embodiments, R is substituted ethyl.

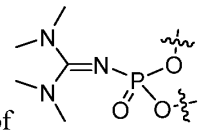
In some embodiments, as described herein, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage.

In some embodiments, a modified internucleotidic linkage (e.g., a non-negatively charged internucleotidic linkage) comprises optionally substituted triazolyl. In some embodiments, R' is or comprises optionally substituted triazolyl. In some embodiments, a modified internucleotidic linkage (e.g., a non-negatively charged internucleotidic linkage) comprises optionally substituted alkynyl. In some embodiments, R' is optionally substituted alkynyl. In some embodiments, R' comprises an optionally substituted triple bond. In some embodiments, a modified internucleotidic linkage comprises a triazole or alkyne moiety. In some embodiments, R' is or comprises an optionally substituted triazole or alkyne moiety. In some embodiments, a triazole moiety, e.g., a triazolyl group, is optionally substituted. In some embodiments, a triazole moiety, e.g., a triazolyl group) is substituted. In some embodiments, a triazole moiety is unsubstituted. In some embodiments, a modified internucleotidic linkage comprises an optionally substituted guanidine moiety. In some embodiments, a modified internucleotidic linkage comprises an optionally substituted cyclic guanidine moiety. In some embodiments, R', R^L, or $-X-R^L$, is or comprises an optionally substituted guanidine moiety. In some embodiments, R', R^L, or $-X-R^L$, is or comprises an optionally substituted cyclic guanidine moiety. In some embodiments, R', R^L, or $-X-R^L$ comprises an optionally substituted cyclic guanidine moiety and an internucleotidic linkage has the structure of:

 ,  , or  , wherein W is O or S. In some embodiments, W is O. In some embodiments, W is S. In some embodiments, a non-negatively charged internucleotidic linkage is stereochemically controlled.

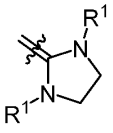
In some embodiments, a non-negatively charged internucleotidic linkage or a neutral internucleotidic linkage is an internucleotidic linkage comprising a triazole moiety. In some embodiments, a non-negatively charged internucleotidic linkage or a non-negatively charged internucleotidic linkage comprises an optionally substituted triazolyl group. In some embodiments, an internucleotidic linkage comprising a triazole moiety (e.g., an optionally substituted triazolyl group) has the structure of  . In some embodiments, an internucleotidic linkage comprising a triazole moiety has the structure of  . In some embodiments, an internucleotidic linkage, e.g., a non-negatively charged internucleotidic linkage, a neutral internucleotidic linkage, comprises a cyclic guanidine moiety. In some embodiments, an internucleotidic linkage comprising a cyclic guanidine moiety has the structure of  . In some embodiments, a non-negatively charged internucleotidic linkage, or a neutral internucleotidic linkage, is or comprising a structure selected from  ,  ,  , or  , wherein W is O or S.

In some embodiments, an internucleotidic linkage comprises a Tmg group (). In some embodiments, an internucleotidic linkage comprises a Tmg group and has the

structure of  (the "Tmg internucleotidic linkage"). In some embodiments, neutral internucleotidic linkages include internucleotidic linkages of PNA and PMO, and an Tmg internucleotidic linkage.

In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 3-20 membered heterocyclyl or heteroaryl group having 1-10 heteroatoms. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 3-20 membered heterocyclyl or heteroaryl group having 1-10 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, such a heterocyclyl or heteroaryl group is of a 5-membered ring. In some embodiments, such a heterocyclyl or heteroaryl group is of a 6-membered ring.

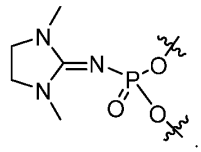
In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-20 membered heteroaryl group having 1-10 heteroatoms. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-20 membered heteroaryl group having 1-10 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-6 membered heteroaryl group having 1-4 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-membered heteroaryl group having 1-4 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, a heteroaryl group is directly bonded to a linkage phosphorus. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-20 membered heterocyclyl group having 1-10 heteroatoms. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-20 membered heterocyclyl group having 1-10 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-6 membered heterocyclyl group having 1-4 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted 5-membered heterocyclyl group having 1-4 heteroatoms, wherein at least one heteroatom is nitrogen. In some embodiments, at least two heteroatoms are nitrogen. In some embodiments, a heterocyclyl group is directly bonded to a linkage phosphorus. In some embodiments, a

heterocyclyl group is bonded to a linkage phosphorus through a linker, e.g., =N− when the heterocyclyl group is part of a guanidine moiety who directed bonded to a linkage phosphorus through its =N−. In some embodiments, a non-negatively charged internucleotidic linkage comprises an optionally substituted  group. In some embodiments, a non-negatively charged internucleotidic linkage comprises an substituted  group. In some embodiments, a non-negatively charged internucleotidic linkage comprises a  group. In some embodiments, each R^1 is independently optionally substituted C_{1-6} alkyl. In some embodiments, each R^1 is independently methyl.

In some embodiments, a non-negatively charged internucleotidic linkage, e.g., a neutral internucleotidic linkage is not chirally controlled. In some embodiments, a non-negatively charged internucleotidic linkage is chirally controlled. In some embodiments, a non-negatively charged internucleotidic linkage is chirally controlled and its linkage phosphorus is Rp. In some embodiments, a non-negatively charged internucleotidic linkage is chirally controlled and its linkage phosphorus is Sp.

In some embodiments, an internucleotidic linkage comprises no linkage phosphorus. In some embodiments, an internucleotidic linkage has the structure of −C(O)−(O)− or −C(O)−N(R')−, wherein R' is as described herein. In some embodiments, an internucleotidic linkage has the structure of −C(O)−(O)−. In some embodiments, an internucleotidic linkage has the structure of −C(O)−N(R')−, wherein R' is as described herein. In various embodiments, −C(O)− is bonded to nitrogen. In some embodiments, an internucleotidic linkage is or comprises −C(O)−O− which is part of a carbamate moiety. In some embodiments, an internucleotidic linkage is or comprises −C(O)−O− which is part of a urea moiety.

In some embodiments, an oligonucleotide comprises 1-20, 1-15, 1-10, 1-5, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more non-negatively charged internucleotidic linkages. In some embodiments, an oligonucleotide comprises 1-20, 1-15, 1-10, 1-5, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more neutral internucleotidic linkages. In some embodiments, each of non-negatively charged internucleotidic linkage and/or neutral internucleotidic linkages is optionally and independently chirally controlled. In some embodiments, each non-negatively charged internucleotidic linkage in an oligonucleotide is independently a chirally controlled

internucleotidic linkage. In some embodiments, each neutral internucleotidic linkage in an oligonucleotide is independently a chirally controlled internucleotidic linkage. In some embodiments, at least one non-negatively charged internucleotidic linkage/neutral internucleotidic linkage has the structure of  . In some embodiments, an oligonucleotide comprises at least one non-negatively charged internucleotidic linkage wherein its linkage phosphorus is in Rp configuration, and at least one non-negatively charged internucleotidic linkage wherein its linkage phosphorus is in Sp configuration.

In many embodiments, as demonstrated extensively, oligonucleotides of the present disclosure comprise two or more different internucleotidic linkages. In some embodiments, an oligonucleotide comprises a phosphorothioate internucleotidic linkage and a non-negatively charged internucleotidic linkage. In some embodiments, an oligonucleotide comprises a phosphorothioate internucleotidic linkage, a non-negatively charged internucleotidic linkage, and a natural phosphate linkage. In some embodiments, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is n001, n003, n004, n006, n008 or n009, n013, n020, n021, n025, n026, n029, n031, n037, n046, n047, n048, n054, or n055). In some embodiments, a non-negatively charged internucleotidic linkage is n001. In some embodiments, each phosphorothioate internucleotidic linkage is independently chirally controlled. In some embodiments, each chiral modified internucleotidic linkage is independently chirally controlled. In some embodiments, one or more non-negatively charged internucleotidic linkage are not chirally controlled.

A typical connection, as in natural DNA and RNA, is that an internucleotidic linkage forms bonds with two sugars (which can be either unmodified or modified as described herein). In many embodiments, as exemplified herein an internucleotidic linkage forms bonds through its oxygen atoms or heteroatoms with one optionally modified ribose or deoxyribose at its 5' carbon, and the other optionally modified ribose or deoxyribose at its 3' carbon. In some embodiments, internucleotidic linkages connect sugars that are not ribose sugars, e.g., sugars comprising N ring atoms and acyclic sugars as described herein.

In some embodiments, each nucleoside units connected by an internucleotidic linkage independently comprises a nucleobase which is independently an optionally substituted A, T, C, G, or U, or an optionally substituted tautomer of A, T, C, G or U.

In some embodiments, an oligonucleotide comprises a modified internucleotidic linkage (e.g., a modified internucleotidic linkage having the structure of Formula **I**, **I-a**, **I-b**, or **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc., or a salt form thereof) as described in US 9394333, US 9744183, US 9605019, US 9598458, US 9982257, US 10160969, US 10479995, US 2020/0056173, US 2018/0216107, US 2019/0127733, US 10450568, US 2019/0077817, US 2019/0249173, US 2019/0375774, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, and/or WO 2019/032612 the internucleotidic linkages (e.g., those of Formula **I**, **I-a**, **I-b**, or **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc.,) of each of which are independently incorporated herein by reference. In some embodiments, a modified internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, provided oligonucleotides comprise one or more non-negatively charged internucleotidic linkages. In some embodiments, a non-negatively charged internucleotidic linkage is a positively charged internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, the present disclosure provides oligonucleotides comprising one or more neutral internucleotidic linkages. In some embodiments, a non-negatively charged internucleotidic linkage or a neutral internucleotidic linkage (e.g., one of Formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc.) is as described in US 9394333, US 9744183, US 9605019, US 9598458, US 9982257, US 10160969, US 10479995, US 2020/0056173, US 2018/0216107, US 2019/0127733, US 10450568, US 2019/0077817, US 2019/0249173, US 2019/0375774, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, and/or WO 2019/032612. In some embodiments, a non-negatively charged internucleotidic linkage or neutral internucleotidic linkage is one of Formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc. as described in WO 2018/223056, WO 2019/032607, WO 2019/075357, WO 2019/032607, WO 2019/075357, WO 2019/200185, WO 2019/217784, and/or WO 2019/032612, such internucleotidic linkages of each of which are independently incorporated herein by reference.

As described herein, various variables can be R, e.g., R', R^L, etc. Various embodiments for R are described in the present disclosure (e.g., when describing variables that can be R). Such embodiments are generally useful for all variables that can be R. In some embodiments,

R is hydrogen. In some embodiments, R is optionally substituted C_{1-30} (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30) aliphatic. In some embodiments, R is optionally substituted C_{1-20} aliphatic. In some embodiments, R is optionally substituted C_{1-10} aliphatic. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted alkyl. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is optionally substituted methyl. In some embodiments, R is methyl. In some embodiments, R is optionally substituted ethyl. In some embodiments, R is optionally substituted propyl. In some embodiments, R is isopropyl. In some embodiments, R is optionally substituted butyl. In some embodiments, R is optionally substituted pentyl. In some embodiments, R is optionally substituted hexyl.

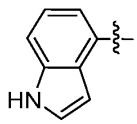
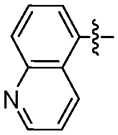
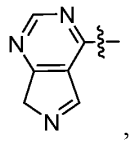
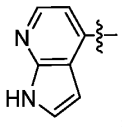
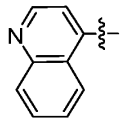
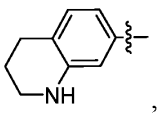
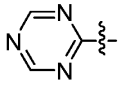
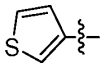
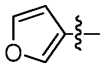
In some embodiments, R is optionally substituted 3-30 membered (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30) cycloaliphatic. In some embodiments, R is optionally substituted cycloalkyl. In some embodiments, cycloaliphatic is monocyclic, bicyclic, or polycyclic, wherein each monocyclic unit is independently saturated or partially saturated. In some embodiments, R is optionally substituted cyclopropyl. In some embodiments, R is optionally substituted cyclobutyl. In some embodiments, R is optionally substituted cyclopentyl. In some embodiments, R is optionally substituted cyclohexyl. In some embodiments, R is optionally substituted adamantyl.

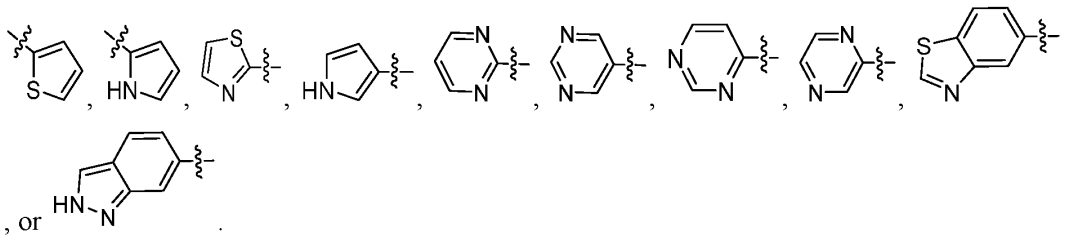
In some embodiments, R is optionally substituted C_{1-30} (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30) heteroaliphatic having 1-10 heteroatoms. In some embodiments, R is optionally substituted C_{1-20} aliphatic having 1-10 heteroatoms. In some embodiments, R is optionally substituted C_{1-10} aliphatic having 1-10 heteroatoms. In some embodiments, R is optionally substituted C_{1-6} aliphatic having 1-3 heteroatoms. In some embodiments, R is optionally substituted heteroalkyl. In some embodiments, R is optionally substituted C_{1-6} heteroalkyl. In some embodiments, R is optionally substituted 3-30 membered (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30) heterocycloaliphatic having 1-10 heteroatoms. In some embodiments, R is optionally substituted heteroclycloalkyl. In some embodiments, heterocycloaliphatic is monocyclic, bicyclic, or polycyclic, wherein each monocyclic unit is independently saturated or partially saturated.

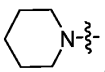
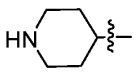
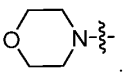
In some embodiments, R is optionally substituted C_{6-30} aryl. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is C_{6-14} aryl. In some embodiments, R is optionally substituted bicyclic aryl. In some embodiments, R is optionally substituted polycyclic aryl. In some embodiments,

R is optionally substituted C_{6-30} arylaliphatic. In some embodiments, R is C_{6-30} arylheteroaliphatic having 1-10 heteroatoms.

In some embodiments, R is optionally substituted 5-30 (5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30) membered heteroaryl having 1-10 heteroatoms. In some embodiments, R is optionally substituted 5-20 membered heteroaryl having 1-10 heteroatoms. In some embodiments, R is optionally substituted 5-10 membered heteroaryl having 1-10 heteroatoms. In some embodiments, R is optionally substituted 5-membered heteroaryl having 1-5 heteroatoms. In some embodiments, R is optionally substituted 5-membered heteroaryl having 1-4 heteroatoms. In some embodiments, R is optionally substituted 5-membered heteroaryl having 1-3 heteroatoms. In some embodiments, R is optionally substituted 5-membered heteroaryl having 1-2 heteroatoms. In some embodiments, R is optionally substituted 5-membered heteroaryl having one heteroatom. In some embodiments, R is optionally substituted 6-membered heteroaryl having 1-5 heteroatoms. In some embodiments, R is optionally substituted 6-membered heteroaryl having 1-4 heteroatoms. In some embodiments, R is optionally substituted 6-membered heteroaryl having 1-3 heteroatoms. In some embodiments, R is optionally substituted 6-membered heteroaryl having 1-2 heteroatoms. In some embodiments, R is optionally substituted 6-membered heteroaryl having one heteroatom. In some embodiments, R is optionally substituted monocyclic heteroaryl. In some embodiments, R is optionally substituted bicyclic heteroaryl. In some embodiments, R is optionally substituted polycyclic heteroaryl. In some embodiments, a heteroatom is nitrogen.

In some embodiments, R is optionally substituted 2-pyridinyl. In some embodiments, R is optionally substituted 3-pyridinyl. In some embodiments, R is optionally substituted 4-pyridinyl. In some embodiments, R is optionally substituted  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,



In some embodiments, R is optionally substituted 3-30 (3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30) membered heterocyclyl having 1-10 heteroatoms. In some embodiments, R is optionally substituted 3-membered heterocyclyl having 1-2 heteroatoms. In some embodiments, R is optionally substituted 4-membered heterocyclyl having 1-2 heteroatoms. In some embodiments, R is optionally substituted 5-20 membered heterocyclyl having 1-10 heteroatoms. In some embodiments, R is optionally substituted 5-10 membered heterocyclyl having 1-10 heteroatoms. In some embodiments, R is optionally substituted 5-membered heterocyclyl having 1-5 heteroatoms. In some embodiments, R is optionally substituted 5-membered heterocyclyl having 1-4 heteroatoms. In some embodiments, R is optionally substituted 5-membered heterocyclyl having 1-3 heteroatoms. In some embodiments, R is optionally substituted 5-membered heterocyclyl having 1-2 heteroatoms. In some embodiments, R is optionally substituted 5-membered heterocyclyl having one heteroatom. In some embodiments, R is optionally substituted 6-membered heterocyclyl having 1-5 heteroatoms. In some embodiments, R is optionally substituted 6-membered heterocyclyl having 1-4 heteroatoms. In some embodiments, R is optionally substituted 6-membered heterocyclyl having 1-3 heteroatoms. In some embodiments, R is optionally substituted 6-membered heterocyclyl having 1-2 heteroatoms. In some embodiments, R is optionally substituted 6-membered heterocyclyl having one heteroatom. In some embodiments, R is optionally substituted monocyclic heterocyclyl. In some embodiments, R is optionally substituted bicyclic heterocyclyl. In some embodiments, R is optionally substituted polycyclic heterocyclyl. In some embodiments, R is optionally substituted saturated heterocyclyl. In some embodiments, R is optionally substituted partially unsaturated heterocyclyl. In some embodiments, a heteroatom is nitrogen. In some embodiments, R is optionally substituted  . In some embodiments, R is optionally substituted  . In some embodiments, R is optionally substituted  .

In some embodiments, two R groups are optionally and independently taken together to form a covalent bond. In some embodiments, two or more R groups on the same atom are

optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms. In some embodiments, two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms.

Various embodiments can comprise an optionally substituted ring, or can be taken together with their intervening atom(s) to form a ring. In some embodiments, a ring is 3-30 (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30) membered. In some embodiments, a ring is 3-20 membered. In some embodiments, a ring is 3-15 membered. In some embodiments, a ring is 3-10 membered. In some embodiments, a ring is 3-8 membered. In some embodiments, a ring is 3-7 membered. In some embodiments, a ring is 3-6 membered. In some embodiments, a ring is 4-20 membered. In some embodiments, a ring is 5-20 membered. In some embodiments, a ring is monocyclic. In some embodiments, a ring is bicyclic. In some embodiments, a ring is polycyclic. In some embodiments, each monocyclic ring or each monocyclic ring unit in bicyclic or polycyclic rings is independently saturated, partially saturated or aromatic. In some embodiments, each monocyclic ring or each monocyclic ring unit in bicyclic or polycyclic rings is independently 3-10 membered and has 0-5 heteroatoms.

In some embodiments, each heteroatom is independently selected oxygen, nitrogen, sulfur, silicon, and phosphorus. In some embodiments, each heteroatom is independently selected oxygen, nitrogen, sulfur, and phosphorus. In some embodiments, each heteroatom is independently selected oxygen, nitrogen, and sulfur. In some embodiments, a heteroatom is in an oxidized form.

As appreciated by those skilled in the art, many other types of internucleotidic linkages may be utilized in accordance with the present disclosure, for example, those described in U.S. Pat. Nos. 3,687,808; 4,469,863; 4,476,301; 5,177,195; 5,023,243; 5,034,506; 5,166,315; 5,185,444; 5,188,897; 5,214,134; 5,216,141; 5,235,033; 5,264,423; 5,264,564; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,938; 5,405,939; 5,434,257; 5,453,496; 5,455,233; 5,466,677; 5,466,677; 5,470,967; 5,476,925; 5,489,677; 5,519,126; 5,536,821; 5,541,307; 5,541,316; 5,550,111; 5,561,225; 5,563,253; 5,571,799; 5,587,361; 5,596,086; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,625,050; 5,633,360; 5,663,312; 5,677,437; 5,677,439; 6,160,109; 6,239,265; 6,028,188; 6,124,445; 6,169,170; 6,172,209; 6,277,603; 6,326,199; 6,346,614; 6,444,423; 6,531,590; 6,534,639; 6,608,035; 6,683,167;

6,858,715; 6,867,294; 6,878,805; 7,015,315; 7,041,816; 7,273,933; 7,321,029; or RE39464. In certain embodiments, a modified internucleotidic linkage is one described in US 9982257, US 20170037399, US 20180216108, WO 2017192664, WO 2017015575, WO2017062862, WO 2018067973, WO 2017160741, WO 2017192679, WO 2017210647, WO 2018098264, PCT/US18/35687, PCT/US18/38835, or PCT/US18/51398, the nucleobases, sugars, internucleotidic linkages, chiral auxiliaries/reagents, and technologies for oligonucleotide synthesis (reagents, conditions, cycles, etc.) of each of which is independently incorporated herein by reference.

In certain embodiments, each internucleotidic linkage in a ds oligonucleotide is independently selected from a natural phosphate linkage, a phosphorothioate linkage, and a non-negatively charged internucleotidic linkage (e.g., n001). In certain embodiments, each internucleotidic linkage in a ds oligonucleotide is independently selected from a natural phosphate linkage, a phosphorothioate linkage, and a neutral internucleotidic linkage (e.g., n001).

In certain embodiments, a ds oligonucleotide comprises one or more nucleotides that independently comprise a phosphorus modification prone to "autorelease" under certain conditions. That is, under certain conditions, a particular phosphorus modification is designed such that it self-cleaves from the ds oligonucleotide to provide, e.g., a natural phosphate linkage. In certain embodiments, such a phosphorus modification has a structure of $-O-L-R^1$, wherein L is L^B as described herein, and R^1 is R' as described herein. In certain embodiments, a phosphorus modification has a structure of $-S-L-R^1$, wherein each L and R^1 is independently as described in the present disclosure. Certain examples of such phosphorus modification groups can be found in US 9982257. In certain embodiments, an autorelease group comprises a morpholino group. In certain embodiments, an autorelease group is characterized by the ability to deliver an agent to the internucleotidic phosphorus linker, which agent facilitates further modification of the phosphorus atom such as, e.g., desulfurization. In certain embodiments, the agent is water and the further modification is hydrolysis to form a natural phosphate linkage.

In certain embodiments, a ds oligonucleotide comprises one or more internucleotidic linkages that improve one or more pharmaceutical properties and/or activities of the oligonucleotide. It is well documented in the art that certain oligonucleotides are rapidly degraded by nucleases and exhibit poor cellular uptake through the cytoplasmic cell membrane (Poijarvi-Virta et al., Curr. Med. Chem. (2006), 13(28);3441-65; Wagner et al., Med. Res. Rev. (2000), 20(6):417-51; Peyrottes et al., Mini Rev. Med. Chem. (2004), 4(4):395-408; Gosselin

et al., (1996), 43(1):196-208; Bologna et al., (2002), Antisense & Nucleic Acid Drug Development 12:33-41). Vives et al. (Nucleic Acids Research (1999), 27(20):4071-76) reported that tert-butyl SATE pro-oligonucleotides displayed markedly increased cellular penetration compared to the parent oligonucleotide under certain conditions.

Double stranded oligonucleotides can comprise various number of natural phosphate linkages. In certain embodiments, 5% or more of the internucleotidic linkages of provided ds oligonucleotides are natural phosphate linkages. In certain embodiments, 10% or more of the internucleotidic linkages of provided ds oligonucleotides are natural phosphate linkages. In certain embodiments, 15% or more of the internucleotidic linkages of provided ds oligonucleotides are natural phosphate linkages. In certain embodiments, 20% or more of the internucleotidic linkages of provided ds oligonucleotides are natural phosphate linkages. In certain embodiments, 25% or more of the internucleotidic linkages of provided ds oligonucleotides are natural phosphate linkages. In certain embodiments, 30% or more of the internucleotidic linkages of provided ds oligonucleotides are natural phosphate linkages. In certain embodiments, 35% or more of the internucleotidic linkages of provided ds oligonucleotides are natural phosphate linkages. In certain embodiments, 40% or more of the internucleotidic linkages of provided ds oligonucleotides are natural phosphate linkages. In certain embodiments, provided ds oligonucleotides comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more natural phosphate linkages. In certain embodiments, provided ds oligonucleotides comprises 4, 5, 6, 7, 8, 9, 10 or more natural phosphate linkages. In certain embodiments, the number of natural phosphate linkages is 2. In certain embodiments, the number of natural phosphate linkages is 3. In certain embodiments, the number of natural phosphate linkages is 4. In certain embodiments, the number of natural phosphate linkages is 5. In certain embodiments, the number of natural phosphate linkages is 6. In certain embodiments, the number of natural phosphate linkages is 7. In certain embodiments, the number of natural phosphate linkages is 8. In certain embodiments, some or all of the natural phosphate linkages are consecutive.

In certain embodiments, the present disclosure demonstrates that, in at least some cases, *S*p internucleotidic linkages, among other things, at the 5'- and/or 3'-end can improve ds oligonucleotide stability. In certain embodiments, the present disclosure demonstrates that, among other things, natural phosphate linkages and/or *R*p internucleotidic linkages may improve removal of ds oligonucleotides from a system. As appreciated by a person having ordinary skill in the art, various assays known in the art can be utilized to assess such properties in accordance with the present disclosure.

In certain embodiments, each phosphorothioate internucleotidic linkage in a ds oligonucleotide or a portion thereof (e.g., a domain, a subdomain, etc.) is independently chirally controlled. In certain embodiments, each is independently *S*p or *R*p. In certain embodiments, a high level is *S*p as described herein. In certain embodiments, each phosphorothioate internucleotidic linkage in a ds oligonucleotide or a portion thereof is chirally controlled and is *S*p. In certain embodiments, one or more, e.g., about 1-5 (e.g., about 1, 2, 3, 4, or 5) is *R*p.

In certain embodiments, as illustrated in certain examples, a ds oligonucleotide or a portion thereof comprises one or more non-negatively charged internucleotidic linkages, each of which is optionally and independently chirally controlled. In certain embodiments, each non-negatively charged internucleotidic linkage is independently n001. In certain embodiments, a chiral non-negatively charged internucleotidic linkage is not chirally controlled. In certain embodiments, each chiral non-negatively charged internucleotidic linkage is not chirally controlled. In certain embodiments, a chiral non-negatively charged internucleotidic linkage is chirally controlled. In certain embodiments, a chiral non-negatively charged internucleotidic linkage is chirally controlled and is *R*p. In certain embodiments, a chiral non-negatively charged internucleotidic linkage is chirally controlled and is *S*p. In certain embodiments, each chiral non-negatively charged internucleotidic linkage is chirally controlled. In certain embodiments, the number of non-negatively charged internucleotidic linkages in a ds oligonucleotide or a portion thereof is about 1-10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In certain embodiments, it is about 1. In certain embodiments, it is about 2. In certain embodiments, it is about 3. In certain embodiments, it is about 4. In certain embodiments, it is about 5. In certain embodiments, it is about 6. In certain embodiments, it is about 7. In certain embodiments, it is about 8. In certain embodiments, it is about 9. In certain embodiments, it is about 10. In certain embodiments, two or more non-negatively charged internucleotidic linkages are consecutive. In certain embodiments, no two non-negatively charged internucleotidic linkages are consecutive. In certain embodiments, all non-negatively charged internucleotidic linkages in a ds oligonucleotide or a portion thereof are consecutive (e.g., 3 consecutive non-negatively charged internucleotidic linkages). In certain embodiments, a non-negatively charged internucleotidic linkage, or two or more (e.g., about 2, about 3, about 4 etc.) consecutive non-negatively charged internucleotidic linkages, are at the 3'-end of a ds oligonucleotide or a portion thereof. In certain embodiments, the last two or three or four internucleotidic linkages of a ds oligonucleotide or a portion thereof comprise at least one internucleotidic linkage that is not a non-negatively charged internucleotidic linkage. In certain embodiments, the last two or three or four internucleotidic linkages of a ds

oligonucleotide or a portion thereof comprise at least one internucleotidic linkage that is not n001. In certain embodiments, the internucleotidic linkage linking the first two nucleosides of a ds oligonucleotide or a portion thereof is a non-negatively charged internucleotidic linkage. In certain embodiments, the internucleotidic linkage linking the last two nucleosides of a ds oligonucleotide or a portion thereof is a non-negatively charged internucleotidic linkage. In certain embodiments, the internucleotidic linkage linking the first two nucleosides of a ds oligonucleotide or a portion thereof is a phosphorothioate internucleotidic linkage. In certain embodiments, it is *S*p. In certain embodiments, the internucleotidic linkage linking the last two nucleosides of a ds oligonucleotide or a portion thereof is a phosphorothioate internucleotidic linkage. In certain embodiments, it is *S*p.

In certain embodiments, one or more chiral internucleotidic linkages are chirally controlled and one or more chiral internucleotidic linkages are not chirally controlled. In certain embodiments, each phosphorothioate internucleotidic linkage is independently chirally controlled, and one or more non-negatively charged internucleotidic linkage are not chirally controlled. In certain embodiments, each phosphorothioate internucleotidic linkage is independently chirally controlled, and each non-negatively charged internucleotidic linkage is not chirally controlled. In certain embodiments, the internucleotidic linkage between the first two nucleosides of a ds oligonucleotide is a non-negatively charged internucleotidic linkage. In certain embodiments, the internucleotidic linkage between the last two nucleosides are each independently a non-negatively charged internucleotidic linkage. In certain embodiments, both are independently non-negatively charged internucleotidic linkages. In certain embodiments, each non-negatively charged internucleotidic linkage is independently neutral internucleotidic linkage. In certain embodiments, each non-negatively charged internucleotidic linkage is independently n001.

In certain embodiments, a controlled level of ds oligonucleotides in a composition are desired ds oligonucleotides. In certain embodiments, of all ds oligonucleotides in a composition that share a common base sequence (e.g., a desired sequence for a purpose), or of all ds oligonucleotides in a composition, level of desired ds oligonucleotides (which may exist in various forms (e.g., salt forms) and typically differ only at non-chirally controlled internucleotidic linkages (various forms of the same stereoisomer can be considered the same for this purpose)) is about 5%-100%, 10%-100%, 20%-100%, 30%-100%, 40%-100%, 50%-100%, 60%-100%, 70%-100%, 80-100%, 90-100%, 95-100%, 50%-90%, about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, or at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%,

65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99%. In certain embodiments, a level is at least about 50%. In certain embodiments, a level is at least about 60%. In certain embodiments, a level is at least about 70%. In certain embodiments, a level is at least about 75%. In certain embodiments, a level is at least about 80%. In certain embodiments, a level is at least about 85%. In certain embodiments, a level is at least about 90%. In certain embodiments, a level is or is at least $(DS)^{nc}$, wherein DS is about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5% and nc is the number of chirally controlled internucleotidic linkages as described in the present disclosure (e.g., 1-50, 1-40, 1-30, 1-25, 1-20, 5-50, 5-40, 5-30, 5-25, 5-20, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 or more). In certain embodiments, a level is or is at least $(DS)^{nc}$, wherein DS is 95%-100%.

Various types of internucleotidic linkages may be utilized in combination of other structural elements, e.g., sugars, to achieve desired ds oligonucleotide properties and/or activities. For example, the present disclosure routinely utilizes modified internucleotidic linkages and modified sugars, optionally with natural phosphate linkages and natural sugars, in designing ds oligonucleotides. In certain embodiments, the present disclosure provides a ds oligonucleotide comprising one or more modified sugars. In certain embodiments, the present disclosure provides a ds oligonucleotide comprising one or more modified sugars and one or more modified internucleotidic linkages, one or more of which are natural phosphate linkages.

Double Stranded Oligonucleotide Compositions

Among other things, the present disclosure provides various ds oligonucleotide compositions. In some embodiments, the present disclosure provides ds oligonucleotide compositions of ds oligonucleotides described herein. In some embodiments, a ds oligonucleotide composition, e.g., a ds oligonucleotide targeting INHBE composition, comprises a plurality of an oligonucleotide described in the present disclosure. In some embodiments, a ds oligonucleotide composition, e.g., a ds oligonucleotide targeting INHBE composition, is chirally controlled. In some embodiments, a ds oligonucleotide composition, e.g., a ds oligonucleotide targeting INHBE composition, is not chirally controlled (stereorandom).

Linkage phosphorus of natural phosphate linkages is achiral. Linkage phosphorus of many modified internucleotidic linkages, e.g., phosphorothioate internucleotidic linkages, are chiral. In some embodiments, during preparation of oligonucleotide compositions (e.g., in traditional phosphoramidite oligonucleotide synthesis), configurations of chiral linkage phosphorus are not purposefully designed or controlled, creating non-chirally controlled

(stereorandom) oligonucleotide compositions (substantially racemic preparations) which are complex, random mixtures of various stereoisomers (diastereoisomers) - for oligonucleotides with n chiral internucleotidic linkages (linkage phosphorus being chiral), typically 2^n stereoisomers (e.g., when n is 10, 2^{10} =1,032; when n is 20, 2^{20} = 1,048,576). These stereoisomers have the same constitution, but differ with respect to the pattern of stereochemistry of their linkage phosphorus.

In some embodiments, stereorandom oligonucleotide compositions have sufficient properties and/or activities for certain purposes and/or applications. In some embodiments, stereorandom oligonucleotide compositions can be cheaper, easier and/or simpler to produce than chirally controlled oligonucleotide compositions. However, stereoisomers within stereorandom compositions may have different properties, activities, and/or toxicities, resulting in inconsistent therapeutic effects and/or unintended side effects by stereorandom compositions, particularly compared to certain chirally controlled oligonucleotide compositions of oligonucleotides of the same constitution.

Chirally Controlled Double Stranded Oligonucleotide Compositions

In some embodiments, the present disclosure encompasses technologies for designing and preparing chirally controlled ds oligonucleotide compositions. In some embodiments, a chirally controlled ds oligonucleotide composition comprises a controlled/pre-determined (not random as in stereorandom compositions) level of a plurality of ds oligonucleotides, wherein the ds oligonucleotides share the same linkage phosphorus stereochemistry at one or more chiral internucleotidic linkages (chirally controlled internucleotidic linkages). In some embodiments, ds oligonucleotides of a plurality share the same pattern of backbone chiral centers (stereochemistry of linkage phosphorus). In some embodiments, a pattern of backbone chiral centers is as described in the present disclosure. In some embodiments, ds oligonucleotides of a plurality share a common constitution. In some embodiments, they are structurally identical.

For example, in some embodiments, the present disclosure provides a ds oligonucleotide composition comprising a plurality of ds oligonucleotides, wherein oligonucleotides of the plurality share:

1) a common base sequence, and

2) the same linkage phosphorus stereochemistry independently at one or more (e.g., about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 5-50, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 or more) chiral internucleotidic linkages (“chirally controlled internucleotidic linkages”);

wherein level of ds oligonucleotides of the plurality in the composition is non-random (e.g., controlled/pre-determined as described herein).

In some embodiments, the present disclosure provides a ds oligonucleotide composition comprising a plurality of oligonucleotides, wherein oligonucleotides of the plurality share:

1) a common base sequence, and

2) the same linkage phosphorus stereochemistry independently at one or more (e.g., about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 5-50, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 or more) chiral internucleotidic linkages ("chirally controlled internucleotidic linkages");

wherein the composition is enriched relative to a substantially racemic preparation of oligonucleotides sharing the common base sequence for oligonucleotides of the plurality.

In some embodiments, the present disclosure provides a ds oligonucleotide composition comprising a plurality of ds oligonucleotides, wherein ds oligonucleotides of the plurality share:

1) a common base sequence, and

2) the same linkage phosphorus stereochemistry independently at one or more (e.g., about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 5-50, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 or more) chiral internucleotidic linkages ("chirally controlled internucleotidic linkages");

wherein about 1%-100%, (e.g., about 5%-100%, 10%-100%, 20%-100%, 30%-100%, 40%-100%, 50%-100%, 60%-100%, 70%-100%, 80-100%, 90-100%, 95-100%, 50%-90%, or about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, or at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) of all ds oligonucleotides in the composition that share the common base sequence are oligonucleotides of the plurality.

In some embodiments, the percentage/level of the ds oligonucleotides of a plurality is or is at least $(DS)^{nc}$, wherein DS is 90%-100%, and nc is the number of chirally controlled internucleotidic linkages. In some embodiments, nc is 5, 6, 7, 8, 9, 10 or more. In some embodiments, a percentage/level is at least 10%. In some embodiments, a percentage/level is at least 20%. In some embodiments, a percentage/level is at least 30%. In some embodiments, a percentage/level is at least 40%. In some embodiments, a percentage/level is at least 50%. In some embodiments, a percentage/level is at least 60%. In some embodiments, a percentage/level is at least 65%. In some embodiments, a percentage/level is at least 70%. In

some embodiments, a percentage/level is at least 75%. In some embodiments, a percentage/level is at least 80%. In some embodiments, a percentage/level is at least 85%. In some embodiments, a percentage/level is at least 90%. In some embodiments, a percentage/level is at least 95%.

In some embodiments, ds oligonucleotides of a plurality share a common pattern of backbone linkages. In some embodiments, each ds oligonucleotide of a plurality independently has an internucleotidic linkage of a particular constitution (e.g., −O−P(O)(SH)−O−) or a salt form thereof (e.g., −O−P(O)(SNa)−O−) independently at each internucleotidic linkage site. In some embodiments, internucleotidic linkages at each internucleotidic linkage site are of the same form. In some embodiments, internucleotidic linkages at each internucleotidic linkage site are of different forms.

In some embodiments, ds oligonucleotides of a plurality share a common constitution. In some embodiments, ds oligonucleotides of a plurality are of the same form of a common constitution. In some embodiments, ds oligonucleotides of a plurality are of two or more forms of a common constitution. In some embodiments, ds oligonucleotides of a plurality are each independently of a particularly ds oligonucleotide or a pharmaceutically acceptable salt thereof, or of a ds oligonucleotide having the same constitution as the particularly ds oligonucleotide or a pharmaceutically acceptable salt thereof. In some embodiments, about 1%-100%, (e.g., about 5%-100%, 10%-100%, 20%-100%, 30%-100%, 40%-100%, 50%-100%, 60%-100%, 70%-100%, 80-100%, 90-100%, 95-100%, 50%-90%, or about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, or at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) of all ds oligonucleotides in the composition that share a common constitution are oligonucleotides of the plurality. In some embodiments, a percentage of a level is or is at least $(DS)^{nc}$, wherein DS is 90%-100%, and nc is the number of chirally controlled internucleotidic linkages. In some embodiments, nc is 5, 6, 7, 8, 9, 10 or more. In some embodiments, a level is at least 10%. In some embodiments, a level is at least 20%. In some embodiments, a level is at least 30%. In some embodiments, a level is at least 40%. In some embodiments, a level is at least 50%. In some embodiments, a level is at least 60%. In some embodiments, a level is at least 65%. In some embodiments, a level is at least 70%. In some embodiments, a level is at least 75%. In some embodiments, a level is at least 80%. In some embodiments, a level is at least 85%. In some embodiments, a level is at least 90%. In some embodiments, a level is at least 95%.

In some embodiments, each phosphorothioate internucleotidic linkage is independently

a chirally controlled internucleotidic linkage.

In some embodiments, the present disclosure provides a chirally controlled ds oligonucleotide composition comprising a plurality of oligonucleotides of a particular oligonucleotide type characterized by:

a) a common base sequence;

b) a common pattern of backbone linkages;

c) a common pattern of backbone chiral centers;

wherein the composition is enriched, relative to a substantially racemic preparation of ds oligonucleotides having the same common base sequence, for ds oligonucleotides of the particular ds oligonucleotide type.

In some embodiments, the present disclosure provides a chirally controlled ds oligonucleotide composition comprising a plurality of ds oligonucleotides of a particular ds oligonucleotide type characterized by:

a) a common base sequence;

b) a common pattern of backbone linkages;

c) a common pattern of backbone chiral centers;

wherein ds oligonucleotides of the plurality comprise at least one internucleotidic linkage comprising a common linkage phosphorus in the *S*p configuration;

wherein the composition is enriched, relative to a substantially racemic preparation of oligonucleotides having the same common base sequence, for ds oligonucleotides of the particular ds oligonucleotide type.

Common patterns of backbone chiral centers, as appreciated by those skilled in the art, comprise at least one *R*p or at least one *S*p. Certain patterns of backbone chiral centers are illustrated in, e.g., Table 1.

In some embodiments, a chirally controlled ds oligonucleotide composition is enriched, relative to a substantially racemic preparation of ds oligonucleotides share the same common base sequence and a common pattern of backbone linkages, for oligonucleotides of the particular ds oligonucleotide type.

In some embodiments, ds oligonucleotides of a plurality, e.g., a particular ds oligonucleotide type, have a common pattern of backbone phosphorus modifications and a common pattern of nucleoside modifications. In some embodiments, ds oligonucleotides of a plurality have a common pattern of sugar modifications. In some embodiments, ds oligonucleotides of a plurality have a common pattern of base modifications. In some embodiments, ds oligonucleotides of a plurality have a common pattern of nucleoside

modifications. In some embodiments, ds oligonucleotides of a plurality have the same constitution. In many embodiments, ds oligonucleotides of a plurality are identical. In some embodiments, ds oligonucleotides of a plurality are of the same oligonucleotide (as those skilled in the art will appreciate, such ds oligonucleotides may each independently exist in one of the various forms of the ds oligonucleotide, and may be the same, or different forms of the oligonucleotide). In some embodiments, ds oligonucleotides of a plurality are each independently of the same ds oligonucleotide or a pharmaceutically acceptable salt thereof.

In some embodiments, the present disclosure provides chirally controlled ds oligonucleotide compositions, e.g., of many ds oligonucleotides in Table 1 whose "stereochemistry/linkage" contain S and/or R. In some embodiments, ds oligonucleotides of a plurality are each independently a particular oligonucleotide in Table 1 whose "stereochemistry/linkage" contains S and/or R, optionally in various forms. In some embodiments, oligonucleotides of a plurality are each independently a particular oligonucleotide in Table 1 whose "stereochemistry/linkage" contains S and/or R, or a pharmaceutically acceptable salt thereof.

In some embodiments, level of a plurality of ds oligonucleotides in a composition can be determined as the product of the diastereopurity of each chirally controlled internucleotidic linkage in the oligonucleotides. In some embodiments, diastereopurity of an internucleotidic linkage connecting two nucleosides in an oligonucleotide (or nucleic acid) is represented by the diastereopurity of an internucleotidic linkage of a dimer connecting the same two nucleosides, wherein the dimer is prepared using comparable conditions, in some instances, identical synthetic cycle conditions.

In some embodiments, all chiral internucleotidic linkages are independently chiral controlled, and the composition is a completely chirally controlled oligonucleotide composition. In some embodiments, not all chiral internucleotidic linkages are chiral controlled internucleotidic linkages, and the composition is a partially chirally controlled oligonucleotide composition.

Oligonucleotides may comprise or consist of various patterns of backbone chiral centers (patterns of stereochemistry of chiral linkage phosphorus). Certain useful patterns of backbone chiral centers are described in the present disclosure. In some embodiments, a plurality of oligonucleotides share a common pattern of backbone chiral centers, which is or comprises a pattern described in the present disclosure (e.g., as in "Stereochemistry and Patterns of Backbone Chiral Centers", a pattern of backbone chiral centers of a chirally controlled oligonucleotide in Table 1, etc.).

In some embodiments, a chirally controlled oligonucleotide composition is chirally pure (or stereopure, stereochemically pure) oligonucleotide composition, wherein the oligonucleotide composition comprises a plurality of oligonucleotides, wherein the oligonucleotides are independently of the same stereoisomer [including that each chiral element of the oligonucleotides, including each chiral linkage phosphorus, is independently defined (stereodefined)]. A chirally pure (or stereopure, stereochemically pure) oligonucleotide composition of an oligonucleotide stereoisomer does not contain other stereoisomers (as appreciated by those skilled in the art, one or more unintended stereoisomers may exist as impurities from, e.g., preparation, storage, etc.).

Chirally controlled oligonucleotide compositions can demonstrate a number of advantages over stereorandom oligonucleotide compositions. Among other things, chirally controlled oligonucleotide compositions are more uniform than corresponding stereorandom oligonucleotide compositions with respect to oligonucleotide structures. By controlling stereochemistry, compositions of individual stereoisomers can be prepared and assessed, so that chirally controlled oligonucleotide composition of stereoisomers with desired properties and/or activities can be developed. In some embodiments, chirally controlled oligonucleotide compositions provides better delivery, stability, clearance, activity, selectivity, and/or toxicity profiles compared to, e.g., corresponding stereorandom oligonucleotide compositions. In some embodiments, chirally controlled oligonucleotide compositions provide better efficacy, fewer side effects, and/or more convenient and effective dosage regimens. Among other things, patterns of backbone chiral centers as described herein can be utilized to provide controlled cleavage of oligonucleotide targets (e.g., transcripts such as pre-mRNA, mature mRNA, etc.; including control of cleavage sites, rate and/or extent of cleavage at cleavage sites, and/or overall rate and extent of cleavage, etc.).

In some embodiments, oligonucleotides in provided compositions, e.g., chirally controlled oligonucleotide compositions, are ds oligonucleotides targeting INHBE as described herein.

In some embodiments, the present disclosure provides a stereorandom oligonucleotide composition, e.g., a stereorandom ds oligonucleotide targeting INHBE composition. In some embodiments, the present disclosure provides a stereorandom ds oligonucleotide targeting INHBE composition which is capable of decreasing the level, activity or expression of a INHBE gene or a gene product thereof. In some embodiments, the present disclosure provides a stereorandom ds oligonucleotide targeting INHBE composition which is capable of decreasing the level, activity or expression of a INHBE gene or a gene product thereof, and

wherein the base sequence of the ds oligonucleotides targeting INHBE is, comprises, or comprises a span (e.g., at least 10 or 15 contiguous bases) of a base sequence disclosed herein (e.g., a base sequence in Table 1, wherein each T may be independently replaced with U and vice versa).

In some embodiments, an oligonucleotide composition comprises one or more internucleotidic linkages which are stereocontrolled (chirally controlled; in some embodiments, stereopure) and one or more internucleotidic linkages which are stereorandom. In some embodiments, a ds oligonucleotide targeting INHBE composition comprises one or more internucleotidic linkages which are stereocontrolled (chirally controlled; in some embodiments, stereopure) and one or more internucleotidic linkages which are stereorandom.

In some embodiments, an oligonucleotide composition comprises one or more internucleotidic linkages which are stereocontrolled (e.g., chirally controlled or stereopure) and one or more internucleotidic linkages which are stereorandom. Such oligonucleotides may target various targets and may have various base sequences, and may be capable of operating via one or more of various modalities (e.g., RNase H mechanism, steric hindrance, double- or single-stranded RNA interference, exon skipping modulation, CRISPR, aptamer, etc.).

In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition, e.g., chirally controlled ds oligonucleotide targeting INHBE composition. In some embodiments, provided chirally controlled oligonucleotide compositions comprise a plurality of oligonucleotides, e.g., ds oligonucleotides targeting INHBE, of the same constitution, and have one or more internucleotidic linkages. In some embodiments, a plurality of oligonucleotides, e.g., in a chirally controlled oligonucleotide composition, is a plurality of an oligonucleotide selected from Table 1, wherein the oligonucleotide comprises at least one *R*p or *S*p linkage phosphorus in a chirally controlled internucleotidic linkage. In some embodiments, a plurality of oligonucleotides, e.g., in a chirally controlled oligonucleotide composition, is a plurality of an oligonucleotide selected from Table 1, wherein each phosphorothioate internucleotidic linkage in the oligonucleotide is independently chirally controlled (each phosphorothioate internucleotidic linkage is independently *R*p or *S*p). In some embodiments, an oligonucleotide composition, e.g., a ds oligonucleotide targeting INHBE composition is a substantially pure preparation of a single oligonucleotide in that oligonucleotides in the composition that are not the single oligonucleotide are impurities from the preparation process of the single oligonucleotide, in some case, after certain purification procedures. In some embodiments, a single oligonucleotide is an oligonucleotide of Table 1, wherein each chiral internucleotidic linkage

of the oligonucleotide is chirally controlled (e.g., indicated as S or R but not X in "Stereochemistry/Linkage").

In some embodiments, a chirally controlled oligonucleotide composition can have, relative to a corresponding stereorandom oligonucleotide composition, increased activity and/or stability, increased delivery, and/or decreased ability to elicit adverse effects such as complement, TLR9 activation, etc. In some embodiments, a stereorandom (non-chirally controlled) oligonucleotide composition differs from a chirally controlled oligonucleotide composition in that its corresponding plurality of oligonucleotides do not contain any chirally controlled internucleotidic linkages but the stereorandom oligonucleotide composition is otherwise identical to the chirally controlled oligonucleotide composition.

In some embodiments, the present disclosure pertains to a chirally controlled ds oligonucleotide targeting INHBE composition which is capable of decreasing the level, activity or expression of a INHBE gene or a gene product thereof.

In some embodiments, the present disclosure provides a chirally controlled ds oligonucleotide targeting INHBE composition which is capable of decreasing the level, activity or expression of a INHBE gene or a gene product thereof, and comprises a plurality of oligonucleotides which share a common base sequence that is or comprises a base sequence disclosed herein (e.g., in Table 1, wherein each T may be independently replaced with U and vice versa).

In some embodiments, a provided chirally controlled oligonucleotide composition is a chirally controlled ds oligonucleotide targeting INHBE composition comprising a plurality of ds oligonucleotides targeting INHBE. In some embodiments, a chirally controlled oligonucleotide composition is a chirally pure (or "stereochemically pure") oligonucleotide composition. In some embodiments, the present disclosure provides a chirally pure oligonucleotide composition of an oligonucleotide in Table 1, wherein each chiral internucleotidic linkage of the oligonucleotide is independently chirally controlled (*R*p or *S*p, e.g., R or S but not X in "Stereochemistry/Linkage"). As one of ordinary skill in the art will understand, chemical selectivity rarely, if ever, achieves completeness (absolute 100%). In some embodiments, a chirally pure oligonucleotide composition comprises a plurality of oligonucleotides, wherein oligonucleotides of the plurality are structurally identical and all have the same structure (the same stereoisomeric form; in the context of oligonucleotide, typically the same diastereomeric form as typically multiple chiral centers exist in an oligonucleotide), and the chirally pure oligonucleotide composition does not contain any other stereoisomers (in the context of oligonucleotide, typically diastereomers as typically multiple

chiral centers exist in an oligonucleotide; to the extent, e.g., achievable by stereoselective preparation). As appreciated by those skilled in the art, stereorandom (or "racemic", "non-chirally controlled") oligonucleotide compositions are random mixtures of many stereoisomers (e.g., 2^n diastereoisomers wherein n is the number of chiral linkage phosphorus for oligonucleotides in which other chiral centers (e.g., carbon chiral centers in sugars) are chirally controlled each independently existing in one configuration and only chiral linkage phosphorus centers are not chirally controlled).

Certain data showing properties and/or activities of chirally controlled oligonucleotide composition, e.g., chirally controlled ds oligonucleotide targeting INHBE compositions in decreasing the level, activity and/or expression of a INHBE target gene or a gene product thereof, are shown in, for example, the Examples section of this document.

In some embodiments, the present disclosure provides an oligonucleotide composition comprising oligonucleotides that comprise at least one chiral linkage phosphorus. In some embodiments, the present disclosure provides a ds oligonucleotide targeting INHBE composition comprising ds oligonucleotides targeting INHBE that comprise at least one chiral linkage phosphorus. In some embodiments, the present disclosure provides a ds oligonucleotide targeting INHBE composition in which the ds oligonucleotides targeting INHBE comprise a chirally controlled phosphorothioate internucleotidic linkage, wherein the linkage phosphorus has a *R*p configuration. In some embodiments, the present disclosure provides a ds oligonucleotide targeting INHBE composition in which the ds oligonucleotides targeting INHBE comprise a chirally controlled phosphorothioate internucleotidic linkage, wherein the linkage phosphorus has a *S*p configuration.

In some embodiments, compared to reference oligonucleotide compositions, provided chirally controlled oligonucleotide compositions (e.g., chirally controlled ds oligonucleotide targeting INHBE compositions) are surprisingly effective. In some embodiments, desired biological effects (e.g., as measured by decreased levels of mRNA, proteins, etc. whose levels are targeted for reduction) can be enhanced by more than 5, 10, 15, 20, 25, 30, 40, 50, or 100 fold (e.g., as measured by remaining levels of mRNA, proteins, etc.). In some embodiments, a change is measured by decrease of an undesired mRNA level compared to a reference condition. In some embodiments, a change is measured by increase of a desired mRNA level compared to a reference condition. In some embodiments, a change is measured by decrease of an undesired mRNA level compared to a reference condition. In some embodiments, a reference condition is absence of treatment, e.g., by a chirally controlled oligonucleotide composition. In some embodiments, a reference condition is a corresponding stereorandom

composition of oligonucleotides having the same constitution.

In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition, e.g., a chirally controlled ds oligonucleotide targeting INHBE composition, wherein the linkage phosphorus of at least one chirally controlled internucleotidic linkage is *S*p. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition, e.g., a chirally controlled ds oligonucleotide targeting INHBE composition, wherein the majority of linkage phosphorus of chirally controlled internucleotidic linkages are *S*p. In some embodiments, about 50%-100%, 55%-100%, 60%-100%, 65%-100%, 70%-100%, 75%-100%, 80%-100%, 85%-100%, 90%-100%, 55%-95%, 60%-95%, 65%-95%, or about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99% or more, of all chirally controlled phosphorothioate internucleotidic linkages are *S*p. In some embodiments, about 50%-100%, 55%-100%, 60%-100%, 65%-100%, 70%-100%, 75%-100%, 80%-100%, 85%-100%, 90%-100%, 55%-95%, 60%-95%, 65%-95%, or about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99% or more, of all phosphorothioate internucleotidic linkages are chirally controlled and are *S*p. In some embodiments, about 50%-100%, 55%-100%, 60%-100%, 65%-100%, 70%-100%, 75%-100%, 80%-100%, 85%-100%, 90%-100%, 55%-95%, 60%-95%, 65%-95%, or about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99% or more, of all chirally controlled internucleotidic linkages (or of all chiral internucleotidic linkages, or of all internucleotidic linkages) are *S*p. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition, e.g., a chirally controlled ds oligonucleotide targeting INHBE composition, wherein the majority of chiral internucleotidic linkages are chirally controlled and are *S*p at their linkage phosphorus. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition, e.g., a chirally controlled ds oligonucleotide targeting INHBE composition, wherein each chiral internucleotidic linkage is chirally controlled and each chiral linkage phosphorus is *S*p. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition, e.g., chirally controlled ds oligonucleotide targeting INHBE composition, wherein at least one chirally controlled internucleotidic linkage has a *R*p linkage phosphorus. In some embodiments, the present disclosure provides a chirally controlled oligonucleotide composition, e.g., a chirally controlled ds oligonucleotide targeting INHBE composition, wherein at least one chirally controlled internucleotidic linkage comprises a *R*p linkage phosphorus and at least one chirally controlled internucleotidic linkage comprises a *S*p linkage phosphorus. In some embodiments, at least one phosphorothioate

internucleotidic linkage is chirally controlled and *R*p. In some embodiments, about 1-5, e.g., about 1, 2, 3, 4, or 5 phosphorothioate internucleotidic linkage is chirally controlled and *R*p. In some embodiments, about 50%-100%, 55%-100%, 60%-100%, 65%-100%, 70%-100%, 75%-100%, 80%-100%, 85%-100%, 90%-100%, 55%-95%, 60%-95%, 65%-95%, or about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99% or more, of all chirally controlled non-negatively charged internucleotidic linkages (e.g., n001) are *R*p. In some embodiments, each chirally controlled n001 is *R*p.

Stereochemistry and Patterns of Backbone Chiral Centers

In contrast to natural phosphate linkages, linkage phosphorus of chiral modified internucleotidic linkages, e.g., phosphorothioate internucleotidic linkages, are chiral. Among other things, the present disclosure provides technologies (e.g., oligonucleotides, compositions, methods, etc.) comprising control of stereochemistry of chiral linkage phosphorus in chiral internucleotidic linkages. In some embodiments, as demonstrated herein, control of stereochemistry can provide improved properties and/or activities, including desired stability, reduced toxicity, improved reduction of target nucleic acids, etc. In some embodiments, the present disclosure provides useful patterns of backbone chiral centers for oligonucleotides and/or regions thereof, which pattern is a combination of stereochemistry of each chiral linkage phosphorus (*R*p or *S*p) of chiral linkage phosphorus, indication of each achiral linkage phosphorus (Op, if any), etc. from 5' to 3'. In some embodiments, patterns of backbone chiral centers can control cleavage patterns of target nucleic acids when they are contacted with provided oligonucleotides or compositions thereof in a cleavage system (e.g., in vitro assay, cells, tissues, organs, organisms, subjects, etc.). In some embodiments, patterns of backbone chiral centers improve cleavage efficiency and/or selectivity of target nucleic acids when they are contacted with provided oligonucleotides or compositions thereof in a cleavage system.

In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region thereof comprises or is any (Np)n(Op)m, wherein Np is *R*p or *S*p, Op represents a linkage phosphorus being achiral (e.g., as for the linkage phosphorus of natural phosphate linkages), and each of n and m is independently as defined and described in the present disclosure. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region thereof comprises or is (*S*p)n(Op)m, wherein each variable is independently as defined and described in the present disclosure. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region thereof comprises or is (*R*p)n(Op)m, wherein each variable is independently as defined and described in the present disclosure. In some

embodiments, n is 1. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region thereof comprises or is (*S*p)(Op)m, wherein m is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region thereof comprises or is (*R*p)(Op)m, wherein m is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, the pattern of backbone chiral centers of a 5'-wing is or comprises (Np)n(Op)m. In some embodiments, the pattern of backbone chiral centers of a 5'-wing is or comprises (*S*p)n(Op)m. In some embodiments, the pattern of backbone chiral centers of a 5'-wing is or comprises (*R*p)n(Op)m. In some embodiments, the pattern of backbone chiral centers of a 5'-wing is or comprises (*S*p)(Op)m. In some embodiments, the pattern of backbone chiral centers of a 5'-wing is or comprises (*R*p)(Op)m. In some embodiments, the pattern of backbone chiral centers of a 5'-wing is (*S*p)(Op)m. In some embodiments, the pattern of backbone chiral centers of a 5'-wing is (*R*p)(Op)m. In some embodiments, the pattern of backbone chiral centers of a 5'-wing is (*S*p)(Op)m, wherein *S*p is the linkage phosphorus configuration of the first internucleotidic linkage of the oligonucleotide from the 5'-end. In some embodiments, the pattern of backbone chiral centers of a 5'-wing is (*R*p)(Op)m, wherein *R*p is the linkage phosphorus configuration of the first internucleotidic linkage of the oligonucleotide from the 5'-end. In some embodiments, as described in the present disclosure, m is 2; in some embodiments, m is 3; in some embodiments, m is 4; in some embodiments, m is 5; in some embodiments, m is 6.

In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region thereof comprises or is (Op)m(Np)n, wherein Np is *R*p or *S*p, Op represents a linkage phosphorus being achiral (e.g., as for the linkage phosphorus of natural phosphate linkages), and each of n and m is independently as defined and described in the present disclosure. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region thereof comprises or is (Op)m(*S*p)n, wherein each variable is independently as defined and described in the present disclosure. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region thereof comprises or is (Op)m(*R*p)n, wherein each variable is independently as defined and described in the present disclosure. In some embodiments, n is 1. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region thereof comprises or is (Op)m(*S*p), wherein m is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region thereof comprises or is (Op)m(*R*p), wherein m is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, the pattern of backbone chiral centers of a 3'-wing is or comprises (Op)m(Np)n. In some embodiments, the pattern of backbone chiral centers of a 3'-wing is or comprises (Op)m(*S*p)n.

In some embodiments, the pattern of backbone chiral centers of a 3'-wing is or comprises (Op)m(*R*p)n. In some embodiments, the pattern of backbone chiral centers of a 3'-wing is or comprises (Op)m(*S*p). In some embodiments, the pattern of backbone chiral centers of a 3'-wing is or comprises (Op)m(*R*p). In some embodiments, the pattern of backbone chiral centers of a 3'-wing is (Op)m(*S*p). In some embodiments, the pattern of backbone chiral centers of a 3'-wing is (Op)m(*R*p). In some embodiments, the pattern of backbone chiral centers of a 3'-wing is (Op)m(*S*p), wherein *S*p is the linkage phosphorus configuration of the last internucleotidic linkage of the oligonucleotide from the 5'-end. In some embodiments, the pattern of backbone chiral centers of a 3'-wing is (Op)m(*R*p), wherein *R*p is the linkage phosphorus configuration of the last internucleotidic linkage of the oligonucleotide from the 5'-end. In some embodiments, as described in the present disclosure, m is 2; in some embodiments, m is 3; in some embodiments, m is 4; in some embodiments, m is 5; in some embodiments, m is 6.

In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region thereof (e.g., a core) comprises or is (*S*p)m(*R*p/Op)n or (*R*p/Op)n(*S*p)m, wherein each variable is independently as described in the present disclosure. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region thereof (e.g., a core) comprises or is (*S*p)m(*R*p)n or (*R*p)n(*S*p)m, wherein each variable is independently as described in the present disclosure. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region thereof (e.g., a core) comprises or is (*S*p)m(Op)n or (Op)n(*S*p)m, wherein each variable is independently as described in the present disclosure. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region thereof (e.g., a core) comprises or is (Np)t[(*R*p/Op)n(*S*p)m]y or [(*R*p/Op)n(*S*p)m]y(Np)t, wherein y is 1-50, and each other variable is independently as described in the present disclosure. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region thereof (e.g., a core) comprises or is (Np)t[(*R*p)n(*S*p)m]y or [(*R*p)n(*S*p)m]y(Np)t, wherein each variable is independently as described in the present disclosure. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region thereof (e.g., a core) comprises or is [(*R*p/Op)n(*S*p)m]y(*R*p)k, [(*R*p/Op)n(*S*p)m]y, (*S*p)t[(*R*p/Op)n(*S*p)m]y, (*S*p)t[(*R*p/Op)n(*S*p)m]y(*R*p)k, wherein k is 1-50, and each other variable is independently as described in the present disclosure. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region thereof (e.g., a core) comprises or is [(Op)n(*S*p)m]y(*R*p)k, [(Op)n(*S*p)m]y, (*S*p)t[(Op)n(*S*p)m]y, (*S*p)t[(Op)n(*S*p)m]y(*R*p)k, wherein each variable is independently as described in the present disclosure. In some embodiments, a pattern of

backbone chiral centers of an oligonucleotide or a region thereof (e.g., a core) comprises or is [(*R*p)n(*S*p)m]y(*R*p)k, [(*R*p)n(*S*p)m]y, (*S*p)t[(*R*p)n(*S*p)m]y, (*S*p)t[(*R*p)n(*S*p)m]y(*R*p)k, wherein each variable is independently as described in the present disclosure. In some embodiments, an oligonucleotide comprises a core region. In some embodiments, an oligonucleotide comprises a core region, wherein each sugar in the core region does not contain a 2'-OR^1, wherein R^1 is as described in the present disclosure. In some embodiments, an oligonucleotide comprises a core region, wherein each sugar in the core region is independently a natural DNA sugar. In some embodiments, the pattern of backbone chiral centers of the core comprises or is (*R*p)(*S*p)m. In some embodiments, the pattern of backbone chiral centers of the core comprises or is (Op)(*S*p)m. In some embodiments, the pattern of backbone chiral centers of the core comprises or is (Np)t[(*R*p/Op)n(*S*p)m]y or [(*R*p/Op)n(*S*p)m]y(Np)t. In some embodiments, the pattern of backbone chiral centers of the core comprises or is (Np)t[(*R*p/Op)n(*S*p)m]y or [(*R*p/Op)n(*S*p)m]y(Np)t. In some embodiments, the pattern of backbone chiral centers of the core comprises or is (Np)t[(*R*p)n(*S*p)m]y or [(*R*p)n(*S*p)m]y(Np)t. In some embodiments, the pattern of backbone chiral centers of a core comprises or is [(*R*p/Op)n(*S*p)m]y(*R*p)k, [(*R*p/Op)n(*S*p)m]y, (*S*p)t[(*R*p/Op)n(*S*p)m]y, (*S*p)t[(*R*p/Op)n(*S*p)m]y(*R*p)k. In some embodiments, a pattern of backbone chiral centers of a core comprises or is [(Op)n(*S*p)m]y(*R*p)k, [(Op)n(*S*p)m]y, (*S*p)t[(Op)n(*S*p)m]y, (*S*p)t[(Op)n(*S*p)m]y(*R*p)k. In some embodiments, a pattern of backbone chiral centers of a core comprises or is [(*R*p)n(*S*p)m]y(*R*p)k, [(*R*p)n(*S*p)m]y, (*S*p)t[(*R*p)n(*S*p)m]y, or (*S*p)t[(*R*p)n(*S*p)m]y(*R*p)k. In some embodiments, a pattern of backbone chiral centers of a core comprises [(*R*p)n(*S*p)m]y(*R*p)k. In some embodiments, a pattern of backbone chiral centers of a core comprises [(*R*p)n(*S*p)m]y(*R*p). In some embodiments, a pattern of backbone chiral centers of a core comprises [(*R*p)n(*S*p)m]y. In some embodiments, a pattern of backbone chiral centers of a core comprises (*S*p)t[(*R*p)n(*S*p)m]y. In some embodiments, a pattern of backbone chiral centers of a core comprises (*S*p)t[(*R*p)n(*S*p)m]y(*R*p)k. In some embodiments, a pattern of backbone chiral centers of a core comprises (*S*p)t[(*R*p)n(*S*p)m]y(*R*p). In some embodiments, a pattern of backbone chiral centers of a core is [(*R*p)n(*S*p)m]y(*R*p)k. In some embodiments, a pattern of backbone chiral centers of a core is [(*R*p)n(*S*p)m]y(*R*p). In some embodiments, a pattern of backbone chiral centers of a core is [(*R*p)n(*S*p)m]y. In some embodiments, a pattern of backbone chiral centers of a core is (*S*p)t[(*R*p)n(*S*p)m]y. In some embodiments, a pattern of backbone chiral centers of a core is (*S*p)t[(*R*p)n(*S*p)m]y(*R*p)k. In some embodiments, a pattern of backbone chiral centers of a core is (*S*p)t[(*R*p)n(*S*p)m]y(*R*p). In some embodiments, each n is 1. In some embodiments, each t is 1. In some embodiments, t is 2, 3, 4, 5, 6, 7, 8, 9, or 10.

In some embodiments, each of t and n is 1. In some embodiments, each m is 2 or more. In some embodiments, k is 1. In some embodiments, k is 2-10.

In some embodiments, a pattern of backbone chiral centers comprises or is (*S*p)m(*R*p)n, (*R*p)n(*S*p)m, (Np)t(*R*p)n(*S*p)m, (*S*p)t(*R*p)n(*S*p)m, (Np)t[(*R*p)n(*S*p)m]2, (*S*p)t[(*R*p)n(*S*p)m]2, (Np)t(Op)n(*S*p)m, (*S*p)t(Op)n(*S*p)m, (Np)t[(Op)n(*S*p)m]2, or (*S*p)t[(Op)n(*S*p)m]2. In some embodiments, a pattern is (Np)t(Op/*R*p)n(*S*p)m(Op/*R*p)n(*S*p)m. In some embodiments, a pattern is (Np)t(Op/*R*p)n(*S*p)1-5(Op/*R*p)n(*S*p)m. In some embodiments, a pattern is (Np)t(Op/*R*p)n(*S*p)2-5(Op/*R*p)n(*S*p)m. In some embodiments, a pattern is (Np)t(Op/*R*p)n(*S*p)2(Op/*R*p)n(*S*p)m. In some embodiments, a pattern is (Np)t(Op/*R*p)n(*S*p)3(Op/*R*p)n(*S*p)m. In some embodiments, a pattern is (Np)t(Op/*R*p)n(*S*p)4(Op/*R*p)n(*S*p)m. In some embodiments, a pattern is (Np)t(Op/*R*p)n(*S*p)5(Op/*R*p)n(*S*p)m.

In some embodiments, Np is *S*p. In some embodiments, (Op/*R*p) is Op. In some embodiments, (Op/*R*p) is *R*p. In some embodiments, Np is *S*p and (Op/*R*p) is *R*p. In some embodiments, Np is *S*p and (Op/*R*p) is Op. In some embodiments, Np is *S*p and at least one (Op/*R*p) is *R*p, and at least one (Op/*R*p) is Op. In some embodiments, a pattern of backbone chiral centers comprises or is (*R*p)n(*S*p)m, (Np)t(*R*p)n(*S*p)m, or (*S*p)t(*R*p)n(*S*p)m, wherein m > 2. In some embodiments, a pattern of backbone chiral centers comprises or is (*R*p)n(*S*p)m, (Np)t(*R*p)n(*S*p)m, or (*S*p)t(*R*p)n(*S*p)m, wherein n is 1, at least one t >1, and at least one m > 2.

In some embodiments, oligonucleotides comprising core regions whose patterns of backbone chiral centers starting with *R*p can provide high activities and/or improved properties. In some embodiments, oligonucleotides comprising core regions whose patterns of backbone chiral centers ending with *R*p can provide high activities and/or improved properties. In some embodiments, oligonucleotides comprising core regions whose patterns of backbone chiral centers starting with *R*p provide high activities (e.g., target cleavage) without significantly impacting its properties, e.g., stability. In some embodiments, oligonucleotides comprising core regions whose patterns of backbone chiral centers ending with *R*p provide high activities (e.g., target cleavage) without significantly impacting its properties, e.g., stability. In some embodiments, patterns of backbone chiral centers start with *R*p and end with *S*p. In some embodiments, patterns of backbone chiral centers start with *R*p and end with *R*p. In some embodiments, patterns of backbone chiral centers start with *S*p and end with *R*p. Typically, for patterns of backbone chiral centers internucleotidic linkages connecting core nucleosides and wing nucleosides are included in the patterns of the core regions. In many embodiments as described in the present disclosure (e.g., various oligonucleotides in Table 1), the wing sugar

connected by such a connecting internucleotidic linkage has a different structure than the core sugar connected by the same connecting internucleotidic linkage (e.g., in some embodiments, the wing sugar comprises a 2'-modification while the core sugar does not contain the same 2'-modification or have two −H at the 2' position). In some embodiments, the wing sugar comprises a sugar modification that the core sugar does not contain. In some embodiments, the wing sugar is a modified sugar while the core sugar is a natural DNA sugar. In some embodiments, the wing sugar comprises a sugar modification at the 2' position (less than two −H at the 2' position), and the core sugar has no modification at the 2'-position (two −H at the 2' position).

In some embodiments, as demonstrated herein, an additional *R*p internucleotidic linkage links a sugar containing no 2'-substituent (*e.g.*, a core sugar) and a sugar comprising a 2'-modification (*e.g.*, 2'-OR', wherein R' is optionally substituted C_{1-6} aliphatic (*e.g.*, 2'-OMe, 2'-MOE, *etc.*), which can be a wing sugar). In some embodiments, an internucleotidic linkage linking a sugar containing no 2'-substituent to the 5'-end (*e.g.*, to the 3'-carbon of the sugar) and a sugar comprising a 2'-modification to the 3'-end (*e.g.*, to the 5'-carbon of the sugar) is a *R*p internucleotidic linkage. In some embodiments, an internucleotidic linkage linking a sugar containing no 2'-substituent to the 3'-end (*e.g.*, to the 5'-carbon of the sugar) and a sugar comprising a 2'-modification to the 5'-end (*e.g.*, to the 3'-carbon of the sugar) is a *R*p internucleotidic linkage. In some embodiments, each internucleotidic linkage linking a sugar containing no 2'-substituent and a sugar comprising a 2'-modification is independently a *R*p internucleotidic linkage. In some embodiments, a *R*p internucleotidic linkage is a *R*p phosphorothioate internucleotidic linkage.

In some embodiments, a pattern of backbone chiral centers of a ds oligonucleotide targeting INHBE or a region thereof (e.g., a core) comprises or is (Op)[(*R*p/Op)n(*S*p)m]y(*R*p)k(Op), (Op)[(*R*p/Op)n(*S*p)m]y(Op), (Op)(*S*p)t[(*R*p/Op)n(*S*p)m]y(Op), or (Op)(*S*p)t[(*R*p/Op)n(*S*p)m]y(*R*p)k(Op), wherein k is 1-50, and each other variable is independently as described in the present disclosure. In some embodiments, a pattern of backbone chiral centers of a ds oligonucleotide targeting INHBE comprises or is (Op)[(*R*p/Op)n(*S*p)m]y(*R*p)k(Op), (Op)[(*R*p/Op)n(*S*p)m]y(Op), (Op)(*S*p)t[(*R*p/Op)n(*S*p)m]y(Op), or (Op)(*S*p)t[(*R*p/Op)n(*S*p)m]y(*R*p)k(Op), wherein each of f, g, h and j is independently 1-50, and each other variable is independently as described in the present disclosure, and the oligonucleotide comprises a core region whose pattern of backbone chiral centers comprises or is [(*R*p/Op)n(*S*p)m]y(*R*p)k, [(*R*p/Op)n(*S*p)m]y, (*S*p)t[(*R*p/Op)n(*S*p)m]y, or (*S*p)t[(*R*p/Op)n(*S*p)m]y(*R*p)k as described in the present disclosure.

In some embodiments, a pattern of backbone chiral centers is or comprises (Op)[(*R*p/Op)n(*S*p)m]y(*R*p)k(Op). In some embodiments, a pattern of backbone chiral centers is or comprises (Op)[(Rp/Op)n(Sp)m]y(Rp)(Op). In some embodiments, a pattern of backbone chiral centers is or comprises (Op)[(*R*p/Op)n(*S*p)m]y(Op). In some embodiments, a pattern of backbone chiral centers is or comprises (Op)(*S*p)t[(*R*p/Op)n(*S*p)m]y(Op). In some embodiments, a pattern of backbone chiral centers is or comprises (Op)(*S*p)t[(*R*p/Op)n(*S*p)m]y(*R*p)k(Op). In some embodiments, a pattern of backbone chiral centers is or comprises (Op)(*S*p)t[(*R*p/Op)n(*S*p)m]y(*R*p)(Op). In some embodiments, a pattern of backbone chiral centers is or comprises (Op)[(Rp)n(Sp)m]y(Rp)k(Op). In some embodiments, a pattern of backbone chiral centers is or comprises (Op)[(*R*p)n(*S*p)m]y(*R*p)(Op). In some embodiments, a pattern of backbone chiral centers is or comprises (Op)[(*R*p)n(*S*p)m]y(Op). In some embodiments, a pattern of backbone chiral centers is or comprises (Op)(*S*p)t[(*R*p)n(*S*p)m]y(Op). In some embodiments, a pattern of backbone chiral centers is or comprises (Op)(*S*p)t[(*R*p)n(*S*p)m]y(*R*p)k(Op). In some embodiments, a pattern of backbone chiral centers is or comprises (Op)(*S*p)t[(*R*p)n(*S*p)m]y(*R*p)(Op). In some embodiments, each n is 1. In some embodiments, k is 1. In some embodiments, k is 2-10.

In some embodiments, a pattern of backbone chiral centers of a ds oligonucleotide targeting INHBE or a region thereof (e.g., a core) comprises or is (Np)f(Op)g[(*R*p/Op)n(*S*p)m]y(*R*p)k(Op)h(Np)j, (Np)f(Op)g[(*R*p/Op)n(*S*p)m]y(Op)h(Np)j, (Np)f(Op)g(*S*p)t[(*R*p/Op)n(*S*p)m]y(Op)h(Np)j, or (Np)f(Op)g(*S*p)t[(*R*p/Op)n(*S*p)m]y(*R*p)k(Op)h(Np)j, wherein each of f, g, h and j is independently 1-50, and each other variable is independently as described in the present disclosure. In some embodiments, a pattern of backbone chiral centers of a ds oligonucleotide targeting INHBE comprises or is (Np)f(Op)g[(*R*p/Op)n(*S*p)m]y(*R*p)k(Op)h(Np)j, (Np)f(Op)g[(*R*p/Op)n(*S*p)m]y(Op)h(Np)j, (Np)f(Op)g(*S*p)t[(*R*p/Op)n(*S*p)m]y(Op)h(Np)j, or (Np)f(Op)g(*S*p)t[(*R*p/Op)n(*S*p)m]y(*R*p)k(Op)h(Np)j, and the oligonucleotide comprises a core region whose pattern of backbone chiral centers comprises or is [(*R*p/Op)n(*S*p)m]y(*R*p)k, [(*R*p/Op)n(*S*p)m]y, (*S*p)t[(*R*p/Op)n(*S*p)m]y, or (*S*p)t[(*R*p/Op)n(*S*p)m]y(*R*p)k as described in the present disclosure. In some embodiments, a pattern of backbone chiral centers of a ds oligonucleotide targeting INHBE is (Np)f(Op)g[(*R*p/Op)n(*S*p)m]y(*R*p)k(Op)h(Np)j, (Np)f(Op)g[(*R*p/Op)n(*S*p)m]y(Op)h(Np)j, (Np)f(Op)g(*S*p)t[(*R*p/Op)n(*S*p)m]y(Op)h(Np)j, or (Np)f(Op)g(Sp)t[(Rp/Op)n(Sp)m]y(Rp)k(Op)h(Np)j, and the oligonucleotide comprises a core region whose pattern of backbone chiral centers comprises or is [(Rp/Op)n(Sp)m]y(Rp)k, [(Rp/Op)n(Sp)m]y, (Sp)t[(Rp/Op)n(Sp)m]y, or (Sp)t[(Rp/Op)n(Sp)m]y(Rp)k as described in

the present disclosure. In some embodiments, a pattern of backbone chiral centers is or comprises (Np)f(Op)g[(Rp/Op)n(Sp)m]y(Rp)k(Op)h(Np)j. In some embodiments, a pattern of backbone chiral centers is or comprises (Np)f(Op)g[(Rp/Op)n(Sp)m]y(Rp)(Op)h(Np)j. In some embodiments, a pattern of backbone chiral centers is or comprises (Np)f(Op)g[(Rp/Op)n(Sp)m]y(Op)h(Np)j. In some embodiments, a pattern of backbone chiral centers is or comprises (Np)f(Op)g(Sp)t[(Rp/Op)n(Sp)m]y(Op)h(Np)j. In some embodiments, a pattern of backbone chiral centers is or comprises (Np)f(Op)g(Sp)t[(Rp/Op)n(Sp)m]y(Rp)k(Op)h(Np)j. In some embodiments, a pattern of backbone chiral centers is or comprises (Np)f(Op)g(Sp)t[(Rp/Op)n(Sp)m]y(Rp)(Op)h(Np)j. In some embodiments, a pattern of backbone chiral centers is or comprises (Np)f(Op)g[(Rp)n(Sp)m]y(Rp)k(Op)h(Np)j. In some embodiments, a pattern of backbone chiral centers is or comprises (Np)f(Op)g[(Rp)n(Sp)m]y(Rp)(Op)h(Np)j. In some embodiments, a pattern of backbone chiral centers is or comprises (Np)f(Op)g[(Rp)n(Sp)m]y(Op)h(Np)j. In some embodiments, a pattern of backbone chiral centers is or comprises (Np)f(Op)g(Sp)t[(Rp)n(Sp)m]y(Op)h(Np)j. In some embodiments, a pattern of backbone chiral centers is or comprises (Np)f(Op)g(Sp)t[(Rp)n(Sp)m]y(Rp)k(Op)h(Np)j. In some embodiments, a pattern of backbone chiral centers is or comprises (Np)f(Op)g(Sp)t[(Rp)n(Sp)m]y(Rp)(Op)h(Np)j. In some embodiments, at least one Np is Sp. In some embodiments, at least one Np is Rp. In some embodiments, the 5' most Np is Sp. In some embodiments, the 3' most Np is Sp. In some embodiments, each Np is Sp. In some embodiments, (Np)f(Op)g[(Rp/Op)n(Sp)m]y(Rp)k(Op)h(Np)j is (Sp)(Op)g[(Rp)n(Sp)m]y(Rp)k(Op)h(Sp). In some embodiments, (Np)f(Op)g[(Rp/Op)n(Sp)m]y(Rp)k(Op)h(Np)j is (Sp)(Op)g[(Rp)n(Sp)m]y(Rp)(Op)h(Sp). In some embodiments, a pattern of backbone chiral center of an oligonucleotide is or comprises (Sp)(Op)g[(Rp)n(Sp)m]y(Rp)(Op)h(Sp). In some embodiments, a pattern of backbone chiral center of an oligonucleotide is (Sp)(Op)g[(Rp)n(Sp)m]y(Rp)(Op)h(Sp). In some embodiments, (Np)f(Op)g[(Rp/Op)n(Sp)m]y(Op)h(Np)j is (Sp)(Op)g[(Rp)n(Sp)m]y(Op)h(Sp). In some embodiments, a pattern of backbone chiral center of an oligonucleotide is or comprises (Sp)(Op)g[(Rp)n(Sp)m]y(Op)h(Sp). In some embodiments, a pattern of backbone chiral center of an oligonucleotide is (Sp)(Op)g[(Rp)n(Sp)m]y(Op)h(Sp). In some embodiments, (Np)f(Op)g(Sp)t[(Rp/Op)n(Sp)m]y(Op)h(Np)j is (Sp)(Op)g(Sp)t[(Rp)n(Sp)m]y(Op)h(Sp). In some embodiments, a pattern of backbone chiral center of an oligonucleotide is or comprises (Sp)(Op)g(Sp)t[(Rp)n(Sp)m]y(Op)h(Sp). In some embodiments, a pattern of backbone chiral

center of an oligonucleotide is (Sp)(Op)g(Sp)t[(Rp)n(Sp)m]y(Op)h(Sp). In some embodiments, (Np)f(Op)g(Sp)t[(Rp/Op)n(Sp)m]y(Rp)k(Op)h(Np)j is (Sp)(Op)g(Sp)t[(Rp)n(Sp)m]y(Rp)k(Op)h(Sp). In some embodiments, (Np)f(Op)g(Sp)t[(Rp/Op)n(Sp)m]y(Rp)k(Op)h(Np)j is (Sp)(Op)g(Sp)t[(Rp)n(Sp)m]y(Rp)(Op)h(Sp). In some embodiments, a pattern of backbone chiral center of an oligonucleotide is or comprises (Sp)(Op)g(Sp)t[(Rp)n(Sp)m]y(Rp)(Op)h(Sp). In some embodiments, a pattern of backbone chiral center of an oligonucleotide is (Sp)(Op)g(Sp)t[(Rp)n(Sp)m]y(Rp)(Op)h(Sp). In some embodiments, each n is 1. In some embodiments, f is 1. In some embodiments, g is 1. In some embodiments, g is greater than 1. In some embodiments, g is 2. In some embodiments, g is 3. In some embodiments, g is 4. In some embodiments, g is 5. In some embodiments, g is 6. In some embodiments, g is 7. In some embodiments, g is 8. In some embodiments, g is 9. In some embodiments, g is 10. In some embodiments, h is 1. In some embodiments, h is greater than 1. In some embodiments, h is 2. In some embodiments, h is 3. In some embodiments, h is 4. In some embodiments, h is 5. In some embodiments, h is 6. In some embodiments, h is 7. In some embodiments, h is 8. In some embodiments, h is 9. In some embodiments, h is 10. In some embodiments, j is 1. In some embodiments, k is 1. In some embodiments, k is 2-10.

In some embodiments, a pattern of backbone chiral centers of a ds oligonucleotide targeting INHBE or a region thereof (e.g., a core) comprises or is [(Rp/Op)n(Sp)m]y, (Sp)t[(Rp/Op)n(Sp)m]y, (Sp)t[(Rp/Op)n(Sp)m]yRp, [(Rp/Op)n(Sp)m]y(Rp)k, (Sp)t[(Rp/Op)n(Sp)m]y(Rp)k, (Sp)t[(Rp/Op)n(Sp)m]y(Rp)k(Op)h, (Sp)t[(Rp/Op)n(Sp)m]y(Rp)k(Op)h(Np)j, wherein each variable is independently as described in the present disclosure.

In some embodiments, in a provided pattern of backbone chiral centers, at least one (*R*p/Op) is *R*p. In some embodiments, at least one (*R*p/Op) is Op. In some embodiments, each (*R*p/Op) is *R*p. In some embodiments, each (*R*p/Op) is Op. In some embodiments, at least one of [(*R*p)n(*S*p)m]y or [(*R*p/Op)n(*S*p)m]y of a pattern is *R*p*S*p. In some embodiments, at least one of [(*R*p)n(*S*p)m]y or [(*R*p/Op)n(*S*p)m]y of a pattern is or comprises *R*p*S*p*S*p. In some embodiments, at least one of [(*R*p)n(*S*p)m]y or [(*R*p/Op)n(*S*p)m]y in a pattern is *R*p*S*p, and at least one of [(*R*p)n(*S*p)m]y or [(*R*p/Op)n(*S*p)m]y in a pattern is or comprises *R*p*S*p*S*p. For example, in some embodiments, [(*R*p)n(*S*p)m]y in a pattern is (*R*p*S*p)[(*R*p)n(*S*p)m]$_{(y-1)}$; in some embodiments, [(*R*p)n(*S*p)m]y in a pattern is (*R*p*S*p)[*R*p*S*p*S*p(*S*p)$_{(m-2)}$][(*R*p)n(*S*p)m]$_{(y-2)}$. In some embodiments, (*S*p)t[(*R*p)n(*S*p)m]y(*R*p) is (*S*p)t(*R*p*S*p)[(*R*p)n(*S*p)m]$_{(y-1)}$(*R*p). In some embodiments, (*S*p)t[(*R*p)n(*S*p)m]y(*R*p) is (*S*p)t(*R*p*S*p)[*R*p*S*p*S*p(*S*p)$_{(m-2)}$][(*R*p)n(*S*p)m]$_{(y-2)}$(*R*p).

In some embodiments, each [(Rp/Op)n(Sp)m] is independently [Rp(Sp)m]. In some embodiments, the first Sp of (Sp)t represents linkage phosphorus stereochemistry of the first internucleotidic linkage of an oligonucleotide from 5' to 3'. In some embodiments, the first Sp of (Sp)t represents linkage phosphorus stereochemistry of the first internucleotidic linkage of a region from 5' to 3', e.g., a core. In some embodiments, the last Np of (Np)j represents linkage phosphorus stereochemistry of the last internucleotidic linkage of the oligonucleotide from 5' to 3'. In some embodiments, the last Np is Sp.

In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region (*e.g.*, of a 5'-wing) is or comprises *S*p(Op)$_3$. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region (*e.g.*, of a 5'-wing) is or comprises *R*p(Op)$_3$. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region (*e.g.*, of a 3'-wing) is or comprises (Op)$_3$*S*p. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region (*e.g.*, of a 3'-wing) is or comprises (Op)$_3$*R*p. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region (*e.g.*, of a core) is or comprises *R*p(*S*p)$_4$*R*p(*S*p)$_4$*R*p. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region (*e.g.*, of a core) is or comprises (*S*p)$_5$*R*p(*S*p)$_4$*R*p. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region (*e.g.*, of a core) is or comprises (*S*p)$_5$*R*p(*S*p)$_5$. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide or a region (*e.g.*, of a core) is or comprises *R*p(*S*p)$_4$*R*p(*S*p)$_5$. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide is or comprises *N*p(Op)$_3$*R*p(*S*p)$_4$*R*p(*S*p)$_4$*R*p(Op)$_3$*N*p. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide is or comprises *N*p(Op)$_3$(*S*p)$_5$*R*p(*S*p)$_4$*R*p(Op)$_3$*N*p. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide is or comprises *N*p(Op)$_3$(*S*p)$_5$*R*p(*S*p)$_5$(Op)$_3$*N*p. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide is or comprises *N*p(Op)$_3$*R*p(*S*p)$_4$*R*p(*S*p)$_5$(Op)$_3$*N*p. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide is or comprises *S*p(Op)$_3$*R*p(*S*p)$_4$*R*p(*S*p)$_4$*R*p(Op)$_3$*S*p. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide is or comprises *S*p(Op)$_3$(*S*p)$_5$*R*p(*S*p)$_4$*R*p(Op)$_3$*S*p. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide is or comprises *S*p(Op)$_3$(*S*p)$_5$*R*p(*S*p)$_5$(Op)$_3$*S*p. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide is or comprises *S*p(Op)$_3$*R*p(*S*p)$_4$*R*p(*S*p)$_5$(Op)$_3$*S*p. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide is or comprises *R*p(Op)$_3$*R*p(*S*p)$_4$*R*p(*S*p)$_4$*R*p(Op)$_3$*R*p. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide is or comprises

*R*p(Op)$_3$(*S*p)$_5$*R*p(*S*p)$_4$*R*p(Op)$_3$*R*p. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide is or comprises *R*p(Op)$_3$(*S*p)$_5$*R*p(*S*p)$_5$(Op)$_3$*R*p. In some embodiments, a pattern of backbone chiral centers of an oligonucleotide is or comprises *R*p(Op)$_3$*R*p(*S*p)$_4$*R*p(*S*p)$_5$(Op)$_3$*R*p.

In some embodiments, each of m, y, t, n, k, f, g, h, and j is independently 1-25.

In some embodiments, m is 1-25. In some embodiments, m is 1-20. In some embodiments, m is 1-15. In some embodiments, m is 1-10. In some embodiments, m is 1-5. In some embodiments, m is 2-20. In some embodiments, m is 2-15. In some embodiments, m is 2-10. In some embodiments, m is 2-5. In some embodiments, m is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25. In some embodiments, in a pattern of backbone chiral centers each m is independently 2 or more. In some embodiments, each m is independently 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, each m is independently 2-3, 2-5, 2-6, or 2-10. In some embodiments, m is 2. In some embodiments, m is 3. In some embodiments, m is 4. In some embodiments, m is 5. In some embodiments, m is 6. In some embodiments, m is 7. In some embodiments, m is 8. In some embodiments, m is 9. In some embodiments, m is 10. In some embodiments, where there are two or more occurrences of m, they can be the same or different, and each of them is independently as described in the present disclosure.

In some embodiments, y is 1-25. In some embodiments, y is 1-20. In some embodiments, y is 1-15. In some embodiments, y is 1-10. In some embodiments, y is 1-5. In some embodiments, y is 2-20. In some embodiments, y is 2-15. In some embodiments, y is 2-10. In some embodiments, y is 2-5. In some embodiments, y is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25. In some embodiments, y is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, y is 1. In some embodiments, y is 2. In some embodiments, y is 3. In some embodiments, y is 4. In some embodiments, y is 5. In some embodiments, y is 6. In some embodiments, y is 7. In some embodiments, y is 8. In some embodiments, y is 9. In some embodiments, y is 10.

In some embodiments, t is 1-25. In some embodiments, t is 1-20. In some embodiments, t is 1-15. In some embodiments, t is 1-10. In some embodiments, t is 1-5. In some embodiments, t is 2-20. In some embodiments, t is 2-15. In some embodiments, t is 2-10. In some embodiments, t is 2-5. In some embodiments, t is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25. In some embodiments, each t is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, t is 2 or more. In some embodiments, t is 1. In some embodiments, t is 2. In some embodiments, t is 3. In some

embodiments, t is 4. In some embodiments, t is 5. In some embodiments, t is 6. In some embodiments, t is 7. In some embodiments, t is 8. In some embodiments, t is 9. In some embodiments, t is 10. In some embodiments, where there are two or more occurrences of t, they can be the same or different, and each of them is independently as described in the present disclosure.

In some embodiments, n is 1-25. In some embodiments, n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4. In some embodiments, n is 5. In some embodiments, n is 6. In some embodiments, n is 7. In some embodiments, n is 8. In some embodiments, n is 9. In some embodiments, n is 10. In some embodiments, where there are two or more occurrences of n, they can be the same or different, and each of them is independently as described in the present disclosure. In many embodiments, in a pattern of backbone chiral centers, at least one occurrence of n is 1; in some cases, each n is 1.

In some embodiments, k is 1-25. In some embodiments, k is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25. In some embodiments, k is 1. In some embodiments, k is 2. In some embodiments, k is 3. In some embodiments, k is 4. In some embodiments, k is 5. In some embodiments, k is 6. In some embodiments, k is 7. In some embodiments, k is 8. In some embodiments, k is 9. In some embodiments, k is 10.

In some embodiments, f is 1-25. In some embodiments, f is 1-20. In some embodiments, f is 1-10. In some embodiments, f is 1-5. In some embodiments, f is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25. In some embodiments, f is 1. In some embodiments, f is 2. In some embodiments, f is 3. In some embodiments, f is 4. In some embodiments, f is 5. In some embodiments, f is 6. In some embodiments, f is 7. In some embodiments, f is 8. In some embodiments, f is 9. In some embodiments, f is 10.

In some embodiments, g is 1-25. In some embodiments, g is 1-20. In some embodiments, g is 1-10. In some embodiments, g is 1-5. In some embodiments, g is 2-10. In some embodiments, g is 2-5. In some embodiments, g is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25. In some embodiments, g is 1. In some embodiments, g is 2. In some embodiments, g is 3. In some embodiments, g is 4. In some embodiments, g is 5. In some embodiments, g is 6. In some embodiments, g is 7. In some embodiments, g is 8. In some embodiments, g is 9. In some embodiments, g is 10.

In some embodiments, h is 1-25. In some embodiments, h is 1-10. In some

embodiments, h is 1-5. In some embodiments, h is 2-10. In some embodiments, h is 2-5. In some embodiments, h is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25. In some embodiments, h is 1. In some embodiments, h is 2. In some embodiments, h is 3. In some embodiments, h is 4. In some embodiments, h is 5. In some embodiments, h is 6. In some embodiments, h is 7. In some embodiments, h is 8. In some embodiments, h is 9. In some embodiments, h is 10.

In some embodiments, j is 1-25. In some embodiments, j is 1-10. In some embodiments, j is 1-5. In some embodiments, j is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25. In some embodiments, j is 1. In some embodiments, j is 2. In some embodiments, j is 3. In some embodiments, j is 4. In some embodiments, j is 5. In some embodiments, j is 6. In some embodiments, j is 7. In some embodiments, j is 8. In some embodiments, j is 9. In some embodiments, j is 10.

In some embodiments, at least one n is 1, and at least one m is no less than 2. In some embodiments, at least one n is 1, at least one t is no less than 2, and at least one m is no less than 3. In some embodiments, each n is 1. In some embodiments, t is 1. In some embodiments, at least one $t > 1$. In some embodiments, at least one $t > 2$. In some embodiments, at least one $t > 3$. In some embodiments, at least one $t > 4$. In some embodiments, at least one $m > 1$. In some embodiments, at least one $m > 2$. In some embodiments, at least one $m > 3$. In some embodiments, at least one $m > 4$. In some embodiments, a pattern of backbone chiral centers comprises one or more achiral natural phosphate linkages. In some embodiments, the sum of m, t, and n (or m and n if no t in a pattern) is no less than 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20. In some embodiments, the sum is 5. In some embodiments, the sum is 6. In some embodiments, the sum is 7. In some embodiments, the sum is 8. In some embodiments, the sum is 9. In some embodiments, the sum is 10. In some embodiments, the sum is 11. In some embodiments, the sum is 12. In some embodiments, the sum is 13. In some embodiments, the sum is 14. In some embodiments, the sum is 15.

In some embodiments, a number of linkage phosphorus in chirally controlled internucleotidic linkages are *Sp*. In some embodiments, at least 10%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% of chirally controlled internucleotidic linkages have *Sp* linkage phosphorus. In some embodiments, at least 10%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% of all chiral internucleotidic linkages are chirally controlled internucleotidic linkages having *Sp* linkage phosphorus. In some embodiments, at least 10%, 20%, 25%, 30%, 35%, 40%, 45%,

50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% of all internucleotidic linkages are chirally controlled internucleotidic linkages having *Sp* linkage phosphorus. In some embodiments, the percentage is at least 20%. In some embodiments, the percentage is at least 30%. In some embodiments, the percentage is at least 40%. In some embodiments, the percentage is at least 50%. In some embodiments, the percentage is at least 60%. In some embodiments, the percentage is at least 65%. In some embodiments, the percentage is at least 70%. In some embodiments, the percentage is at least 75%. In some embodiments, the percentage is at least 80%. In some embodiments, the percentage is at least 90%. In some embodiments, the percentage is at least 95%. In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 internucleotidic linkages are chirally controlled internucleotidic linkages having *Sp* linkage phosphorus. In some embodiments, at least 5 internucleotidic linkages are chirally controlled internucleotidic linkages having *Sp* linkage phosphorus. In some embodiments, at least 6 internucleotidic linkages are chirally controlled internucleotidic linkages having *Sp* linkage phosphorus. In some embodiments, at least 7 internucleotidic linkages are chirally controlled internucleotidic linkages having *Sp* linkage phosphorus. In some embodiments, at least 8 internucleotidic linkages are chirally controlled internucleotidic linkages having *Sp* linkage phosphorus. In some embodiments, at least 9 internucleotidic linkages are chirally controlled internucleotidic linkages having *Sp* linkage phosphorus. In some embodiments, at least 10 internucleotidic linkages are chirally controlled internucleotidic linkages having *Sp* linkage phosphorus. In some embodiments, at least 11 internucleotidic linkages are chirally controlled internucleotidic linkages having *Sp* linkage phosphorus. In some embodiments, at least 12 internucleotidic linkages are chirally controlled internucleotidic linkages having *Sp* linkage phosphorus. In some embodiments, at least 13 internucleotidic linkages are chirally controlled internucleotidic linkages having *Sp* linkage phosphorus. In some embodiments, at least 14 internucleotidic linkages are chirally controlled internucleotidic linkages having *Sp* linkage phosphorus. In some embodiments, at least 15 internucleotidic linkages are chirally controlled internucleotidic linkages having *Sp* linkage phosphorus. In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 internucleotidic linkages are chirally controlled internucleotidic linkages having *Rp* linkage phosphorus. In some embodiments, no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 internucleotidic linkages are chirally controlled internucleotidic linkages having *Rp* linkage phosphorus. In some embodiments, one and no more than one internucleotidic linkage in an oligonucleotide is a chirally controlled internucleotidic linkage

having *R*p linkage phosphorus. In some embodiments, 2 and no more than 2 internucleotidic linkages in an oligonucleotide are chirally controlled internucleotidic linkages having *R*p linkage phosphorus. In some embodiments, 3 and no more than 3 internucleotidic linkages in an oligonucleotide are chirally controlled internucleotidic linkages having *R*p linkage phosphorus. In some embodiments, 4 and no more than 4 internucleotidic linkages in an oligonucleotide are chirally controlled internucleotidic linkages having *R*p linkage phosphorus. In some embodiments, 5 and no more than 5 internucleotidic linkages in an oligonucleotide are chirally controlled internucleotidic linkages having *R*p linkage phosphorus.

In some embodiments, all, essentially all or most of the internucleotidic linkages in an oligonucleotide are in the *S*p configuration (e.g., about 50%-100%, 55%-100%, 60%-100%, 65%-100%, 70%-100%, 75%-100%, 80%-100%, 85%-100%, 90%-100%, 55%-95%, 60%-95%, 65%-95%, or about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99% or more of all chirally controlled internucleotidic linkages, or of all chiral internucleotidic linkages, or of all internucleotidic linkages in the oligonucleotide) except for one or a minority of internucleotidic linkages (e.g., 1, 2, 3, 4, or 5, and/or less than 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, or 5% of all chirally controlled internucleotidic linkages, or of all chiral internucleotidic linkages, or of all internucleotidic linkages in the oligonucleotide) being in the *R*p configuration. In some embodiments, all, essentially all or most of the internucleotidic linkages in a core are in the *S*p configuration (e.g., about 50%-100%, 55%-100%, 60%-100%, 65%-100%, 70%-100%, 75%-100%, 80%-100%, 85%-100%, 90%-100%, 55%-95%, 60%-95%, 65%-95%, or about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99% or more of all chirally controlled internucleotidic linkages, or of all chiral internucleotidic linkages, or of all internucleotidic linkages, in the core) except for one or a minority of internucleotidic linkages (e.g., 1, 2, 3, 4, or 5, and/or less than 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, or 5% of all chirally controlled internucleotidic linkages, or of all chiral internucleotidic linkages, or of all internucleotidic linkages, in the core) being in the *R*p configuration. In some embodiments, all, essentially all or most of the internucleotidic linkages in the core are a phosphorothioate in the *S*p configuration (e.g., about 50%-100%, 55%-100%, 60%-100%, 65%-100%, 70%-100%, 75%-100%, 80%-100%, 85%-100%, 90%-100%, 55%-95%, 60%-95%, 65%-95%, or about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99% or more of all chirally controlled internucleotidic linkages, or of all chiral internucleotidic linkages, or of all internucleotidic linkages, in the core) except for one or a minority of internucleotidic linkages (e.g., 1, 2, 3, 4, or 5, and/or less than 50%, 45%, 40%, 35%, 30%,

25%, 20%, 15%, 10%, or 5% of all chirally controlled internucleotidic linkages, or of all chiral internucleotidic linkages, or of all internucleotidic linkages, in the core) being a phosphorothioate in the *R*p configuration. In some embodiments, each internucleotidic linkage in the core is a phosphorothioate in the *S*p configuration except for one phosphorothioate in the *R*p configuration. In some embodiments, each internucleotidic linkage in the core is a phosphorothioate in the *S*p configuration except for one phosphorothioate in the *R*p configuration.

In some embodiments, an oligonucleotide comprises one or more *R*p internucleotidic linkages. In some embodiments, an oligonucleotide comprises one and no more than one *R*p internucleotidic linkages. In some embodiments, an oligonucleotide comprises two or more *R*p internucleotidic linkages. In some embodiments, an oligonucleotide comprises three or more *R*p internucleotidic linkages. In some embodiments, an oligonucleotide comprises four or more *R*p internucleotidic linkages. In some embodiments, an oligonucleotide comprises five or more *R*p internucleotidic linkages. In some embodiments, about 5%-50% of all chirally controlled internucleotidic linkages in an oligonucleotide are *R*p. In some embodiments, about 5%-40% of all chirally controlled internucleotidic linkages in an oligonucleotide are *R*p. In some embodiments, about 10%-40% of all chirally controlled internucleotidic linkages in an oligonucleotide are *R*p. In some embodiments, about 15%-40% of all chirally controlled internucleotidic linkages in an oligonucleotide are *R*p. In some embodiments, about 20%-40% of all chirally controlled internucleotidic linkages in an oligonucleotide are *R*p. In some embodiments, about 25%-40% of all chirally controlled internucleotidic linkages in an oligonucleotide are *R*p. In some embodiments, about 30%-40% of all chirally controlled internucleotidic linkages in an oligonucleotide are *R*p. In some embodiments, about 35%-40% of all chirally controlled internucleotidic linkages in an oligonucleotide are *R*p.

In some embodiments, instead of an *R*p internucleotidic linkage, a natural phosphate linkage may be similarly utilized, optionally with a modification, e.g., a sugar modification (e.g., a 5'-modification such as R^{5s} as described herein). In some embodiments, a modification improves stability of a natural phosphate linkage.

In some embodiments, the present disclosure provides an oligonucleotide having a pattern of backbone chiral centers as described herein. In some embodiments, oligonucleotides in a chirally controlled oligonucleotide composition share a common pattern of backbone chiral centers as described herein.

In some embodiments, at least about 25% of the internucleotidic linkages of a ds oligonucleotide targeting INHBE are chirally controlled and have *S*p linkage phosphorus. In some embodiments, at least about 30% of the internucleotidic linkages of an oligonucleotide are chirally controlled and have *S*p linkage phosphorus. In some embodiments, at least about 40% of the internucleotidic linkages of a provided oligonucleotide are chirally controlled and have *S*p linkage phosphorus. In some embodiments, at least about 50% of the internucleotidic linkages of a provided oligonucleotide are chirally controlled and have *S*p linkage phosphorus. In some embodiments, at least about 60% of the internucleotidic linkages of a provided oligonucleotide are chirally controlled and have *S*p linkage phosphorus. In some embodiments, at least about 65% of the internucleotidic linkages of a provided oligonucleotide are chirally controlled and have *S*p linkage phosphorus. In some embodiments, at least about 70% of the internucleotidic linkages of a provided oligonucleotide are chirally controlled and have *S*p linkage phosphorus. In some embodiments, at least about 75% of the internucleotidic linkages of a provided oligonucleotide are chirally controlled and have *S*p linkage phosphorus. In some embodiments, at least about 80% of the internucleotidic linkages of a provided oligonucleotide are chirally controlled and have *S*p linkage phosphorus. In some embodiments, at least about 85% of the internucleotidic linkages of a provided oligonucleotide are chirally controlled and have *S*p linkage phosphorus. In some embodiments, at least about 90% of the internucleotidic linkages of a provided oligonucleotide are chirally controlled and have *S*p linkage phosphorus. In some embodiments, at least about 95% of the internucleotidic linkages of a provided oligonucleotide are chirally controlled and have *S*p linkage phosphorus.

In some embodiments, the present disclosure provides chirally controlled oligonucleotide compositions, e.g., chirally controlled ds oligonucleotide targeting INHBE compositions, wherein the composition comprises a non-random or controlled level of a plurality of oligonucleotides, wherein oligonucleotides of the plurality share a common base sequence, and share the same configuration of linkage phosphorus independently at 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 5-50, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 or more chiral internucleotidic linkages.

In some embodiments, ds oligonucleotides targeting INHBE comprise 2-30 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotide compositions comprise 5-30 chirally controlled internucleotidic linkages. In some embodiments, provided oligonucleotide compositions comprise 10-30 chirally controlled

internucleotidic linkages.

In some embodiments, a percentage is about 5%-100%. In some embodiments, a percentage is at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 965, 96%, 98%, or 99%. In some embodiments, a percentage is about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 965, 96%, 98%, or 99%.

In some embodiments, a pattern of backbone chiral centers in a ds oligonucleotide targeting INHBE comprises a pattern of i^o-i^s-i^o-i^s-i^o, i^o-i^s-i^s-i^s-i^o, i^o-i^s-i^s-i^s-i^o-i^s, i^s-i^o-i^s-i^o, i^s-i^o-i^s-i^o, i^s-i^o-i^s-i^o-i^s, i^s-i^o-i^s-i^o-i^s-i^o, i^s-i^o-i^s-i^o-i^s-i^o-i^s, i^s-i^o-i^s-i^s-i^s-i^o, i^s-i^s-i^o-i^s-i^s-i^s-i^o-i^s-i^s, i^s-i^s-i^s-i^o-i^s-i^o-i^s-i^s-i^s, i^s-i^s-i^s-i^s-i^o-i^s-i^o-i^s-i^s-i^s-i^s, i^s-i^s-i^s-i^s-i^s, i^s-i^s-i^s-i^s-i^s-i^s, i^s-i^s-i^s-i^s-i^s-i^s-i^s, i^s-i^s-i^s-i^s-i^s-i^s-i^s-i^s, i^s-i^s-i^s-i^s-i^s-i^s-i^s-i^s-i^s, or i^r-i^r-i^r, wherein i^s represents an internucleotidic linkage in the *S*p configuration; i^o represents an achiral internucleotidic linkage; and i^r represents an internucleotidic linkage in the *R*p configuration.

In some embodiments, an internucleotidic linkage in the *S*p configuration (having a *S*p linkage phosphorus) is a phosphorothioate internucleotidic linkage. In some embodiments, an achiral internucleotidic linkage is a natural phosphate linkage. In some embodiments, an internucleotidic linkage in the *R*p configuration (having a *R*p linkage phosphorus) is a phosphorothioate internucleotidic linkage. In some embodiments, each internucleotidic linkage in the *S*p configuration is a phosphorothioate internucleotidic linkage. In some embodiments, each achiral internucleotidic linkage is a natural phosphate linkage. In some embodiments, each internucleotidic linkage in the *R*p configuration is a phosphorothioate internucleotidic linkage. In some embodiments, each internucleotidic linkage in the *S*p configuration is a phosphorothioate internucleotidic linkage, each achiral internucleotidic linkage is a natural phosphate linkage, and each internucleotidic linkage in the *R*p configuration is a phosphorothioate internucleotidic linkage.

In some embodiments, a pattern of backbone chiral centers (e.g., a pattern of backbone chiral centers in an oligonucleotide, e.g., a ds oligonucleotide targeting INHBE or in a core or a wing or in two wings of an oligonucleotide, e.g., a ds oligonucleotide targeting INHBE) comprises a pattern of Op*S*pOp*S*pOp, Op*S*p*S*pOp, Op*S*p*S*pOp*S*p, *S*pOp*S*pOp, *S*pOp*S*pOp, *S*pOp*S*pOp*S*p, *S*pOp*S*pOp*S*pOp, *S*pOp*S*pOp*S*pOp*S*pOp, *S*pOp*S*p*S*pOp, *S*p*S*pOp*S*p*S*p*S*pOp*S*p*S*p, *S*p*S*p*S*pOp*S*pOp*S*p*S*p*S*p, *S*p*S*p*S*p*S*pOp*S*pOp*S*p*S*p*S*p*S*p, *S*p*S*p*S*p*S*p*S*p, *S*p*S*p*S*p*S*p*S*p*S*p, *S*p*S*p*S*p*S*p*S*p*S*p*S*p, *S*p*S*p*S*p*S*p*S*p*S*p*S*p*S*p, or *R*p*R*p*R*p, wherein each *R*p and *S*p is independently the linkage phosphorus configuration of a chirally controlled internucleotidic linkage (in some embodiments, each *R*p and *S*p is independently the linkage phosphorus configuration of a chirally controlled phosphorothioate internucleotidic

linkage), and each Op independently represents linkage phosphorus being achiral in a natural phosphate linkage.

In some embodiments, a pattern of backbone chiral centers (e.g., of an oligonucleotide, e.g., a ds oligonucleotide targeting INHBE, or a portion thereof) is or comprises a pattern of backbone chiral centers described in Table 1.

In some embodiments, an internucleotidic linkage bonded to a wing nucleoside and a core nucleoside is considered one of the core internucleotidic linkages, for example, when describing types, modifications, numbers, and/or patterns of core internucleotidic linkages. In some embodiments, each internucleotidic linkage bonded to a wing nucleoside and a core nucleoside is considered one of the core internucleotidic linkages, for example, when describing types, modifications, numbers, and/or patterns of core internucleotidic linkages. In some embodiments, a core internucleotidic linkage is bonded to two core nucleosides. In some embodiments, a core internucleotidic linkage is bonded to a core nucleoside and a wing nucleoside. In some embodiments, each core internucleotidic linkage is independently bonded to two core nucleosides, or a core nucleoside and a wing nucleoside. In some embodiments, each wing internucleotidic linkage is independently bonded to two wing nucleosides.

In some embodiments, ds oligonucleotides targeting INHBE in chirally controlled oligonucleotide compositions each comprise different types of internucleotidic linkages. In some embodiments, ds oligonucleotides targeting INHBE comprise at least one natural phosphate linkage and at least one modified internucleotidic linkage. In some embodiments, ds oligonucleotides targeting INHBE comprise at least one natural phosphate linkage and at least two modified internucleotidic linkages. In some embodiments, ds oligonucleotides targeting INHBE comprise at least one natural phosphate linkage and at least three modified internucleotidic linkages. In some embodiments, ds oligonucleotides targeting INHBE comprise at least one natural phosphate linkage and at least four modified internucleotidic linkages. In some embodiments, ds oligonucleotides targeting INHBE comprise at least one natural phosphate linkage and at least five modified internucleotidic linkages. In some embodiments, ds oligonucleotides targeting INHBE comprise at least one natural phosphate linkage and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 modified internucleotidic linkages. In some embodiments, a modified internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, each modified internucleotidic linkage is a phosphorothioate internucleotidic linkage. In some embodiments, a modified internucleotidic linkage is a phosphorothioate triester internucleotidic linkage. In

some embodiments, each modified internucleotidic linkage is a phosphorothioate triester internucleotidic linkage. In some embodiments, ds oligonucleotides targeting INHBE comprise at least one natural phosphate linkage and at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 consecutive modified internucleotidic linkages. In some embodiments, ds oligonucleotides targeting INHBE comprise at least one natural phosphate linkage and at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 consecutive phosphorothioate internucleotidic linkages. In some embodiments, ds oligonucleotides targeting INHBE comprise at least one natural phosphate linkage and at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 consecutive phosphorothioate triester internucleotidic linkages.

In some embodiments, oligonucleotides in a chirally controlled oligonucleotide composition each comprise at least two internucleotidic linkages that have different stereochemistry and/or different P-modifications relative to one another. In some embodiments, at least two internucleotidic linkages have different stereochemistry relative to one another, and the oligonucleotides each comprise a pattern of backbone chiral centers comprising alternating linkage phosphorus stereochemistry.

In some embodiments, a linkage comprises a chiral auxiliary, which, for example, is used to control the stereoselectivity of a reaction, e.g., a coupling reaction in an oligonucleotide synthesis cycle. In some embodiments, a phosphorothioate triester linkage does not comprise a chiral auxiliary. In some embodiments, a phosphorothioate triester linkage is intentionally maintained until and/or during the administration of the oligonucleotide composition to a subject.

In some embodiments, purity, particularly stereochemical purity, and particularly diastereomeric purity of many oligonucleotides and compositions thereof wherein all other chiral centers in the oligonucleotides but the chiral linkage phosphorus centers have been stereodefined (e.g., carbon chiral centers in the sugars, which are defined in, *e.g.*, phosphoramidites for oligonucleotide synthesis), can be controlled by stereoselectivity (as appreciated by those skilled in this art, diastereoselectivity in many cases of oligonucleotide synthesis wherein the oligonucleotide comprise more than one chiral centers) at chiral linkage phosphorus in coupling steps when forming chiral internucleotidic linkages. In some embodiments, a coupling step has a stereoselectivity (diastereoselectivity when there are other chiral centers) of 60% at the linkage phosphorus. After such a coupling step, the new internucleotidic linkage formed may be referred to have a 60% stereochemical purity (for

oligonucleotides, typically diastereomeric purity in view of the existence of other chiral centers). In some embodiments, each coupling step independently has a stereoselectivity of at least 60%. In some embodiments, each coupling step independently has a stereoselectivity of at least 70%. In some embodiments, each coupling step independently has a stereoselectivity of at least 80%. In some embodiments, each coupling step independently has a stereoselectivity of at least 85%. In some embodiments, each coupling step independently has a stereoselectivity of at least 90%. In some embodiments, each coupling step independently has a stereoselectivity of at least 91%. In some embodiments, each coupling step independently has a stereoselectivity of at least 92%. In some embodiments, each coupling step independently has a stereoselectivity of at least 93%. In some embodiments, each coupling step independently has a stereoselectivity of at least 94%. In some embodiments, each coupling step independently has a stereoselectivity of at least 95%. In some embodiments, each coupling step independently has a stereoselectivity of at least 96%. In some embodiments, each coupling step independently has a stereoselectivity of at least 97%. In some embodiments, each coupling step independently has a stereoselectivity of at least 98%. In some embodiments, each coupling step independently has a stereoselectivity of at least 99%. In some embodiments, each coupling step independently has a stereoselectivity of at least 99.5%. In some embodiments, each coupling step independently has a stereoselectivity of virtually 100%. In some embodiments, a coupling step has a stereoselectivity of virtually 100% in that each detectable product from the coupling step analyzed by an analytical method (e.g., NMR, HPLC, etc.) has the intended stereoselectivity. In some embodiments, a chirally controlled internucleotidic linkage is typically formed with a stereoselectivity of at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99.5% or virtually 100% (in some embodiments, at least 90%; in some embodiments, at least 95%; in some embodiments, at least 96%; in some embodiments, at least 97%; in some embodiments, at least 98%; in some embodiments, at least 99%). In some embodiments, a chirally controlled internucleotidic linkage has a stereochemical purity (typically diastereomeric purity for oligonucleotides with multiple chiral centers) of at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99.5% or virtually 100% (in some embodiments, at least 90%; in some embodiments, at least 95%; in some embodiments, at least 96%; in some embodiments, at least 97%; in some embodiments, at least 98%; in some embodiments, at least 99%) at its chiral linkage phosphorus. In some embodiments, each chirally controlled internucleotidic linkage independently has a stereochemical purity (typically diastereomeric purity for oligonucleotides with multiple chiral centers) of at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99.5% or virtually 100% (in some embodiments, at least 90%; in some embodiments, at least

95%; in some embodiments, at least 96%; in some embodiments, at least 97%; in some embodiments, at least 98%; in some embodiments, at least 99%) at its chiral linkage phosphorus. In some embodiments, a non-chirally controlled internucleotidic linkage is typically formed with a stereoselectivity of less than 60%, 70%, 80%, 85%, or 90% (in some embodiments, less than 60%; in some embodiments, less than 70%; in some embodiments, less than 80%; in some embodiments, less than 85%; in some embodiments, less than 90%). In some embodiments, each non-chirally controlled internucleotidic linkage is independently formed with a stereoselectivity of less than 60%, 70%, 80%, 85%, or 90% (in some embodiments, less than 60%; in some embodiments, less than 70%; in some embodiments, less than 80%; in some embodiments, less than 85%; in some embodiments, less than 90%). In some embodiments, a non-chirally controlled internucleotidic linkage has a stereochemical purity (typically diastereomeric purity for oligonucleotides with multiple chiral centers) of less than 60%, 70%, 80%, 85%, or 90% (in some embodiments, less than 60%; in some embodiments, less than 70%; in some embodiments, less than 80%; in some embodiments, less than 85%; in some embodiments, less than 90%) at its chiral linkage phosphorus. In some embodiments, each non-chirally controlled internucleotidic linkage independently has a stereochemical purity (typically diastereomeric purity for oligonucleotides with multiple chiral centers) of less than 60%, 70%, 80%, 85%, or 90% (in some embodiments, less than 60%; in some embodiments, less than 70%; in some embodiments, less than 80%; in some embodiments, less than 85%; in some embodiments, less than 90%) at its chiral linkage phosphorus.

In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 couplings of a monomer (as appreciated by those skilled in the art in many embodiments a phosphoramidite for oligonucleotide synthesis) independently have a stereoselectivity less than about 60%, 70%, 80%, 85%, or 90% [for oligonucleotide synthesis, typically diastereoselectivity with respect to formed linkage phosphorus chiral center(s)]. In some embodiments, at least one coupling has a stereoselectivity less than about 60%, 70%, 80%, 85%, or 90%. In some embodiments, at least two couplings independently have a stereoselectivity less than about 60%, 70%, 80%, 85%, or 90%. In some embodiments, at least three couplings independently have a stereoselectivity less than about 60%, 70%, 80%, 85%, or 90%. In some embodiments, at least four couplings independently have a stereoselectivity less than about 60%, 70%, 80%, 85%, or 90%. In some embodiments, at least five couplings independently have a stereoselectivity less than about 60%, 70%, 80%, 85%, or 90%. In some embodiments, each coupling independently has a stereoselectivity less than about 60%, 70%, 80%, 85%, or 90%. In some embodiments,

each non-chirally controlled internucleotidic linkage is independently formed with a stereoselectivity less than about 60%, 70%, 80%, 85%, or 90%. In some embodiments, a stereoselectivity is less than about 60%. In some embodiments, a stereoselectivity is less than about 70%. In some embodiments, a stereoselectivity is less than about 80%. In some embodiments, a stereoselectivity is less than about 90%. In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 couplings independently have a stereoselectivity less than about 90%. In some embodiments, at least one coupling has a stereoselectivity less than about 90%. In some embodiments, at least two couplings have a stereoselectivity less than about 90%. In some embodiments, at least three couplings have a stereoselectivity less than about 90%. In some embodiments, at least four couplings have a stereoselectivity less than about 90%. In some embodiments, at least five couplings have a stereoselectivity less than about 90%. In some embodiments, each coupling independently has a stereoselectivity less than about 90%. In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 couplings independently have a stereoselectivity less than about 85%. In some embodiments, each coupling independently has a stereoselectivity less than about 85%. In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 couplings independently have a stereoselectivity less than about 80%. In some embodiments, each coupling independently has a stereoselectivity less than about 80%. In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 couplings independently have a stereoselectivity less than about 70%. In some embodiments, each coupling independently has a stereoselectivity less than about 70%.

In some embodiments, oligonucleotides and compositions of the present disclosure have high purity. In some embodiments, oligonucleotides and compositions of the present disclosure have high stereochemical purity. In some embodiments, a stereochemical purity, e.g., diastereomeric purity, is about 60%-100%. In some embodiments, a diastereomeric purity, is about 60%-100%. In some embodiments, the percentage is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 93%, 95%, 96%, 97%, 98%, or 99%. In some embodiments, the percentage is at least 80%, 85%, 90%, 91%, 92%, 93%, 93%, 95%, 96%, 97%, 98%, or 99%. In some embodiments, the percentage is at least 90%, 91%, 92%, 93%, 93%, 95%, 96%, 97%, 98%, or 99%. In some embodiments, a diastereomeric purity is at least 60%. In some embodiments, a diastereomeric purity is at least 70%. In some embodiments, a diastereomeric purity is at least 80%. In some embodiments, a diastereomeric purity is at least 85%. In some embodiments, a diastereomeric purity is at least 90%. In some embodiments, a

diastereomeric purity is at least 91%. In some embodiments, a diastereomeric purity is at least 92%. In some embodiments, a diastereomeric purity is at least 93%. In some embodiments, a diastereomeric purity is at least 94%. In some embodiments, a diastereomeric purity is at least 95%. In some embodiments, a diastereomeric purity is at least 96%. In some embodiments, a diastereomeric purity is at least 97%. In some embodiments, a diastereomeric purity is at least 98%. In some embodiments, a diastereomeric purity is at least 99%. In some embodiments, a diastereomeric purity is at least 99.5%.

In some embodiments, compounds of the present disclosure (e.g., oligonucleotides, chiral auxiliaries, etc.) comprise multiple chiral elements (e.g., multiple carbon and/or phosphorus (e.g., linkage phosphorus of chiral internucleotidic linkages) chiral centers). In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or more chiral elements of a provided compound (e.g., an oligonucleotide) each independently have a diastereomeric purity as described herein. In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or more chiral carbon centers of a provided compound each independently have a diastereomeric purity as described herein. In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or more chiral phosphorus centers of a provided compound each independently have a diastereomeric purity as described herein. In some embodiments, each chiral element independently has a diastereomeric purity as described herein. In some embodiments, each chiral center independently has a diastereomeric purity as described herein. In some embodiments, each chiral carbon center independently has a diastereomeric purity as described herein. In some embodiments, each chiral phosphorus center independently has a diastereomeric purity as described herein. In some embodiments, each chiral phosphorus center independently has a diastereomeric purity of at least 90%, 91%, 92%, 93%, 93%, 95%, 96%, 97%, 98%, or 99% or more.

As understood by a person having ordinary skill in the art, in some embodiments, diastereoselectivity of a coupling or diastereomeric purity of a chiral linkage phosphorus center can be assessed through the diastereoselectivity of a dimer formation or diastereomeric purity of a dimer prepared under the same or comparable conditions, wherein the dimer has the same 5'- and 3'-nucleosides and internucleotidic linkage.

Various technologies can be utilized for identifying or confirming stereochemistry of chiral elements (e.g., configuration of chiral linkage phosphorus) and/or patterns of backbone chiral centers, and/or for assessing stereoselectivity (e.g., diastereoselectivity of couple steps in oligonucleotide synthesis) and/or stereochemical purity (e.g., diastereomeric purity of internucleotidic linkages, compounds (e.g., oligonucleotides), etc.). Example technologies include NMR [e.g., 1D (one-dimensional) and/or 2D (two-dimensional) ^{1}H-^{31}P HETCOR

(heteronuclear correlation spectroscopy)], HPLC, RP-HPLC, mass spectrometry, LC-MS, and cleavage of internucleotidic linkages by stereospecific nucleases, etc., which may be utilized individually or in combination. Example useful nucleases include benzonase, micrococcal nuclease, and svPDE (snake venom phosphodiesterase), which are specific for certain internucleotidic linkages with *R*p linkage phosphorus (e.g., a *R*p phosphorothioate linkage); and nuclease P1, mung bean nuclease, and nuclease S1, which are specific for internucleotidic linkages with *S*p linkage phosphorus (e.g., a *S*p phosphorothioate linkage). Without wishing to be bound by any particular theory, the present disclosure notes that, in at least some cases, cleavage of oligonucleotides by a particular nuclease may be impacted by structural elements, e.g., chemical modifications (e.g., 2'-modifications of a sugars), base sequences, or stereochemical contexts. For example, it is observed that in some cases, benzonase and micrococcal nuclease, which are specific for internucleotidic linkages with *R*p linkage phosphorus, were unable to cleave an isolated *R*p phosphorothioate internucleotidic linkage flanked by *S*p phosphorothioate internucleotidic linkages.

In some embodiments, oligonucleotides sharing a common base sequence, a common pattern of backbone linkages, and a common pattern of backbone chiral centers share a common pattern of backbone phosphorus modifications and a common pattern of base modifications. In some embodiments, oligonucleotide compositions sharing a common base sequence, a common pattern of backbone linkages, and a common pattern of backbone chiral centers share a common pattern of backbone phosphorus modifications and a common pattern of nucleoside modifications. In some embodiments, oligonucleotides share a common base sequence, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have identical structures.

In some embodiments, the present disclosure provides an oligonucleotide composition comprising a plurality of oligonucleotides capable of directing INHBE knockdown, wherein oligonucleotides of the plurality are of a particular oligonucleotide type, which composition is chirally controlled in that it is enriched, relative to a substantially racemic preparation of oligonucleotides having the same base sequence, for oligonucleotides of the particular oligonucleotide type.

In some embodiments, oligonucleotides having a common base sequence, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have a common pattern of backbone phosphorus modifications and a common pattern of base modifications. In some embodiments, oligonucleotides having a common base sequence, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have a common pattern

of backbone phosphorus modifications and a common pattern of nucleoside modifications. In some embodiments, oligonucleotides having a common base sequence, a common pattern of backbone linkages, and a common pattern of backbone chiral centers have identical structures.

In some embodiments, the present disclosure provides ds oligonucleotide targeting INHBE compositions comprising a plurality of oligonucleotides. In some embodiments, the present disclosure provides chirally controlled oligonucleotide compositions of ds oligonucleotides targeting INHBE. In some embodiments, the present disclosure provides a ds oligonucleotide targeting INHBE whose base sequence is or is complementary to a INHBE sequence disclosed herein or a portion thereof (e.g., various bases sequences in Table 1, wherein each T may be independently replaced with U and vice versa). In some embodiments, the present disclosure provides a ds oligonucleotide targeting INHBE whose base sequence comprises a base sequence that is or is complementary to a INHBE sequence disclosed herein or a portion thereof (e.g., various bases sequences in Table 1). In some embodiments, the present disclosure provides a ds oligonucleotide targeting INHBE whose base sequence comprises 15 contiguous bases of a base sequence that is or is complementary to a INHBE sequence disclosed herein or a portion thereof (e.g., various bases sequences in Table 1, wherein each T may be independently replaced with U and vice versa). In some embodiments, the present disclosure provides a ds oligonucleotide targeting INHBE which has a base sequence comprising 15 contiguous bases with 0-3 mismatches of a base sequence that is or is complementary to a INHBE sequence disclosed herein or a portion thereof (e.g., various bases sequences in Table 1, wherein each T may be independently replaced with U and vice versa). In some embodiments, the present disclosure provides a ds oligonucleotide targeting INHBE composition wherein the ds oligonucleotides targeting INHBE comprise at least one chiral internucleotidic linkage which is not chirally controlled. In some embodiments, the present disclosure provides a ds oligonucleotide targeting INHBE comprising a non-chirally controlled chiral internucleotidic linkage, wherein the base sequence of the ds oligonucleotide targeting INHBE comprises a base sequence that is or is complementary to a INHBE sequence disclosed herein or a portion thereof (e.g., various bases sequences in Table 1, wherein each T may be independently replaced with U and vice versa). In some embodiments, the present disclosure provides a ds oligonucleotide targeting INHBE composition comprising a non-chirally controlled chiral internucleotidic linkage, wherein the base sequence of the ds oligonucleotide targeting INHBE is a base sequence that is or is complementary to a INHBE sequence disclosed herein or a portion thereof (e.g., various bases sequences in Table 1, wherein each T may be independently replaced with U and vice versa). In some embodiments, the present disclosure

provides a ds oligonucleotide targeting INHBE comprising a non-chirally controlled chiral internucleotidic linkage, wherein the base sequence of the ds oligonucleotide targeting INHBE comprises 15 contiguous bases of a base sequence that is or is complementary to a INHBE sequence disclosed herein or a portion thereof (e.g., various bases sequences in Table 1, wherein each T may be independently replaced with U and vice versa). In some embodiments, the present disclosure provides a ds oligonucleotide targeting INHBE comprising a non-chirally controlled chiral internucleotidic linkage, wherein the base sequence of the ds oligonucleotides targeting INHBE comprises 15 contiguous bases with 0-3 mismatches of a base sequence that is or is complementary to a INHBE sequence disclosed herein or a portion thereof (e.g., various bases sequences in Table 1, wherein each T may be independently replaced with U and vice versa). In some embodiments, the present disclosure provides a ds oligonucleotide targeting INHBE comprising a chirally controlled chiral internucleotidic linkage, wherein the base sequence of the ds oligonucleotide targeting INHBE comprises a base sequence that is or is complementary to a INHBE sequence disclosed herein or a portion thereof (e.g., various bases sequences in Table 1, wherein each T may be independently replaced with U and vice versa). In some embodiments, the present disclosure provides a ds oligonucleotide targeting INHBE composition comprising a chirally controlled chiral internucleotidic linkage, wherein the base sequence of the ds oligonucleotide targeting INHBE is a base sequence that is or is complementary to a INHBE sequence disclosed herein or a portion thereof (e.g., various bases sequences in Table 1, wherein each T may be independently replaced with U and vice versa). In some embodiments, the present disclosure provides a ds oligonucleotide targeting INHBE comprising a chirally controlled chiral internucleotidic linkage, wherein the base sequence of the ds oligonucleotide targeting INHBE comprises 15 contiguous bases of a base sequence that is or is complementary to a INHBE sequence disclosed herein or a portion thereof (e.g., various bases sequences in Table 1, wherein each T may be independently replaced with U and vice versa). In some embodiments, the present disclosure provides a ds oligonucleotide targeting INHBE comprising a chirally controlled chiral internucleotidic linkage, wherein the base sequence of the ds oligonucleotides targeting INHBE comprises 15 contiguous bases with 0-3 mismatches of a base sequence that is or is complementary to a INHBE sequence disclosed herein or a portion thereof (e.g., various bases sequences in Table 1, wherein each T may be independently replaced with U and vice versa).

In some embodiments, oligonucleotides of the same oligonucleotide type have a common pattern of backbone phosphorus modifications and a common pattern of nucleoside modifications. In some embodiments, oligonucleotides of the same oligonucleotide type have

a common pattern of sugar modifications. In some embodiments, oligonucleotides of the same oligonucleotide type have a common pattern of base modifications. In some embodiments, oligonucleotides of the same oligonucleotide type have a common pattern of nucleoside modifications. In some embodiments, oligonucleotides of the same oligonucleotide type have the same constitution. In many embodiments, oligonucleotides of the same oligonucleotide type are identical. In some embodiments, oligonucleotides of the same oligonucleotide type are of the same oligonucleotide (as those skilled in the art will appreciate, such oligonucleotides may each independently exist in one of the various forms of the oligonucleotide, and may be the same, or different forms of the oligonucleotide). In some embodiments, oligonucleotides of the same oligonucleotide type are each independently of the same oligonucleotide or a pharmaceutically acceptable salt thereof.

In some embodiments, a plurality of oligonucleotides or oligonucleotides of a particular oligonucleotide type in a provided oligonucleotide composition are ds oligonucleotides targeting INHBE. In some embodiments, the present disclosure provides a chirally controlled ds oligonucleotide targeting INHBE composition comprising a plurality of ds oligonucleotides targeting INHBE, wherein the oligonucleotides share:

1) a common base sequence;

2) a common pattern of backbone linkages; and

3) the same linkage phosphorus stereochemistry at one or more chiral internucleotidic linkages (chirally controlled internucleotidic linkages),

wherein the composition is enriched, relative to a substantially racemic preparation of oligonucleotides sharing the common base sequence and pattern of backbone linkages, for oligonucleotides of the plurality.

In some embodiments, as used herein, “one or more” or “at least one” is 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 5-50, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more.

In some embodiments, an oligonucleotide type is further defined by: 4) additional chemical moiety, if any.

In some embodiments, the percentage is at least about 10%. In some embodiments, the percentage is at least about 20%. In some embodiments, the percentage is at least about 30%. In some embodiments, the percentage is at least about 40%. In some embodiments, the percentage is at least about 50%. In some embodiments, the percentage is at least about 60%. In some embodiments, the percentage is at least about 70%. In some embodiments, the percentage is at least about 75%. In some embodiments, the percentage is at least about 80%.

In some embodiments, the percentage is at least about 85%. In some embodiments, the percentage is at least about 90%. In some embodiments, the percentage is at least about 91%. In some embodiments, the percentage is at least about 92%. In some embodiments, the percentage is at least about 93%. In some embodiments, the percentage is at least about 94%. In some embodiments, the percentage is at least about 95%. In some embodiments, the percentage is at least about 96%. In some embodiments, the percentage is at least about 97%. In some embodiments, the percentage is at least about 98%. In some embodiments, the percentage is at least about 99%. In some embodiments, the percentage is or is greater than $(DS)^{nc}$, wherein DS and nc are each independently as described in the present disclosure.

In some embodiments, a plurality of oligonucleotides, e.g., ds oligonucleotides targeting INHBE, share the same constitution. In some embodiments, a plurality of oligonucleotides, e.g., ds oligonucleotides targeting INHBE, are identical (the same stereoisomer). In some embodiments, a chirally controlled oligonucleotide composition, e.g., a chirally controlled ds oligonucleotide targeting INHBE composition, is a stereopure oligonucleotide composition wherein oligonucleotides of the plurality are identical (the same stereoisomer), and the composition does not contain any other stereoisomers. Those skilled in the art will appreciate that one or more other stereoisomers may exist as impurities as processes, selectivities, purifications, etc. may not achieve completeness.

In some embodiments, a provided composition is characterized in that when it is contacted with a target nucleic acid (e.g., a INHBE transcript (e.g., pre-mRNA, mature mRNA, other types of RNA, etc. that hybridizes with oligonucleotides of the composition)), levels of the target nucleic acid and/or a product encoded thereby is reduced compared to that observed under a reference condition. In some embodiments, a reference condition is selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof. In some embodiments, a reference condition is absence of the composition. In some embodiments, a reference condition is presence of a reference composition. In some embodiments, a reference composition is a composition whose oligonucleotides do not hybridize with the target nucleic acid. In some embodiments, a reference composition is a composition whose oligonucleotides do not comprise a sequence that is sufficiently complementary to the target nucleic acid. In some embodiments, a provided composition is a chirally controlled oligonucleotide composition and a reference composition is a non-chirally controlled oligonucleotide composition which is otherwise identical but is not chirally controlled (e.g., a racemic preparation of oligonucleotides of the same constitution as oligonucleotides of a plurality in the chirally controlled oligonucleotide composition).

In some embodiments, the present disclosure provides a chirally controlled ds oligonucleotide targeting INHBE composition comprising a plurality of ds oligonucleotides targeting INHBE capable of directing INHBE knockdown, wherein the oligonucleotides share:

1) a common base sequence,

2) a common pattern of backbone linkages, and

3) the same linkage phosphorus stereochemistry at one or more (e.g., 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 5-50, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) chiral internucleotidic linkages (chirally controlled internucleotidic linkages),

wherein the composition is enriched, relative to a substantially racemic preparation of oligonucleotides sharing the common base sequence and pattern of backbone linkages, for oligonucleotides of the plurality,

the oligonucleotide composition being characterized in that, when it is contacted with a INHBE transcript in a INHBE knockdown system, knockdown of the transcript is improved relative to that observed under reference conditions selected from the group consisting of absence of the composition, presence of a reference composition, and combinations thereof.

As noted above and understood in the art, in some embodiments, the base sequence of an oligonucleotide may refer to the identity and/or modification status of nucleoside residues (e.g., of sugar and/or base components, relative to standard naturally occurring nucleotides such as adenine, cytosine, guanosine, thymine, and uracil) in the oligonucleotide and/or to the hybridization character (i.e., the ability to hybridize with particular complementary residues) of such residues.

As demonstrated herein, oligonucleotide structural elements (e.g., patterns of sugar modifications, backbone linkages, backbone chiral centers, backbone phosphorus modifications, etc.) and combinations thereof can provide surprisingly improved properties and/or bioactivities.

In some embodiments, oligonucleotide compositions are capable of reducing the expression, level and/or activity of a target gene or a gene product thereof. In some embodiments, oligonucleotide compositions are capable of reducing in the expression, level and/or activity of a target gene or a gene product thereof by sterically blocking translation after annealing to a target gene mRNA, by cleaving mRNA (pre-mRNA or mature mRNA), and/or by altering or interfering with mRNA splicing. In some embodiments, provided ds oligonucleotide targeting INHBE compositions are capable of reducing the expression, level and/or activity of a INHBE target gene or a gene product thereof. In some embodiments,

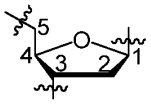
provided ds oligonucleotide targeting INHBE compositions are capable of reducing in the expression, level and/or activity of a INHBE target gene or a gene product thereof by sterically blocking translation after annealing to a INHBE target gene mRNA, by cleaving INHBE mRNA (pre-mRNA or mature mRNA), and/or by altering or interfering with mRNA splicing.

In some embodiments, an oligonucleotide composition, e.g., a ds oligonucleotide targeting INHBE composition, is a substantially pure preparation of a single oligonucleotide stereoisomer, e.g., a ds oligonucleotide targeting INHBE stereoisomer, in that oligonucleotides in the composition that are not of the oligonucleotide stereoisomer are impurities from the preparation process of said oligonucleotide stereoisomer, in some case, after certain purification procedures.

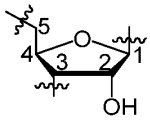
In some embodiments, the present disclosure provides oligonucleotides and oligonucleotide compositions that are chirally controlled, and in some embodiments, stereopure. For instance, in some embodiments, a provided composition contains non-random or controlled levels of one or more individual oligonucleotide types as described herein. In some embodiments, oligonucleotides of the same oligonucleotide type are identical.

Sugars

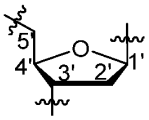
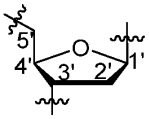
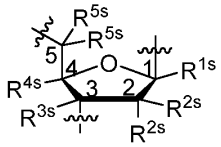
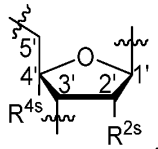
Various sugars, including modified sugars, can be utilized in accordance with the present disclosure. In some embodiments, the present disclosure provides sugar modifications and patterns thereof optionally in combination with other structural elements (e.g., internucleotidic linkage modifications and patterns thereof, pattern of backbone chiral centers thereof, etc.) that when incorporated into oligonucleotides can provide improved properties and/or activities.

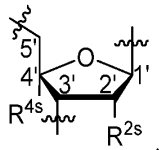
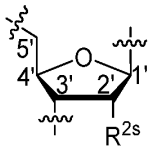
The most common naturally occurring nucleosides comprise ribose sugars (e.g., in RNA) or deoxyribose sugars (e.g., in DNA) linked to the nucleobases adenosine (A), cytosine (C), guanine (G), thymine (T) or uracil (U). In some embodiments, a sugar, e.g., various sugars in many oligonucleotides in Table 1 (unless otherwise notes), is a natural DNA sugar (in DNA nucleic acids or oligonucleotides, having the structure of 

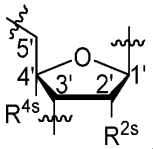
, wherein a nucleobase is attached to the 1' position, and the 3' and 5' positions are connected to internucleotidic linkages (as appreciated by those skilled in the art, if at the 5'-end of an oligonucleotide, the 5' position may be connected to a 5'-end group (e.g., −OH), and if at the 3'-end of an oligonucleotide, the 3' position may be connected to a 3'-end group (e.g., −OH). In some

embodiments, a sugar is a natural RNA sugar (in RNA nucleic acids or oligonucleotides, having the structure of  , wherein a nucleobase is attached to the 1' position, and the 3' and 5' positions are connected to internucleotidic linkages (as appreciated by those skilled in the art, if at the 5'-end of an oligonucleotide, the 5' position may be connected to a 5'-end group (e.g., −OH), and if at the 3'-end of an oligonucleotide, the 3' position may be connected to a 3'-end group (e.g., −OH). In some embodiments, a sugar is a modified sugar in that it is not a natural DNA sugar or a natural RNA sugar. Among other things, modified sugars may provide improved stability. In some embodiments, modified sugars can be utilized to alter and/or optimize one or more hybridization characteristics. In some embodiments, modified sugars can be utilized to alter and/or optimize target recognition. In some embodiments, modified sugars can be utilized to optimize Tm. In some embodiments, modified sugars can be utilized to improve oligonucleotide activities.

Sugars can be bonded to internucleotidic linkages at various positions. As non-limiting examples, internucleotidic linkages can be bonded to the 2', 3', 4' or 5' positions of sugars. In some embodiments, as most commonly in natural nucleic acids, an internucleotidic linkage connects with one sugar at the 5' position and another sugar at the 3' position unless otherwise indicated.

In some embodiments, a sugar is an optionally substituted natural DNA or RNA sugar. In some embodiments, a sugar is optionally substituted  . In some embodiments, the 2' position is optionally substituted. In some embodiments, a sugar is  . In some embodiments, a sugar has the structure of  or  , wherein each of R^{1s}, R^{2s}, R^{3s}, R^{4s}, and R^{5s} is independently −H, a suitable substituent or suitable sugar modification (e.g., those described in US 9394333, US 9744183, US 9605019, US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264,

WO 2018/022473, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/032612, and/or WO 2020/191252, the substituents, sugar modifications, descriptions of R^{1s}, R^{2s}, R^{3s}, R^{4s}, and R^{5s}, and modified sugars of each of which are independently incorporated herein by reference). In some embodiments, a sugar has the structure of  . In some embodiments, R^{4s} is −H. In some embodiments, a sugar has the structure of  , wherein R^{2s} is −H, halogen, or −OR, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{2s} is −H. In some embodiments, R^{2s} is −F. In some embodiments, R^{2s} is −OMe. In some embodiments, R^{2s} is $-OCH_2CH_2OMe$.

In some embodiments, a sugar has the structure of  , wherein R^{2s} and R^{4s} are taken together to form $-L^s-$, wherein L^s is a covalent bond or optionally substituted bivalent C_{1-6} aliphatic or heteroaliphatic having 1-4 heteroatoms. In some embodiments, each heteroatom is independently selected from nitrogen, oxygen or sulfur). In some embodiments, L^s is optionally substituted C2−O−CH_2−C4. In some embodiments, L^s is C2−O−CH_2−C4. In some embodiments, L^s is C2−O−(*R*)-$CH(CH_2CH_3)$−C4. In some embodiments, L^s is C2−O−(*S*)-$CH(CH_2CH_3)$−C4.

In some embodiments, a sugar is a bicyclic sugar, e.g., sugars wherein R^{2s} and R^{4s} are taken together to form a link as described in the present disclosure. In some embodiments, a sugar is selected from LNA sugars, BNA sugars, cEt sugars, etc. In some embodiments, a bridge is between the 2' and 4'-carbon atoms (corresponding to R^{2s} and R^{4s} taken together with their intervening atoms to form an optionally substituted ring as described herein). In some embodiments, examples of bicyclic sugars include alpha-L-methyleneoxy (4'-CH_2-O-2') LNA, beta-D-methyleneoxy (4'-CH_2-O-2') LNA, ethyleneoxy (4' -$(CH_2)_2$-O-2') LNA, aminooxy (4' -CH_2-O-N(R)-2') LNA, and oxyamino (4'-CH_2-N(R)-O-2') LNA. In some embodiments, a bicyclic sugar, e.g., a LNA or BNA sugar, is sugar having at least one bridge between two sugar carbons. In some embodiments, a bicyclic sugar in a nucleoside may have the

stereochemical configurations of alpha-L-ribofuranose or beta-D-ribofuranose. In some embodiments, a sugar is a sugar described in WO 1999014226. In some embodiments, a 4'-2' bicyclic sugar or 4' to 2' bicyclic sugar is a bicyclic sugar comprising a furanose ring which comprises a bridge connecting the 2' carbon atom and the 4' carbon atom of the sugar ring. In some embodiments, a bicyclic sugar, e.g., a LNA or BNA sugar, comprises at least one bridge between two pentofuranosyl sugar carbons. In some embodiments, a LNA or BNA sugar, comprises at least one bridge between the 4' and the 2' pentofuranosyl sugar carbons.

In some embodiments, a bicyclic sugar is a sugar of alpha-L-methyleneoxy (4'-CH_2-O-2') BNA, beta-D-methyleneoxy (4'-CH_2-O-2') BNA, ethyleneoxy (4'-$(CH_2)_2$-O-2') BNA, aminooxy (4'-CH_2-O-N(R)-2') BNA, oxyamino (4'-CH_2-N(R)-O-2') BNA, methyl(methyleneoxy) (4'-$CH(CH_3)$-O-2') BNA (also referred to as constrained ethyl or cEt), methylene-thio (4'-CH_2-S-2') BNA, methylene-amino (4'-CH_2-N(R)-2') BNA, methyl carbocyclic (4'-CH_2-$CH(CH_3)$-2') BNA, propylene carbocyclic (4'-$(CH_2)_3$-2') BNA, or vinyl BNA.

In some embodiments, a sugar modification is 2'-OMe, 2'-MOE, 2'-LNA, 2'-F, 5'-vinyl, or S-cEt. In some embodiments, a modified sugar is a sugar of FRNA, FANA, or morpholino. In some embodiments, an oligonucleotide comprises a nucleic acid analog, e.g., GNA, LNA, PNA, TNA, F-HNA (F-THP or 3'-fluoro tetrahydropyran), MNA (mannitol nucleic acid, e.g., Leumann 2002 Bioorg. Med. Chem. 10: 841-854), ANA (anitol nucleic acid), or morpholino, or a portion thereof. In some embodiments, a sugar modification replaces a natural sugar with another cyclic or acyclic moiety. Examples of such moieties are widely known in the art, e.g., those used in morpholino, glycol nucleic acids, etc. and may be utilized in accordance with the present disclosure. As appreciated by those skilled in the art, when utilized with modified sugars, in some embodiments internucleotidic linkages may be modified, e.g., as in morpholino, PNA, etc.

In some embodiments, a sugar is a 6'-modified bicyclic sugar that have either (R) or (S)-chirality at the 6-position, e.g., those described in US 7399845. In some embodiments, a sugar is a 5'-modified bicyclic sugar that has either (R) or (S)-chirality at the 5-position, e.g., those described in US 20070287831.

In some embodiments, a modified sugar contains one or more substituents at the 2' position (typically one substituent, and often at the axial position) independently selected from –F; $–CF_3$, –CN, $–N_3$, –NO, $–NO_2$, –OR', –SR', or $–N(R')_2$, wherein each R' is independently optionally substituted C_{1-10} aliphatic; –O–(C_1–C_{10} alkyl), –S–(C_1–C_{10} alkyl), –NH–(C_1–C_{10}

alkyl), or –N(C_1–C_{10} alkyl)$_2$; –O–(C_2–C_{10} alkenyl), –S–(C_2–C_{10} alkenyl), –NH–(C_2–C_{10} alkenyl), or –N(C_2–C_{10} alkenyl)$_2$; –O–(C_2–C_{10} alkynyl), –S–(C_2–C_{10} alkynyl), –NH–(C_2–C_{10} alkynyl), or –N(C_2–C_{10} alkynyl)$_2$; or –O—(C_1–C_{10} alkylene)–O—(C_1–C_{10} alkyl), –O–(C_1–C_{10} alkylene)–NH–(C_1–C_{10} alkyl) or –O–(C_1–C_{10} alkylene)–NH(C_1–C_{10} alkyl)$_2$, –NH–(C_1–C_{10} alkylene)–O–(C_1–C_{10} alkyl), or –N(C_1–C_{10} alkyl)–(C_1–C_{10} alkylene)–O–(C_1–C_{10} alkyl), wherein each of the alkyl, alkylene, alkenyl and alkynyl is independently and optionally substituted. In some embodiments, a substituent is –O(CH_2)$_n$$OCH_3$, –O($CH_2$)$_n$$NH_2$, MOE, DMAOE, or DMAEOE, wherein n is from 1 to about 10. In some embodiments, a modified sugar is one described in WO 2001/088198; and Martin et al., Helv. Chim. Acta, 1995, 78, 486-504. In some embodiments, a modified sugar comprises one or more groups selected from a substituted silyl group, an RNA cleaving group, a reporter group, a fluorescent label, an intercalator, a group for improving the pharmacokinetic properties of a nucleic acid, a group for improving the pharmacodynamic properties of a nucleic acid, or other substituents having similar properties. In some embodiments, modifications are made at one or more of the 2', 3', 4', or 5' positions, including the 3' position of the sugar on the 3'-terminal nucleoside or in the 5' position of the 5'-terminal nucleoside.

In some embodiments, the 2'-OH of a ribose is replaced with a group selected from –H, –F; –CF_3, –CN, –N_3, –NO, –NO_2, –OR', –SR', or –N(R')$_2$, wherein each R' is independently described in the present disclosure; –O–(C_1–C_{10} alkyl), –S–(C_1–C_{10} alkyl), –NH–(C_1–C_{10} alkyl), or –N(C_1–C_{10} alkyl)$_2$; –O–(C_2–C_{10} alkenyl), –S–(C_2–C_{10} alkenyl), –NH–(C_2–C_{10} alkenyl), or –N(C_2–C_{10} alkenyl)$_2$; –O–(C_2–C_{10} alkynyl), –S–(C_2–C_{10} alkynyl), –NH–(C_2–C_{10} alkynyl), or –N(C_2–C_{10} alkynyl)$_2$; or –O—(C_1–C_{10} alkylene)–O—(C_1–C_{10} alkyl), –O–(C_1–C_{10} alkylene)–NH–(C_1–C_{10} alkyl) or –O–(C_1–C_{10} alkylene)–NH(C_1–C_{10} alkyl)$_2$, –NH–(C_1–C_{10} alkylene)–O–(C_1–C_{10} alkyl), or –N(C_1–C_{10} alkyl)–(C_1–C_{10} alkylene)–O–(C_1–C_{10} alkyl), wherein each of the alkyl, alkylene, alkenyl and alkynyl is independently and optionally substituted. In some embodiments, the 2'–OH is replaced with –H (deoxyribose). In some embodiments, the 2'–OH is replaced with –F. In some embodiments, the 2'–OH is replaced with –OR'. In some embodiments, the 2'–OH is replaced with –OMe. In some embodiments, the 2'–OH is replaced with –OCH_2CH_2OMe.

In some embodiments, a sugar modification is a 2'-modification. Commonly used 2'-modifications include but are not limited to 2'–OR, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, a modification is 2'–OR, wherein R is optionally substituted C_{1-6} alkyl. In some embodiments, a modification is 2'–OMe. In some embodiments, a

modification is 2'-MOE. In some embodiments, a 2'-modification is S-cEt. In some embodiments, a modified sugar is an LNA sugar. In some embodiments, a 2'-modification is −F. In some embodiments, a 2'-modification is FANA. In some embodiments, a 2'-modification is FRNA. In some embodiments, a sugar modification is a 5'-modification, e.g., 5'-Me. In some embodiments, a sugar modification changes the size of the sugar ring. In some embodiments, a sugar modification is the sugar moiety in FHNA.

In some embodiments, a sugar modification replaces a sugar moiety with another cyclic or acyclic moiety. Examples of such moieties are widely known in the art, including but not limited to those used in morpholino (optionally with its phosphorodiamidate linkage), glycol nucleic acids, etc.

In some embodiments, one or more of the sugars of a ds oligonucleotide targeting INHBE are modified. In some embodiments, each sugar of an oligonucleotide is independently modified. In some embodiments, a modified sugar comprises a 2'-modification. In some embodiments, each modified sugar independently comprises a 2'-modification. In some embodiments, a 2'-modification is 2'-OR, wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, a 2'-modification is a 2'-OMe. In some embodiments, a 2'-modification is a 2'-MOE. In some embodiments, a 2'-modification is an LNA sugar modification. In some embodiments, a 2'-modification is 2'-F. In some embodiments, each sugar modification is independently a 2'-modification. In some embodiments, each sugar modification is independently 2'-OR. In some embodiments, each sugar modification is independently 2'-OR, wherein R is optionally substituted C_{1-6} alkyl. In some embodiments, each sugar modification is 2'-OMe. In some embodiments, each sugar modification is 2'-MOE. In some embodiments, each sugar modification is independently 2'-OMe or 2'-MOE. In some embodiments, each sugar modification is independently 2'-OMe, 2'-MOE, or a LNA sugar.

In some embodiments, a modified sugar is an optionally substituted ENA sugar. In some embodiments, a sugar is one described in, e.g., Seth et al., J Am Chem Soc. 2010 October 27; 132(42): 14942–14950. In some embodiments, a modified sugar is a sugar in XNA (xenonucleic acid), for instance, arabinose, anhydrohexitol, threose, 2'fluoroarabinose, or cyclohexene.

Modified sugars include cyclobutyl or cyclopentyl moieties in place of a pentofuranosyl sugar. Representative examples of such modified sugars include those described in US 4,981,957, US 5,118,800, US 5,319,080, or US 5,359,044. In some embodiments, the oxygen

atom within the ribose ring is replaced by nitrogen, sulfur, selenium, or carbon. In some embodiments, −O− is replaced with −N(R')−, −S−, −Se− or −C(R')$_2$−. In some embodiments, a modified sugar is a modified ribose wherein the oxygen atom within the ribose ring is replaced with nitrogen, and wherein the nitrogen is optionally substituted with an alkyl group (e.g., methyl, ethyl, isopropyl, etc.).

In some embodiments, sugars are connected by internucleotidic linkages, in some embodiments, modified internucleotidic linkage. In some embodiments, an internucleotidic linkage does not contain a linkage phosphorus. In some embodiments, an internucleotidic linkage is −L−. In some embodiments, an internucleotidic linkage is −OP(O)(−C≡CH)O−, −OP(O)(R)O− (e.g., R is −CH_3), 3' −NHP(O)(OH)O− 5', 3' −OP(O)(CH_3)OCH_2− 5', 3'−CH_2C(O)NHCH_2−5', 3'−S$CH_2O CH_2$−5', 3'−OCH_2OCH_2−5', 3'−CH_2NR'CH_2−5', 3'−CH_2N(Me)OCH_2−5', 3'−NHC(O)CH_2CH_2−5', 3'−NR'C(O)CH_2CH_2−5', 3'-CH_2CH_2NR'−5', 3'-CH_2CH_2NH−5', or 3'−OCH_2CH_2N(R')−5'. In some embodiments, a 5' carbon may be optionally substituted with =O.

In some embodiments, a modified sugar is an optionally substituted pentose or hexose. In some embodiments, a modified sugar is an optionally substituted pentose. In some embodiments, a modified sugar is an optionally substituted hexose. In some embodiments, a modified sugar is an optionally substituted ribose or hexitol. In some embodiments, a modified sugar is an optionally substituted ribose. In some embodiments, a modified sugar is an optionally substituted hexitol.

In some embodiments, a sugar modification is 5'-vinyl (R or S), 5'-methyl (R or S), 2'-SH, 2'-F, 2'-OCH_3, 2'-OCH_2CH_3, 2'-OCH_2CH_2F or 2'-O(CH_2)$_{20}CH_3$. In some embodiments, a substituent at the 2' position, e.g., a 2'-modification, is allyl, amino, azido, thio, O-allyl, O-C_1-C_{10} alkyl, OCF_3, OCH_2F, O(CH_2)$_2SCH_3$, O(CH_2)$_2$-O-N(R_m)(R_n), O-CH_2-C(=O)-N(R_m)(R_n), and O-CH_2-C(=O)-N(R_1)-(CH_2)$_2$-N(R_m)(R_n), wherein each allyl, amino and alkyl is optionally substituted, and each of R_l, R_m and R_n is independently R' as described in the present disclosure. In some embodiments, each of R_l, R_m and R_n is independently −H or optionally substituted C_1-C_{10} alkyl.

In some embodiments, a sugar is a tetrahydropyran or THP sugar. In some embodiments, a modified nucleoside is tetrahydropyran nucleoside or THP nucleoside which is a nucleoside having a six-membered tetrahydropyran sugar substituted for a pentofuranosyl residue in typical natural nucleosides. THP sugars and/or nucleosides include those used in hexitol nucleic acid (HNA), anitol nucleic acid (ANA), mannitol nucleic acid (MNA) (e.g.,

Leumann, Bioorg. Med. Chem., 2002, 10, 841-854) or fluoro HNA (F-HNA).

In some embodiments, sugars comprise rings having more than 5 atoms and/or more than one heteroatom, e.g., morpholino sugars.

As those skilled in the art will appreciate, modifications of sugars, nucleobases, internucleotidic linkages, etc. can and are often utilized in combination in oligonucleotides, e.g., see various oligonucleotides in Table 1. For example, a combination of sugar modification and nucleobase modification is 2'-F (sugar) 5-methyl (nucleobase) modified nucleosides. In some embodiments, a combination is replacement of a ribosyl ring oxygen atom with S and substitution at the 2'-position.

In some embodiments, a 2'-modified sugar is a furanosyl sugar modified at the 2' position. In some embodiments, a 2'-modification is halogen, −R' (wherein R' is not −H), −OR' (wherein R' is not −H), −SR', $-N(R')_2$, optionally substituted $-CH_2-CH=CH_2$, optionally substituted alkenyl, or optionally substituted alkynyl. In some embodiments, a 2'-modifications is selected from $-O[(CH_2)_nO]_mCH_3$, $-O(CH_2)_nNH_2$, $-O(CH_2)_nCH_3$, $-O(CH_2)_nF$, $-O(CH_2)_nONH_2$, $-OCH_2C(=O)N(H)CH_3$, and $-O(CH_2)_nON[(CH_2)_nCH_3]_2$, wherein each n and m is independently from 1 to about 10. In some embodiments, a 2'-modification is optionally substituted C_1-C_{12} alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkaryl, optionally substituted aralkyl, optionally substituted −O−alkaryl, optionally substituted −O−aralkyl, −SH, $-SCH_3$, −OCN, −Cl, −Br, −CN, −F, $-CF_3$, $-OCF_3$, $-SOCH_3$, $-SO_2CH_3$, $-ONO_2$, $-NO_2$, $-N_3$, $-NH_2$, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkaryl, optionally substituted aminoalkylamino, optionally substituted polyalkylamino, substituted silyl, a reporter group, an intercalator, a group for improving pharmacokinetic properties, a group for improving the pharmacodynamic properties, and other substituents. In some embodiments, a 2'-modification is a 2'-MOE modification.

In some embodiments, a 2'-modified or 2'-substituted sugar or nucleoside is a sugar or nucleoside comprising a substituent at the 2' position of the sugar which is other than −H (typically not considered a substituent) or −OH. In some embodiments, a 2'-modified sugar is a bicyclic sugar comprising a bridge connecting two carbon atoms of the sugar ring one of which is the 2' carbon. In some embodiments, a 2'-modification is non-bridging, e.g., allyl, amino, azido, thio, optionally substituted −O−allyl, optionally substituted −O−C_1-C_{10} alkyl, $-OCF_3$, $-O(CH_2)_2OCH_3$, 2'-$O(CH_2)_2SCH_3$, $-O(CH_2)_2ON(R_m)(R_n)$, or $-OCH_2C(=O)N(R_m)(R_n)$, where each R_m and R_n is independently −H or optionally substituted C_1-C_{10} alkyl.

In some embodiments, a sugar is the sugar of N-methanocarba, LNA, cMOE BNA, cEt BNA, α-L-LNA or related analogs, HNA, Me-ANA, MOE-ANA, Ara-FHNA, FHNA, R-6'-Me-FHNA, S-6'-Me-FHNA, ENA, or c-ANA. In some embodiments, a modified internucleotidic linkage is C3-amide (e.g., sugar that has the amide modification attached to the C3', Mutisya et al. 2014 Nucleic Acids Res. 2014 Jun 1; 42(10): 6542–6551), formacetal, thioformacetal, MMI [e.g., methylene(methylimino), Peoc'h et al. 2006 Nucleosides and Nucleotides 16 (7-9)], a PMO (phosphorodiamidate linked morpholino) linkage (which connects two sugars), or a PNA (peptide nucleic acid) linkage.

In some embodiments, a sugar is one described in US 9394333, US 9744183, US 9605019, US 9598458, US 9982257, US 10160969, US 10479995, US 2020/0056173, US 2018/0216107, US 2019/0127733, US 10450568, US 2019/0077817, US 2019/0249173, US 2019/0375774, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, and/or WO 2020/191252, the sugars of each of which is incorporated herein by reference.

Various additional sugars useful for preparing oligonucleotides or analogs thereof are known in the art and may be utilized in accordance with the present disclosure.

Nucleobases

Various nucleobases may be utilized in provided oligonucleotides in accordance with the present disclosure. In some embodiments, a nucleobase is a natural nucleobase, the most commonly occurring ones being A, T, C, G and U. In some embodiments, a nucleobase is a modified nucleobase in that it is not A, T, C, G or U. In some embodiments, a nucleobase is optionally substituted A, T, C, G or U, or a substituted tautomer of A T, C, G or U. In some embodiments, a nucleobase is optionally substituted A, T, C, G or U, e.g., 5mC, 5-hydroxymethyl C, etc. In some embodiments, a nucleobase is alkyl-substituted A, T, C, G or U. In some embodiments, a nucleobase is A. In some embodiments, a nucleobase is T. In some embodiments, a nucleobase is C. In some embodiments, a nucleobase is G. In some embodiments, a nucleobase is U. In some embodiments, a nucleobase is 5mC. In some embodiments, a nucleobase is substituted A, T, C, G or U. In some embodiments, a nucleobase is a substituted tautomer of A, T, C, G or U. In some embodiments, substitution protects certain functional groups in nucleobases to minimize undesired reactions during oligonucleotide synthesis. Suitable technologies for nucleobase protection in oligonucleotide synthesis are widely known in the art and may be utilized in accordance with the present disclosure. In some

embodiments, modified nucleobases improves properties and/or activities of oligonucleotides. For example, in many cases, 5mC may be utilized in place of C to modulate certain undesired biological effects, e.g., immune responses. In some embodiments, when determining sequence identity, a substituted nucleobase having the same hydrogen-bonding pattern is treated as the same as the unsubstituted nucleobase, e.g., 5mC may be treated the same as C [e.g., an oligonucleotide having 5mC in place of C (e.g., AT5mCG) is considered to have the same base sequence as an oligonucleotide having C at the corresponding location(s) (e.g., ATCG)].

In some embodiments, an oligonucleotide comprises one or more A, T, C, G or U. In some embodiments, an oligonucleotide comprises one or more optionally substituted A, T, C, G or U. In some embodiments, an oligonucleotide comprises one or more 5-methylcytidine, 5-hydroxymethylcytidine, 5-formylcytosine, or 5-carboxylcytosine. In some embodiments, an oligonucleotide comprises one or more 5-methylcytidine. In some embodiments, each nucleobase in an oligonucleotide is selected from the group consisting of optionally substituted A, T, C, G and U, and optionally substituted tautomers of A, T, C, G and U. In some embodiments, each nucleobase in an oligonucleotide is optionally protected A, T, C, G and U. In some embodiments, each nucleobase in an oligonucleotide is optionally substituted A, T, C, G or U. In some embodiments, each nucleobase in an oligonucleotide is selected from the group consisting of A, T, C, G, U, and 5mC.

In some embodiments, a nucleobase is optionally substituted 2AP or DAP. In some embodiments, a nucleobase is optionally substituted 2AP. In some embodiments, a nucleobase is optionally substituted DAP. In some embodiments, a nucleobase is 2AP. In some embodiments, a nucleobase is DAP.

In some embodiments, a nucleobase is a natural nucleobase or a modified nucleobase derived from a natural nucleobase. Examples include uracil, thymine, adenine, cytosine, and guanine optionally having their respective amino groups protected by acyl protecting groups, 2-fluorouracil, 2-fluorocytosine, 5-bromouracil, 5-iodouracil, 2,6-diaminopurine, azacytosine, pyrimidine analogs such as pseudoisocytosine and pseudouracil and other modified nucleobases such as 8-substituted purines, xanthine, or hypoxanthine (the latter two being the natural degradation products). Certain examples of modified nucleobases are disclosed in Chiu and Rana, RNA, 2003, 9, 1034-1048, Limbach et al. Nucleic Acids Research, 1994, 22, 2183-2196 and Revankar and Rao, Comprehensive Natural Products Chemistry, vol. 7, 313. In some embodiments, a modified nucleobase is substituted uracil, thymine, adenine, cytosine, or guanine. In some embodiments, a modified nucleobase is a functional replacement, e.g., in

terms of hydrogen bonding and/or base pairing, of uracil, thymine, adenine, cytosine, or guanine. In some embodiments, a nucleobase is optionally substituted uracil, thymine, adenine, cytosine, 5-methylcytosine, or guanine. In some embodiments, a nucleobase is uracil, thymine, adenine, cytosine, 5-methylcytosine, or guanine.

In some embodiments, a provided oligonucleotide comprises one or more 5-methylcytosine. In some embodiments, the present disclosure provides an oligonucleotide whose base sequence is disclosed herein, e.g., in Table 1, wherein each T may be independently replaced with U and vice versa, and each cytosine is optionally and independently replaced with 5-methylcytosine or vice versa. As appreciated by those skilled in the art, in some embodiments, 5mC may be treated as C with respect to base sequence of an oligonucleotide - such oligonucleotide comprises a nucleobase modification at the C position (e.g., see various oligonucleotides in Table 1). In description of oligonucleotides, typically unless otherwise noted, nucleobases, sugars and internucleotidic linkages are non-modified.

In some embodiments, a modified base is optionally substituted adenine, cytosine, guanine, thymine, or uracil, or a tautomer thereof. In some embodiments, a modified nucleobase is a modified adenine, cytosine, guanine, thymine or uracil, modified by one or more modifications by which:

(1) a nucleobase is modified by one or more optionally substituted groups independently selected from acyl, halogen, amino, azide, alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, heteroaryl, carboxyl, hydroxyl, biotin, avidin, streptavidin, substituted silyl, and combinations thereof;

(2) one or more atoms of a nucleobase are independently replaced with a different atom selected from carbon, nitrogen and sulfur;

(3) one or more double bonds in a nucleobase are independently hydrogenated; or

(4) one or more aryl or heteroaryl rings are independently inserted into a nucleobase.

In some embodiments, a modified nucleobase is a modified nucleobase known in the art, e.g., WO2017/210647. In some embodiments, modified nucleobases are expanded-size nucleobases in which one or more aryl and/or heteroaryl rings, such as phenyl rings, have been added.

In some embodiments, a modified nucleobase is 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, xanthine, hypoxanthine, 2-aminoadenine, 6-N-methylguanine, 6-N- methyladenine, 2-propyladenine, 2-

thiouracil, 2-thiothymine and 2-thiocytosine, 5-propynyl (−C≡C-CH_3) 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-isobutyrylguanine, 4-N-benzoylcytosine, 4-N-benzoyluracil, 5-methyl 4-N-benzoylcytosine, 5-methyl 4-N-benzoyluracil, universal bases, hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases. In some embodiments, modified nucleobases are tricyclic pyrimidines, such as l,3-diazaphenoxazine-2-one, l,3-diazaphenothiazine-2-one or 9-(2-aminoethoxy)-l,3-diazaphenoxazine-2- one (G-clamp). In some embodiments, modified nucleobases are those in which the purine or pyrimidine base is replaced with other heterocycles, for example, 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine or 2- pyridone.

In some embodiments, a modified nucleobase is substituted. In some embodiments, a modified nucleobase is substituted such that it contains, e.g., heteroatoms, alkyl groups, or linking moieties connected to fluorescent moieties, biotin or avidin moieties, or other protein or peptides. In some embodiments, a modified nucleobase is a “universal base” that is not a nucleobase in the most classical sense, but that functions similarly to a nucleobase. One example of a universal base is 3-nitropyrrole.

In some embodiments, nucleosides that can be utilized in provided technologies comprise modified nucleobases and/or modified sugars, e.g., 4-acetylcytidine; 5-(carboxyhydroxylmethyl)uridine; 2’-O-methylcytidine; 5-carboxymethylaminomethyl-2-thiouridine; 5-carboxymethylaminomethyluridine; dihydrouridine; 2’-O-methylpseudouridine; beta,D-galactosylqueosine; 2’-O-methylguanosine; N^6-isopentenyladenosine; 1-methyladenosine; 1-methylpseudouridine; 1-methylguanosine; l-methylinosine; 2,2-dimethylguanosine; 2-methyladenosine; 2-methylguanosine; N^7-methylguanosine; 3-methyl-cytidine; 5-methylcytidine; 5-hydroxymethylcytidine; 5-formylcytosine; 5-carboxylcytosine; N^6-methyladenosine; 7-methylguanosine; 5-methylaminoethyluridine; 5-methoxyaminomethyl-2-thiouridine; beta,D-mannosylqueosine; 5-methoxycarbonylmethyluridine; 5-methoxyuridine; 2-methylthio-N^6-isopentenyladenosine; N-((9-beta,D-ribofuranosyl-2-methylthiopurine-6-yl)carbamoyl)threonine; N-((9-beta,D-ribofuranosylpurine-6-yl)-N-methylcarbamoyl)threonine; uridine-5-oxyacetic acid methylester; uridine-5-oxyacetic acid (v); pseudouridine; queosine; 2-thiocytidine; 5-methyl-

2-thiouridine; 2-thiouridine; 4-thiouridine; 5-methyluridine; 2'-O-methyl-5-methyluridine; and 2'-O-methyluridine.

In some embodiments, a nucleobase, e.g., a modified nucleobase comprises one or more biomolecule binding moieties such as e.g., antibodies, antibody fragments, biotin, avidin, streptavidin, receptor ligands, or chelating moieties. In other embodiments, a nucleobase is 5-bromouracil, 5-iodouracil, or 2,6-diaminopurine. In some embodiments, a nucleobase comprises substitution with a fluorescent or biomolecule binding moiety. In some embodiments, a substituent is a fluorescent moiety. In some embodiments, a substituent is biotin or avidin.

In some embodiments, a nucleobase is one described in US 9394333, US 9744183, US 9605019, US 9598458, US 9982257, US 10160969, US 10479995, US 2020/0056173, US 2018/0216107, US 2019/0127733, US 10450568, US 2019/0077817, US 2019/0249173, US 2019/0375774, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, and/or WO 2020/191252, the nucleobases of each of which is incorporated herein by reference.

Additional Chemical Moieties

In some embodiments, a ds oligonucleotide targeting INHBE comprises one or more additional chemical moieties. Various additional chemical moieties, e.g., targeting moieties, carbohydrate moieties, lipid moieties, etc. are known in the art and can be utilized in accordance with the present disclosure to modulate properties and/or activities of ds oligonucleotides targeting INHBE, e.g., stability, half life, activities, delivery, pharmacodynamics properties, pharmacokinetic properties, etc. In some embodiments, certain additional chemical moieties facilitate delivery of oligonucleotides to desired cells, tissues and/or organs, including but not limited the cells of the central nervous system. In some embodiments, certain additional chemical moieties facilitate internalization of oligonucleotides. In some embodiments, certain additional chemical moieties increase oligonucleotide stability. In some embodiments, the present disclosure provides technologies for incorporating various additional chemical moieties into oligonucleotides.

In certain embodiments, a ds oligonucleotide comprises an additional chemical moiety demonstrates increased delivery to and/or activity in a tissue compared to a reference oligonucleotide, e.g., a reference oligonucleotide which does not have the additional chemical

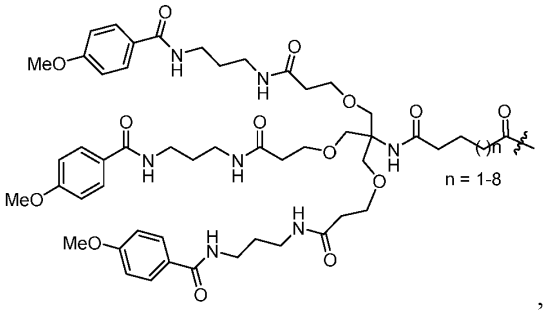
moiety but is otherwise identical.

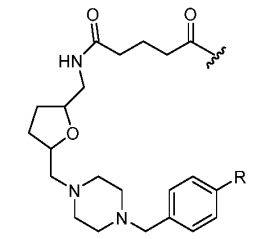
In certain embodiments, non-limiting examples of additional chemical moieties include carbohydrate moieties, targeting moieties, etc., which, when incorporated into oligonucleotides, can improve one or more properties. In certain embodiments, an additional chemical moiety is selected from: glucose, GluNAc (N-acetyl amine glucosamine) and anisamide moieties. In certain embodiments, a provided ds oligonucleotide can comprise two or more additional chemical moieties, wherein the additional chemical moieties are identical or non-identical, or are of the same category (e.g., carbohydrate moiety, sugar moiety, targeting moiety, etc.) or not of the same category.

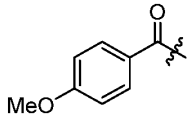
In certain embodiments, an additional chemical moiety is a targeting moiety. In certain embodiments, an additional chemical moiety is or comprises a carbohydrate moiety. In certain embodiments, an additional chemical moiety is or comprises a lipid moiety. In certain embodiments, an additional chemical moiety is or comprises a ligand moiety for, e.g., cell receptors such as a sigma receptor, an asialoglycoprotein receptor, etc. In certain embodiments, a ligand moiety is or comprises an anisamide moiety, which may be a ligand moiety for a sigma receptor. In certain embodiments, a ligand moiety is or comprises a GalNAc moiety, which may be a ligand moiety for an asialoglycoprotein receptor. In certain embodiments, an additional chemical moiety facilitates delivery to liver.

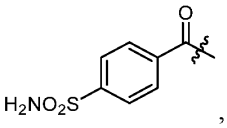
In certain embodiments, a provided ds oligonucleotide can comprise one or more linkers and additional chemical moieties (e.g., targeting moieties), and/or can be chirally controlled or not chirally controlled, and/or have a bases sequence and/or one or more modifications and/or formats as described herein.

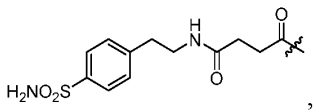
Various linkers, carbohydrate moieties and targeting moieties, including many known in the art, can be utilized in accordance with the present disclosure. In certain embodiments, a carbohydrate moiety is a targeting moiety. In certain embodiments, a targeting moiety is a carbohydrate moiety.In certain embodiments, a provided ds oligonucleotide comprises an additional chemical moiety suitable for delivery, e.g., glucose, GluNAc (N-acetyl amine glucosamine), anisamide, or a structure selected from:

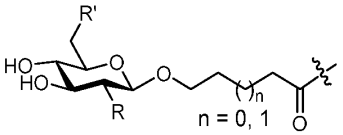




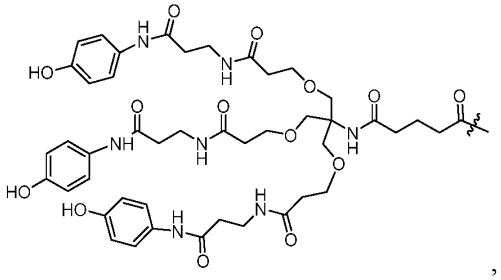


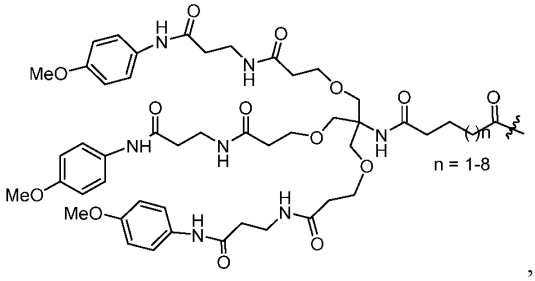


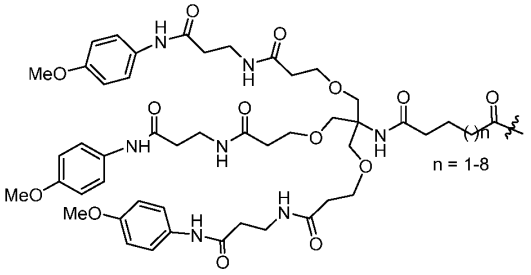


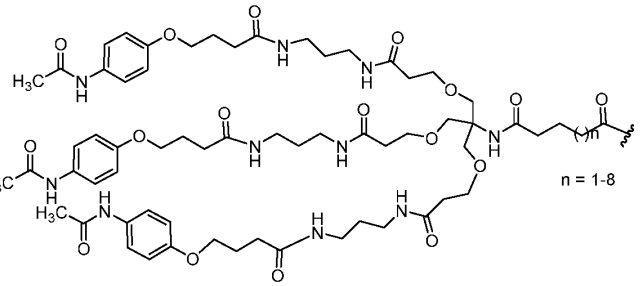


R = NHAc, R' = OH; R = NHCOC6H4OMe(p-anisoyl), R'=OH;
R = NHAc, R' = NHCOC6H4OMe(p-anisoyl);
R = OH, R' = NHCOC6H4OMe(p-anisoyl)









, and . In certain embodiments, n is 1. In certain embodiments, n is 2. In certain embodiments, n is 3. In certain embodiments, n is 4. In certain embodiments, n is 5. In certain embodiments, n is 6. In certain embodiments, n is 7. In certain embodiments, n is 8.

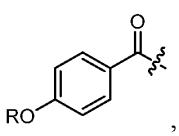
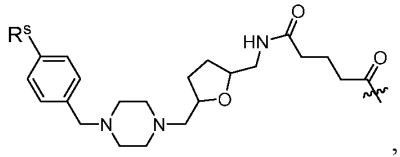
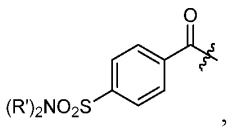
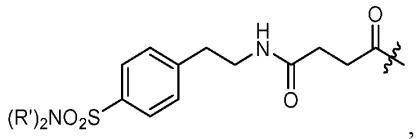
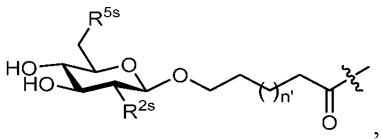
In certain embodiments, additional chemical moieties are any of ones described in the Examples, including examples of various additional chemical moieties incorporated into

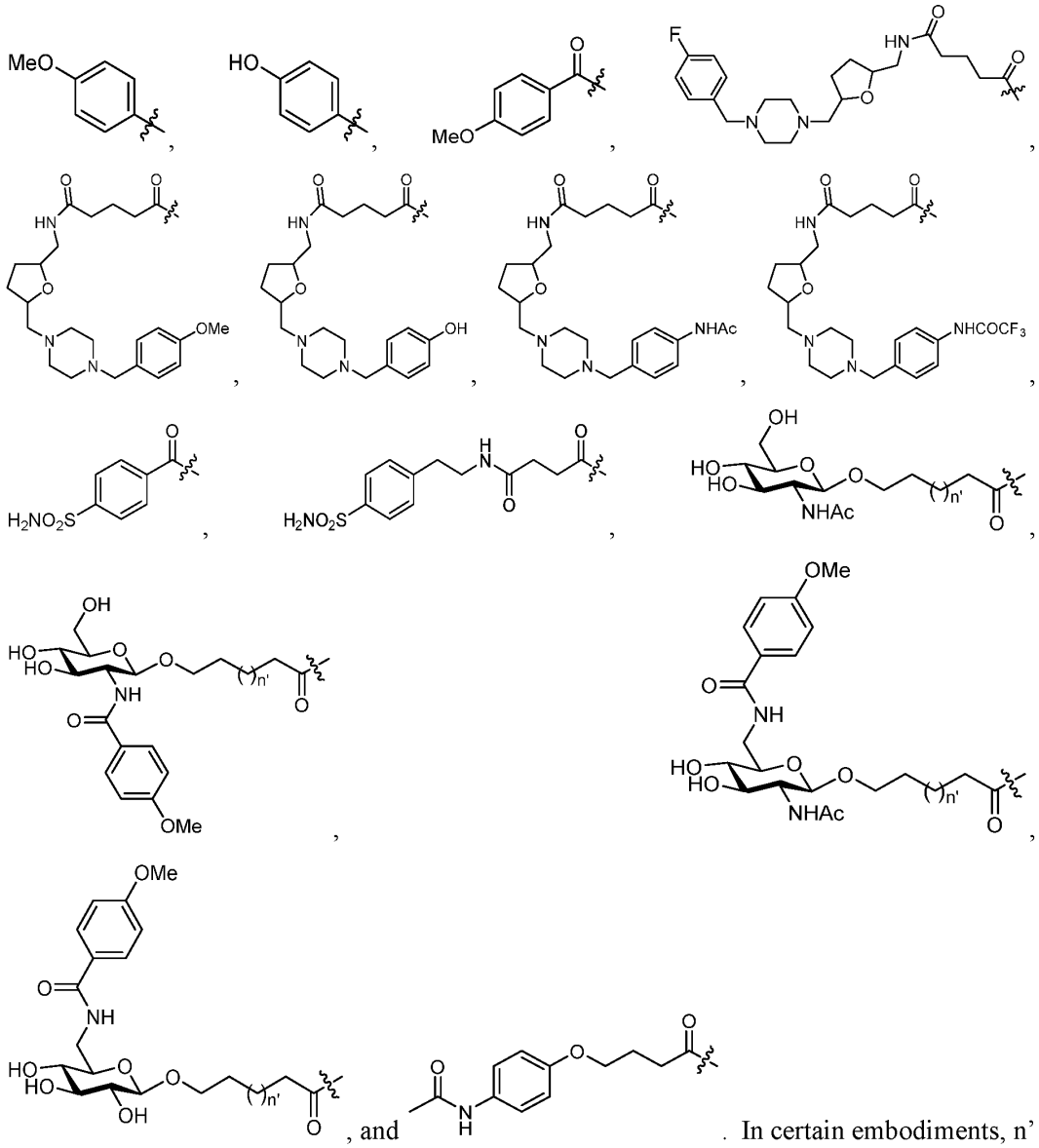
various ds oligonucleotides.

In certain embodiments, an additional chemical moiety conjugated to a ds oligonucleotide is capable of targeting the ds oligonucleotide to a cell in the central nervous system.

In certain embodiments, an additional chemical moiety comprises or is a cell receptor ligand. In certain embodiments, an additional chemical moiety comprises or is a protein binder, e.g., one binds to a cell surface protein. Such moieties among other things can be useful for targeted delivery of ds oligonucleotides to cells expressing the corresponding receptors or proteins. In certain embodiments, an additional chemical moiety of a provided ds oligonucleotide comprises anisamide or a derivative or an analog thereof and is capable of targeting the ds oligonucleotide to a cell expressing a particular receptor, such as the sigma 1 receptor.

In certain embodiments, a provided ds oligonucleotide is formulated for administration to a body cell and/or tissue expressing its target. In certain embodiments, an additional chemical moiety conjugated to a ds oligonucleotide is capable of targeting the oligonucleotide to a cell.

In certain embodiments, an additional chemical moiety is selected from optionally substituted phenyl,  ,  ,  ,  , and  , wherein n' is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, and each other variable is as described in the present disclosure. In certain embodiments, R^s is F. In certain embodiments, R^s is OMe. In certain embodiments, R^s is OH. In certain embodiments, R^s is NHAc. In certain embodiments, R^s is $NHCOCF_3$. In certain embodiments, R' is H. In certain embodiments, R is H. In certain embodiments, R^{2s} is NHAc, and R^{5s} is OH. In certain embodiments, R^{2s} is p-anisoyl, and R^{5s} is OH. In certain embodiments, R^{2s} is NHAc and R^{5s} is p-anisoyl. In certain embodiments, R^{2s} is OH, and R^{5s} is p-anisoyl. In certain embodiments, an additional chemical moiety is selected from

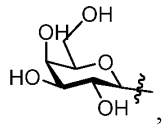
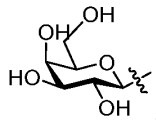
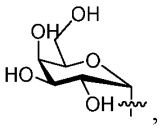
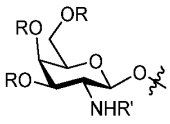
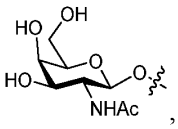
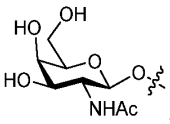
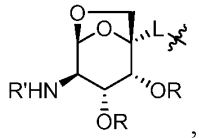
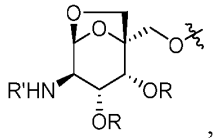
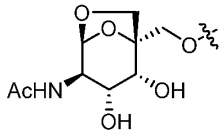


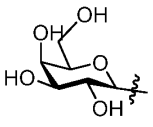
, and . In certain embodiments, n' is 1. In certain embodiments, n' is 0. In certain embodiments, n" is 1. In certain embodiments, n" is 2.

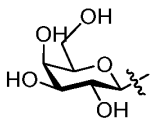
In certain embodiments, an additional chemical moiety is or comprises an asialoglycoprotein receptor (ASGPR) ligand.

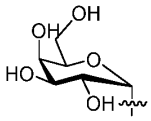
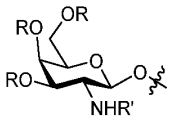
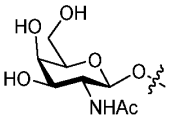
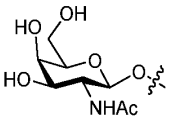
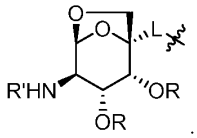
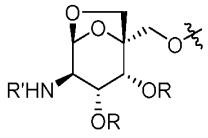
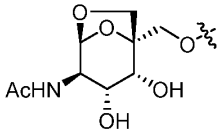
Without wishing to be bound by any particular theory, the present disclosure notes that ASGPR1 has also been reported to be expressed in the hippocampus region and/or cerebellum Purkinje cell layer of the mouse. http://mouse.brain-map.org/experiment/show/2048

Various other ASGPR ligands are known in the art and can be utilized in accordance with the present disclosure. In certain embodiments, an ASGPR ligand is a carbohydrate. In

certain embodiments, an ASGPR ligand is GalNac or a derivative or an analog thereof. In certain embodiments, an ASGPR ligand is one described in Sanhueza et al. J. Am. Chem. Soc., 2017, 139 (9), pp 3528–3536. In certain embodiments, an ASGPR ligand is one described in Mamidyala et al. J. Am. Chem. Soc., 2012, 134, pp 1978−1981. In certain embodiments, an ASGPR ligand is one described in US 20160207953. In certain embodiments, an ASGPR ligand is a substituted-6,8-dioxabicyclo[3.2.1]octane-2,3-diol derivative disclosed in, e.g., US 20160207953. In certain embodiments, an ASGPR ligand is one described in, e.g., US 20150329555. In certain embodiments, an ASGPR ligand is a substituted-6,8-dioxabicyclo[3.2.1]octane-2,3-diol derivative disclosed e.g., in US 20150329555. In certain embodiments, an ASGPR ligand is one described in US 8877917, US 20160376585, US 10086081, or US 8106022. ASGPR ligands described in these documents are incorporated herein by reference. Those skilled in the art will appreciate that various technologies are known in the art, including those described in these documents, for assessing binding of a chemical moiety to ASGPR and can be utilized in accordance with the present disclosure. In certain embodiments, a provided ds oligonucleotide is conjugated to an ASGPR ligand. In certain embodiments, a provided ds oligonucleotide comprises an ASGPR ligand. In certain embodiments, an additional chemical moiety comprises an ASGPR ligand is  ,  ,  ,  ,  ,  , ,  ,  , or  , wherein each variable is independently as described in the present disclosure. In certain embodiments, R is −H. In certain embodiments, R’ is −C(O)R.

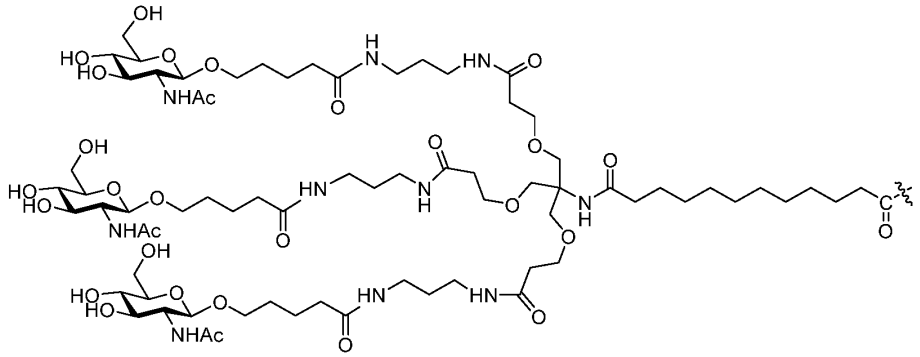
In certain embodiments, an additional chemical moiety is or comprises  .

In certain embodiments, an additional chemical moiety is or comprises  . In

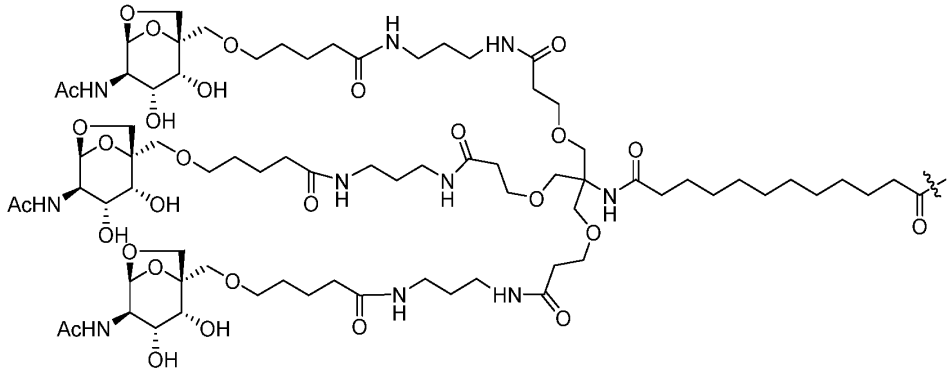
certain embodiments, an additional chemical moiety is or comprises  . In certain embodiments, an additional chemical moiety is or comprises  . In certain embodiments, an additional chemical moiety is or comprises optionally substituted  . In certain embodiments, an additional chemical moiety is or comprises  . In certain embodiments, an additional chemical moiety is or comprises [OBJ]. In certain embodiments, an additional chemical moiety is or comprises  . In certain embodiments, an additional chemical moiety is or comprises  . In certain embodiments, an additional chemical moiety is or comprises  .

In certain embodiments, an additional chemical moiety comprises one or more moieties that can bind to, e.g., oligonucleotide target cells. For example, in certain embodiments, an additional chemistry moiety comprises one or more protein ligand moieties, e.g., in certain embodiments, an additional chemical moiety comprises multiple moieties, each of which independently is an ASGPR ligand. In certain embodiments, as in Mod 001, Mod083, Mod071, Mod153, and Mod155, an additional chemical moiety comprises three such ligands.

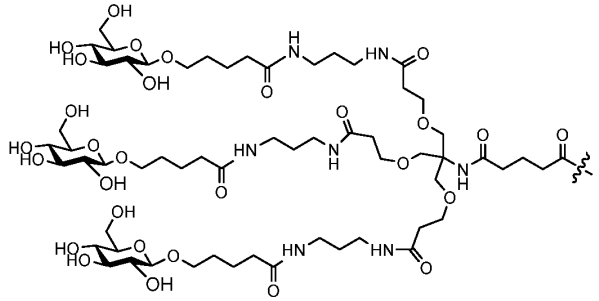
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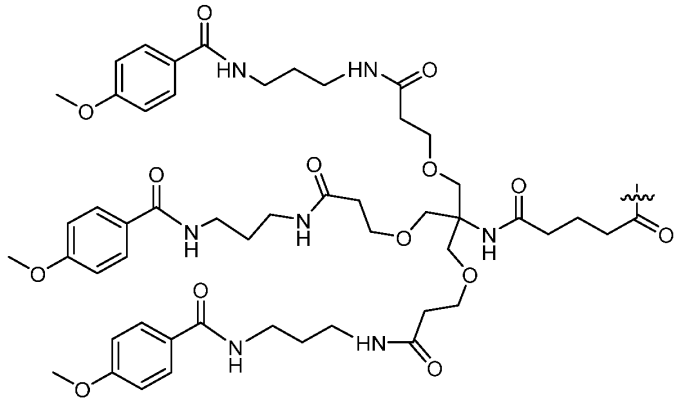
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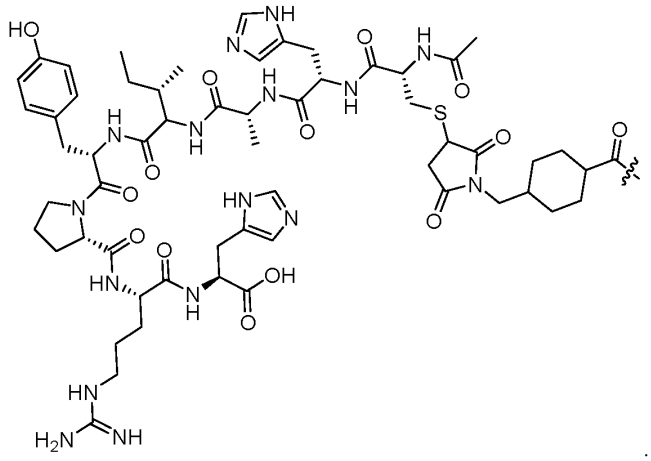
Mod071



Mod077

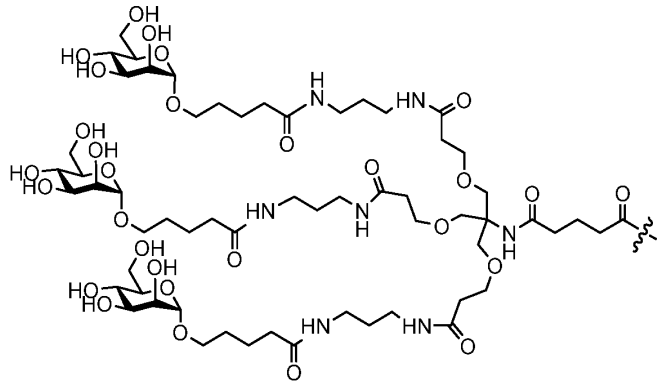


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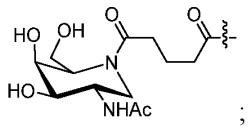
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Mod105:



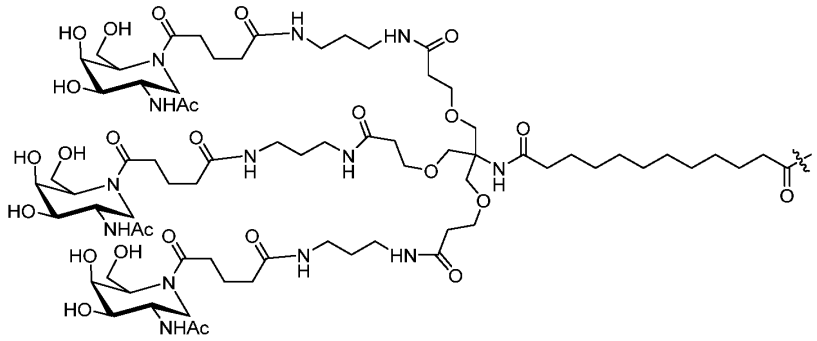
.

Mod152 (in certain embodiments, −C(O)− connects to −NH− of a linker such as Mod153):

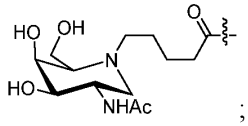


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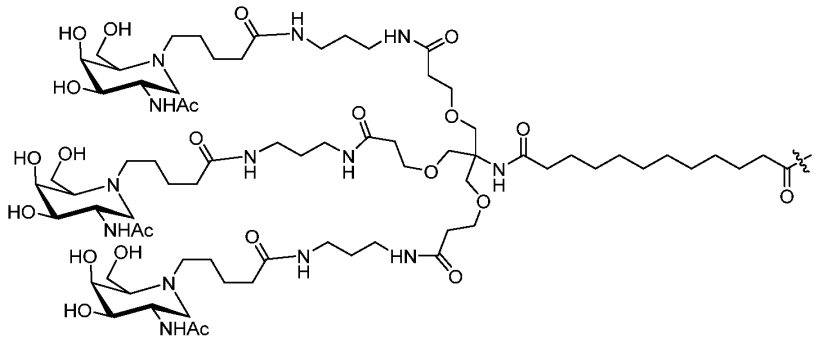
Mod153



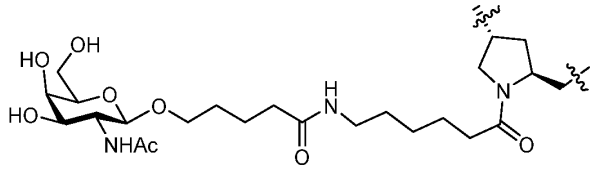
Mod154 (in certain embodiments, −C(O)− connects to −NH− of a linker such as Mod155):


;

Mod155


.

In some embodiments, an oligonucleotide comprises


(L025). In some embodiments, the $-CH_2-$ connection site is utilized as a C5 connection site in a sugar. In some embodiments, the connection site on the ring is utilized as a C3 connection site in a sugar. Such moieties may be introduced utilizing, e.g., phosphoramidites (those skilled in the art appreciate that one or more groups, such as protection groups for −OH, $-NH_2-$, $-N(i\text{-}Pr)_2$, $-OCH_2CH_2CN$, etc., may be alternatively utilized, and protection groups can be removed under various suitable conditions, sometimes during oligonucleotide de-protection and/or cleavage steps). In some embodiments, an oligonucleotide comprises 2, 3 or more (e.g., 3 and no more than 3). In some embodiments, an oligonucleotide comprises 2, 3 or more (e.g., 3 and no more than 3). In some embodiments, copies of such moieties are linked by internucleotidic linkages, e.g., natural

phosphate linkages, as described herein. In some embodiments, when at a 5'-end, a $-CH_2-$ connection site is bonded to $-OH$. In some embodiments, each $-OR'$ is $-OAc$, and $-N(R')_2$ is $-NHAc$.

In certain embodiments, an additional chemical moiety is a Mod group described herein, e.g., in Table 1.

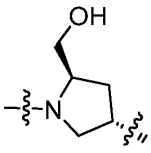
In certain embodiments, an additional chemical moiety is Mod001. In certain embodiments, an additional chemical moiety is Mod083. In certain embodiments, an additional chemical moiety, e.g., a Mod group, is directly conjugated (e.g., without a linker) to the remainder of the ds oligonucleotide. In certain embodiments, an additional chemical moiety is conjugated via a linker to the remainder of the ds oligonucleotide. In certain embodiments, additional chemical moieties, e.g., Mod groups, may be directly connected, and/or via a linker, to nucleobases, sugars and/or internucleotidic linkages of ds oligonucleotides. In certain embodiments, Mod groups are connected, either directly or via a linker, to sugars. In certain embodiments, Mod groups are connected, either directly or via a linker, to 5'-end sugars. In certain embodiments, Mod groups are connected, either directly or via a linker, to 5'-end sugars via 5' carbon. For examples, see various ds oligonucleotides in Table 1. In certain embodiments, Mod groups are connected, either directly or via a linker, to 3'-end sugars. In certain embodiments, Mod groups are connected, either directly or via a linker, to 3'-end sugars via 3' carbon. In certain embodiments, Mod groups are connected, either directly or via a linker, to nucleobases. In certain embodiments, Mod groups are connected, either directly or via a linker, to internucleotidic linkages. In certain embodiments, provided oligonucleotides comprise Mod001 connected to 5'-end of oligonucleotide chains through L001.

As appreciated by those skilled in the art, an additional chemical moiety may be connected to a ds oligonucleotide chain at various locations, e.g., 5'-end, 3'-end, or a location in the middle (e.g., on a sugar, a base, an internucleotidic linkage, etc.). In certain embodiments, it is connected at a 5'-end. In certain embodiments, it is connected at a 3'-end. In certain embodiments, it is connected at a nucleotide in the middle.

Certain additional chemical moieties (e.g., lipid moieties, targeting moieties, carbohydrate moieties), including but not limited to Mod012, Mod039, Mod062, Mod085, Mod086, and Mod094, and various linkers for connecting additional chemical moieties to ds oligonucleotide chains, including but not limited to L001, L003, L004, L008, L009, and L010, are described in WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/022473, WO 2018/223056, WO

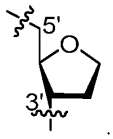
2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO2019032612, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, and/or WO 2019/032612, the additional chemical moieties and linkers of each of which are independently incorporated herein by reference, and can be utilized in accordance with the present disclosure. In certain embodiments, an additional chemical moiety is digoxigenin or biotin or a derivative thereof.

In certain embodiments, a ds oligonucleotide comprises a linker, e.g., L001 L004, L008, and/or an additional chemical moiety, e.g., Mod012, Mod039, Mod062, Mod085, Mod086, or Mod094. In certain embodiments, a linker, *e.g.*, L001, L003, L004, L008, L009, L110, *etc.* is linked to a Mod, *e.g.*, Mod012, Mod039, Mod062, Mod085, Mod086, Mod094, Mod152, Mod153, Mod154, Mod155 *etc.* L001: $-NH-(CH_2)_6-$ linker (also known as a C6 linker, C6 amine linker or C6 amino linker), connected to Mod, if any, through −NH−, and the 5'-end or 3'-end of the ds oligonucleotide chain through either a phosphate linkage (−O−P(O)(OH)−O−, which may exist as a salt form, and may be indicated as O or PO) or a phosphorothioate linkage (−O−P(O)(SH)−O−, which may exist as a salt form, and may be indicated as * if the phosphorothioate is not chirally controlled; or *S, S, or *Sp*, if the phosphorothioate is chirally controlled and has an *Sp* configuration, or *R, R, or *Rp*, if the phosphorothioate is chirally controlled and has an *Rp* configuration) as indicated at the $-CH_2-$ connecting site. If no Mod is present, L001 is connected to −H through −NH−;

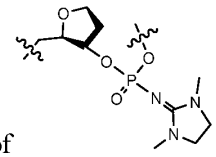
L003:  linker. In certain embodiments, it is connected to Mod, if any (if no Mod, −H), through its amino group, and the 5'-end or 3'-end of an oligonucleotide chain e.g., via a linkage (e.g., a phosphate linkage (O or PO) or a phosphorothioate linkage (can be either not chirally controlled or chirally controlled (*Sp* or *Rp*))); L004: linker having the structure of $-NH(CH_2)_4CH(CH_2OH)CH_2-$, wherein −NH− is connected to Mod (through −C(O)−) or −H, and the $-CH_2-$ connecting site is connected to an oligonucleotide chain (e.g., at the 3'-end) through a linkage, e.g., phosphodiester (−O−P(O)(OH)−O−, which may exist as a salt form, and may be indicated as O or PO), phosphorothioate (−O−P(O)(SH)−O−, which may exist as a salt form, and may be indicated as * if the phosphorothioate is not chirally controlled; or *S, S, or *Sp*, if the phosphorothioate is chirally controlled and has an *Sp* configuration, or *R, R, or *Rp*, if the phosphorothioate is chirally controlled and has an *Rp* configuration), or phosphorodithioate (−O−P(S)(SH)−O−, which may exist as a salt form, and may be indicated

as PS2 or : or D) linkage. For example, an asterisk immediately preceding a L004 (e.g., *L004) indicates that the linkage is a phosphorothioate linkage, and the absence of an asterisk immediately preceding L004 indicates that the linkage is a phosphodiester linkage. For example, in an oligonucleotide which terminates in ...mAL004, the linker L004 is connected (via the $-CH_2-$ site) through a phosphodiester linkage to the 3' position of the 3'-terminal sugar (which is 2'-OMe modified and connected to the nucleobase A), and the L004 linker is connected via $-NH-$ to $-H$. Similarly, in one or more oligonucleotides, the L004 linker is connected (via the $-CH_2-$ site) through the phosphodiester linkage to the 3' position of the 3'-terminal sugar, and the L004 is connected via $-NH-$ to, e.g., Mod012, Mod085, Mod086, etc.; L008: linker having the structure of $-C(O)-(CH_2)_9-$, wherein $-C(O)-$ is connected to Mod (through $-NH-$) or $-OH$ (if no Mod indicated), and the $-CH_2-$ connecting site is connected to an oligonucleotide chain (e.g., at the 5'-end) through a linkage, e.g., phosphodiester ($-O-P(O)(OH)-O-$, which may exist as a salt form, and may be indicated as O or PO), phosphorothioate ($-O-P(O)(SH)-O-$, which may exist as a salt form, and may be indicated as * if the phosphorothioate is not chirally controlled; or *S, S, or *Sp*, if the phosphorothioate is chirally controlled and has an *Sp* configuration, or *R, R, or *Rp*, if the phosphorothioate is chirally controlled and has an *Rp* configuration), or phosphorodithioate ($-O-P(S)(SH)-O-$, which may exist as a salt form, and may be indicated as PS2 or : or D) linkage. For example, in an example oligonucleotide which has the sequence of 5'-L008mN * mN * mN * mN * N * N * N * N * N * N * N * N * N * N * N * N * mN * mN * mN * mN-3', and which has a Stereochemistry/Linkage of OXXXXXXXXX XXXXXXXX, wherein N is a base, wherein O is a natural phosphate internucleotidic linkage, and wherein X is a stereorandom phosphorothioate, L008 is connected to $-OH$ through $-C(O)-$, and the 5'-end of an oligonucleotide chain through a phosphate linkage (indicated as "O" in "Stereochemistry/Linkage"); in another example oligonucleotide, which has the sequence of 5'-Mod062L008mN * mN * mN * mN * N * N * N * N * N * N * N * N * N * N * N * mN * mN * mN * mN-3', and which has a Stereochemistry/Linkage of OXXXXXXXXX XXXXXXXX, wherein N is a base, L008 is connected to Mod062 through $-C(O)-$, and the 5'-end of an oligonucleotide chain through a phosphate linkage (indicated as "O" in "Stereochemistry/Linkage");

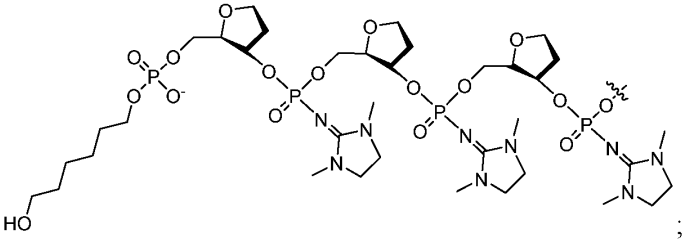
L009: $-CH_2CH_2CH_2-$. In certain embodiments, when L009 is present at the 5'-end of an oligonucleotide without a Mod, one end of L009 is connected to $-OH$ and the other end connected to a 5'-carbon of the oligonucleotide chain e.g., via a linkage (e.g., a phosphate linkage (O or PO) or a phosphorothioate linkage (can be either not chirally controlled or



chirally controlled (*S*p or *Rp*))); L010: . In certain embodiments, when L010 is present at the 5'-end of an oligonucleotide without a Mod, the 5'-carbon of L010 is connected to −OH and the 3'-carbon connected to a 5'-carbon of the oligonucleotide chain e.g., via a linkage (e.g., a phosphate linkage (O or PO) or a phosphorothioate linkage (can be either not chirally controlled or chirally controlled (*S*p or *Rp*))); Mod012 (in certain embodiments, −C(O)− connects to −NH− of a linker such as L001, L004, L008, *etc.*):

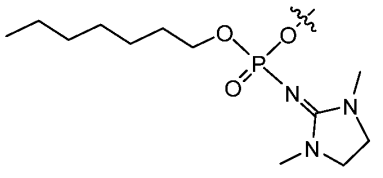


L010 is utilized with n001R to form L010n001R, which has the structure of and wherein the configuration of linkage phosphorus is *R*p. In some embodiments, multiple L010n001R may be utilized. For example, L023L010n001RL010n001RL010n001R, which has the following structure (which is bonded to the 5'-carbon at the 5'-end of the oligonucleotide chain, and each linkage phosphorus is independently *R*p):



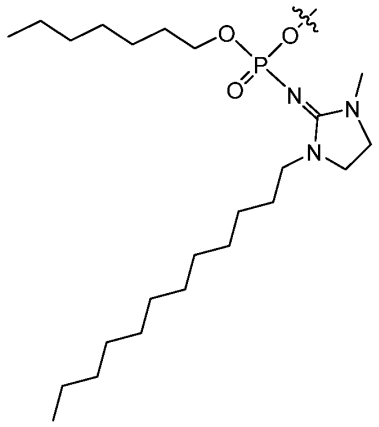
;

L023 is utilized with n001 to form L023n001, which has the structure of



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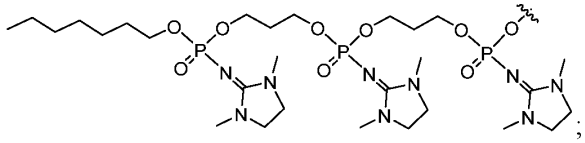
L023 is utilized with n009 to form L023n009, as in WV-42644 which has the structure of



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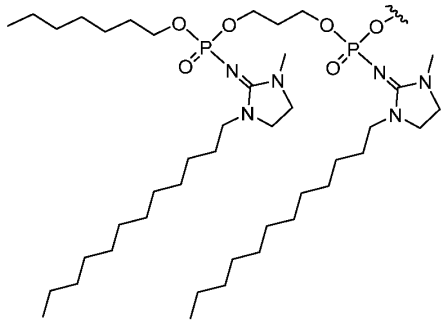
In some embodiments, L023n001L009n001L009n001 may be utilized. For example,

L023n001L009n001L009n001 as in WV-42643



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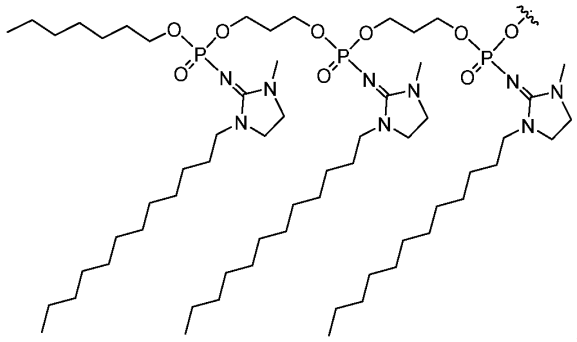
In some embodiments, L023n009L009n009 may be utilized. For example, as in WV-42646



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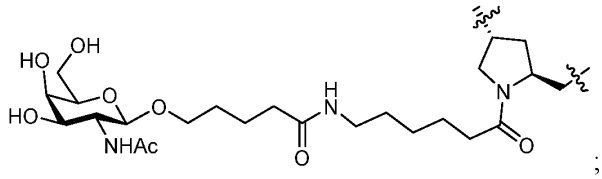
In some embodiments, L023n009L009n009L009n009 may be utilized. For example, as in

WV-42648

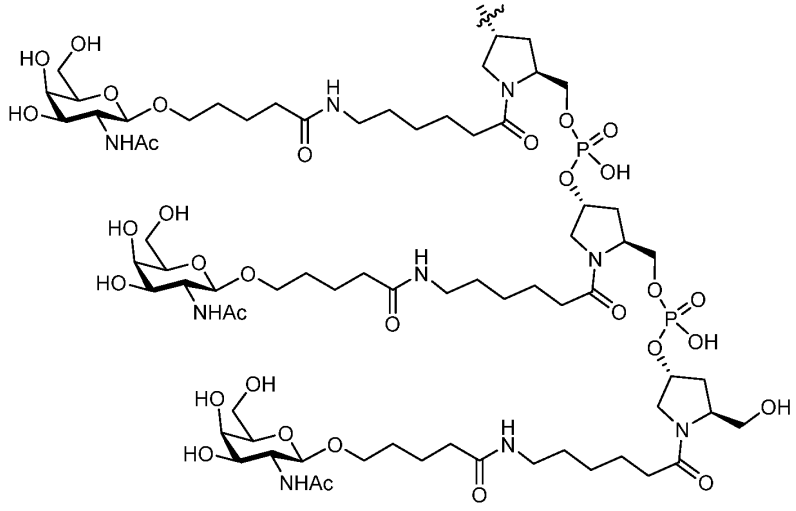


;

In some embodiments L025 may be utilized; as in WV-41390,

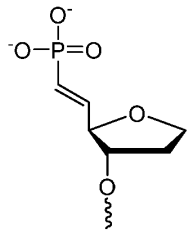


; wherein the $-CH_2-$ connection site is utilized as a C5 connection site of a sugar (e.g., a DNA sugar) and is connected to another unit (e.g., 3' of a sugar), and the connection site on the ring is utilized as a C3 connection site and is connected to another unit (e.g., a 5'-carbon of a carbon), each of which is independently, e.g., via a linkage (e.g., a phosphate linkage (O or PO) or a phosphorothioate linkage (can be either not chirally controlled or chirally controlled (*S*p or *R*p))). When L025 is at a5'-end without any modifications, its $-CH_2-$ connection site is bonded to $-OH$. For example, L025L025L025− in various oligonucleotides has the structure of



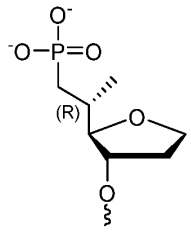
(may exist as various salt forms) and is connected to 5'-carbon of an oligonucleotide chain via a linkage as indicated (e.g., a phosphate linkage (O or PO) or a phosphorothioate linkage (can be either not chirally controlled or chirally controlled (*S*p or *R*p)));

In some embodiments L026 may be utilized; as in WV-44444,



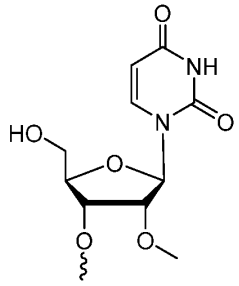
;

In some embodiments L027 may be utilized; as in WV-44445,



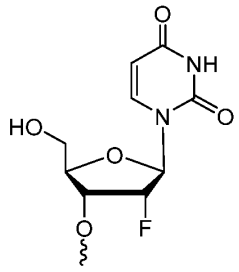
;

In some embodiments mU may be utilized; as in WV-42079,



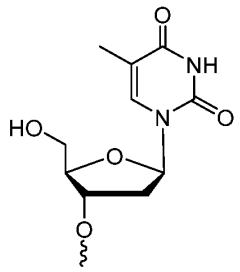
;

In some embodiments fU may be utilized; as in WV-44433,



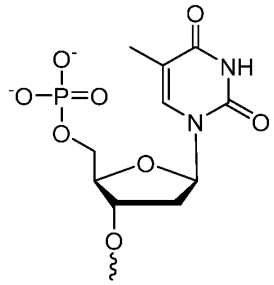
;

In some embodiments dT may be utilized; as in WV-44434,



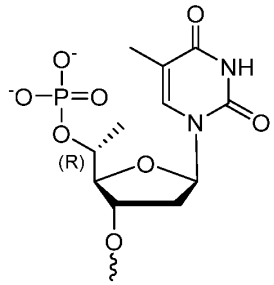
;

In some embodiments POdT or PO4-dTmay be utilized; as in WV-44435,



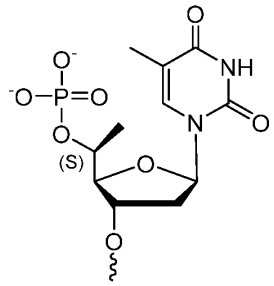
;

In some embodiments PO5MRdT may be utilized; as in WV-44436,



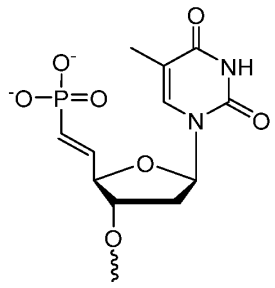
;

In some embodiments PO5MSdT may be utilized; as in WV-44437,



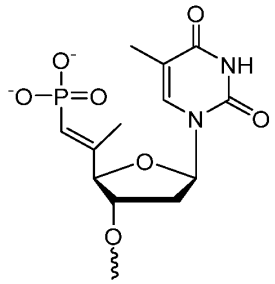
;

In some embodiments VPdT may be utilized; as in WV-44438,



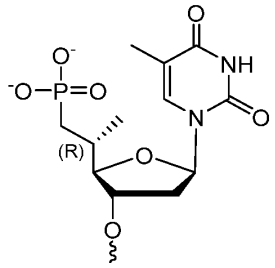
;

In some embodiments 5mvpdT may be utilized; as in WV-44439,



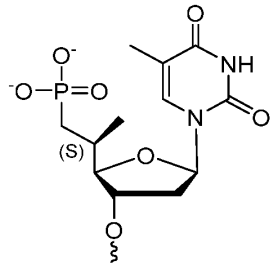
;

In some embodiments 5mrpdT may be utilized; as in WV-44440,



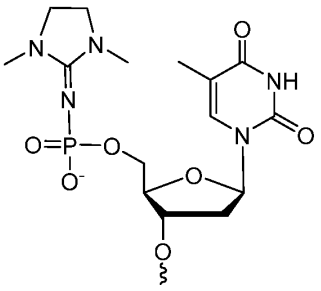
;

In some embodiments 5mspdT or p[Rm5d5m]T may be utilized; as in WV-44441,



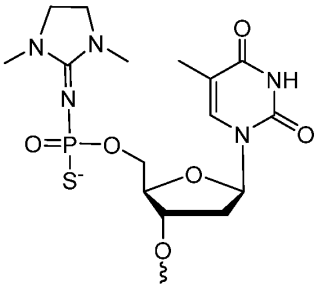
;

In some embodiments PNdT may be utilized; as in WV-44442,



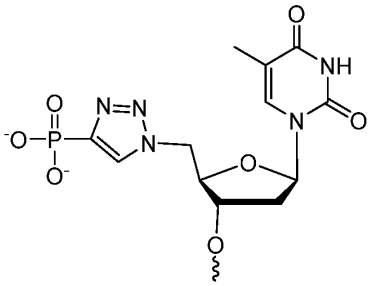
;

In some embodiments SPNdT may be utilized; as in WV-44443,

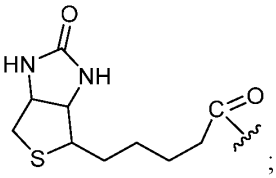


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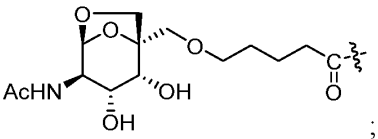
In some embodiments 5ptzdT may be utilized; as in WV-44446,



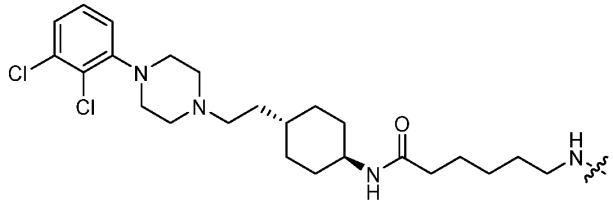
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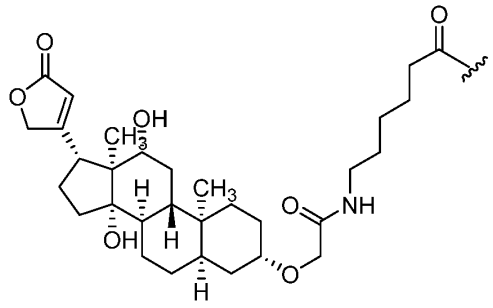
; Mod039 (in certain embodiments, −C(O)− connects to −NH− of a linker such as L001, L003, L004, L008, L009, L110, *etc.*):



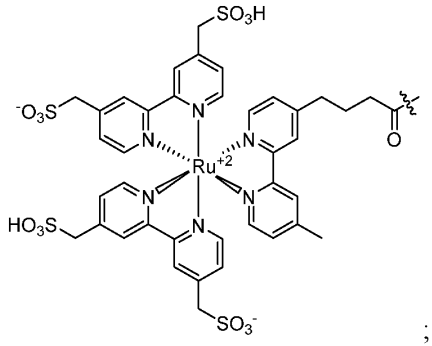
; Mod062 (in certain embodiments, −C(O)− connects to −NH− of a linker such as L001, L003, L004, L008, L009, L110, *etc.*):



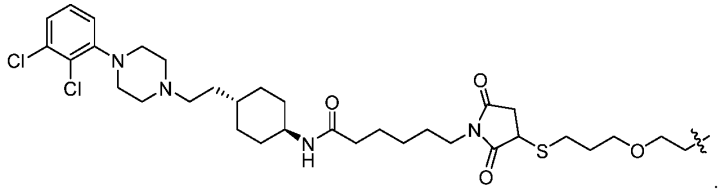
; Mod085 (in certain embodiments, −C(O)− connects to −NH− of a linker such as L001, L003, L004, L008, L009, L110, *etc.*):



; Mod086 (in certain embodiments, −C(O)− connects to −NH− of a linker such as L001, L003, L004, L008, L009, L110, *etc.*):



; Mod094 (in certain embodiments, connects to an internucleotidic linkage, or to the 5'-end or 3'-end of an oligonucleotide via a linkage, *e.g.*, a phosphate linkage, a phosphorothioate linkage (which is optionally chirally controlled), *etc.*. For example, in an example oligonucleotide which has the sequence of 5'-mN * mN * mN * mN * N * N * N * N * N * N * N * N * N * N * N * mN * mN * mN * mNMod094-3', and which has a Stereochemistry/Linkage of XXXXX XXXXX XXXXX XXO, wherein N is a base, Mod094 is connected to the 3'-end of the oligonucleotide chain (3'-carbon of the 3'-end sugar) through a phosphate group (which is not shown below and which may exist as a salt form; and which is indicated as "O" in "Stereochemistry/Linkage" (...XXXX**O**))):



.

In certain embodiments, an additional chemical moiety is one described in WO 2012/030683. In certain embodiments, a provided ds oligonucleotide comprises a chemical structure (e.g., a linker, lipid, solubilizing group, and/or targeting ligand) described in WO 2012/030683.

In certain embodiments, a provided ds oligonucleotide comprises an additional chemical moiety and/or a modification (e.g., of nucleobase, sugar, internucleotidic linkage, etc.) described in: U.S. Pat. Nos. 5,688,941; 6,294,664; 6,320,017; 6,576,752; 5,258,506; 5,591,584; 4,958,013; 5,082,830; 5,118,802; 5,138,045; 6,783,931; 5,254,469; 5,414,077; 5,486,603; 5,112,963; 5,599,928; 6,900,297; 5,214,136; 5,109,124; 5,512,439; 4,667,025; 5,525,465; 5,514,785; 5,565,552; 5,541,313; 5,545,730; 4,835,263; 4,876,335; 5,578,717; 5,580,731; 5,451,463; 5,510,475; 4,904,582; 5,082,830; 4,762,779; 4,789,737; 4,824,941; 4,828,979; 5,595,726; 5,214,136; 5,245,022; 5,317,098; 5,371,241; 5,391,723; 4,948,882; 5,218,105; 5,112,963; 5,567,810; 5,574,142; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 5,585,481; 5,292,873; 5,552,538; 5,512,667; 5,597,696; 5,599,923; 7,037,646; 5,587,371; 5,416,203; 5,262,536; 5,272,250; or 8,106,022.

In certain embodiments, an additional chemical moiety, e.g., a Mod, is connected via a linker. Various linkers are available in the art and may be utilized in accordance with the present disclosure, for example, those utilized for conjugation of various moieties with proteins (e.g., with antibodies to form antibody-drug conjugates), nucleic acids, etc. Certain useful linkers are described in US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/223056, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, and/or WO 2019/032612, the linker moieties of each which are independently incorporated herein by reference. In certain embodiments, a linker is, as non-limiting examples, L001, L004, L009 or L010. In certain embodiments, an oligonucleotide comprises a linker, but not an additional chemical moiety other than the linker. In certain embodiments, a ds oligonucleotide comprises a linker, but not an additional chemical moiety other than the linker, wherein the linker is L001, L004, L009, or L010.

As demonstrated herein, provided technologies can provide high levels of activities and/or desired properties, in certain embodiments, without utilizing particular structural elements (e.g., modifications, linkage configurations and/or patterns, etc.) reported to be desired and/or necessary (e.g., those reported in WO 2019/219581), though certain such

structural elements may be incorporated into ds oligonucleotides in combination with various other structural elements in accordance with the present disclosure. For example, in certain embodiments, ds oligonucleotides of the present disclosure have fewer nucleosides 3' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine), contain one or more phosphorothioate internucleotidic linkages at one or more positions where a phosphorothioate internucleotidic linkage was reportedly not favored or not allowed, contain one or more Sp phosphorothioate internucleotidic linkages at one or more positions where a Sp phosphorothioate internucleotidic linkage was reportedly not favored or not allowed, contain one or more Rp phosphorothioate internucleotidic linkages at one or more positions where a Rp phosphorothioate internucleotidic linkage was reportedly not favored or not allowed, and/or contain different modifications (e.g., internucleotidic linkage modifications, sugar modifications, etc.) and/or stereochemistry at one or more locations compared to those reportedly favorable or required for certain oligonucleotide properties and/or activities (e.g., presence of 2'-MOE, absence of phosphorothioate linkages at certain positions, absence of *S*p phosphorothioate linkages at certain positions, and/or absence of *R*p phosphorothioate linkages at certain positions were reportedly favorable or required for certain oligonucleotide properties and/or activities; as demonstrated herein, provided technologies can provide desired properties and/or high activities without utilizing 2'-MOE, without avoiding phosphorothioate linkages at one or more such certain positions, without avoiding *S*p phosphorothioate linkages at one or more such certain positions, and/or without avoiding *R*p phosphorothioate linkages at one or more such certain positions). Additionally or alternatively, provided ds oligonucleotides incorporates structural elements that were not previously recognized such as utilization of certain modifications (e.g., base modifications, sugar modifications (e.g., 2'-F), linkage modifications (e.g., non-negatively charged internucleotidic linkages), additional moieties, etc.) and levels, patterns, and combinations thereof.

For example, in certain embodiments, as described herein, provided d oligonucleotides contain no more than 5, 6, 7, 8, 9, 10, 11 or 12 nucleosides 3' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine).

Alternatively or additionally, as described herein (e.g., illustrated in certain Examples), for structural elements 3' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine), in certain embodiments, about 50%-100% (e.g., about or at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%) of internucleotidic linkages 3' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are each independently a modified internucleotidic linkage, which is optionally chirally controlled. In certain embodiments, no

more than 1, 2, or 3 internucleotidic linkages 3' to a nucleoside opposite to a target nucleoside are natural phosphate linkages. In certain embodiments, no such internucleotidic linkage is natural phosphate linkages. In certain embodiments, no more than 1 such internucleotidic linkage is natural phosphate linkages. In certain embodiments, no more than 2 such internucleotidic linkages are natural phosphate linkages. In certain embodiments, no more than 3 such internucleotidic linkages are natural phosphate linkages. In certain embodiments, each modified internucleotidic linkage is independently a phosphorothioate or a non-negatively charged internucleotidic linkage (e.g., n001). In certain embodiments, each phosphorothioate internucleotidic linkage is chirally controlled. In certain embodiments, no more than 1, 2, or 3 internucleotidic linkages 3' to a nucleoside opposite to a target nucleoside are *R*p phosphorothioate internucleotidic linkage.

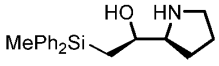
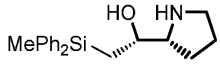
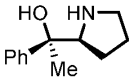
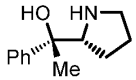
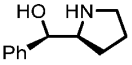
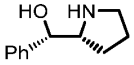
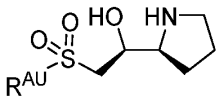
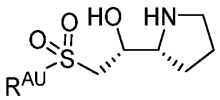
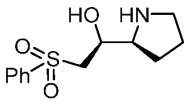
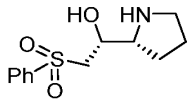
Alternatively or additionally, as described herein (e.g., illustrated in certain Examples), in certain embodiments, about 50%-100% (e.g., about or at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) of internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are each independently a modified internucleotidic linkage, which is optionally chirally controlled. In certain embodiments, no or no more than 1, 2, or 3 internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are not modified internucleotidic linkages. In certain embodiments, no or no more than 1, 2, or 3 internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are not phosphorothioate internucleotidic linkages. In certain embodiments, no or no more than 1, 2, or 3 internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are not *S*p phosphorothioate internucleotidic linkages. In certain embodiments, no more than 1, 2, or 3 internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are natural phosphate linkages. In certain embodiments, no such internucleotidic linkage is natural phosphate linkages. In certain embodiments, no more than 1 such internucleotidic linkage is natural phosphate linkages. In certain embodiments, no more than 2 such internucleotidic linkages are natural phosphate linkages. In certain embodiments, no more than 3 such internucleotidic linkages are natural phosphate linkages. In certain embodiments, each modified internucleotidic linkage is independently a phosphorothioate or a non-negatively charged internucleotidic linkage (e.g., n001). In certain embodiments, there are no 2, 3, or 4 consecutive internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside, each of which is not a phosphorothioate internucleotidic linkage. In certain embodiments, there are no 2, 3, or 4 consecutive internucleotidic linkages 5' to a nucleoside

opposite to a target nucleoside, each of which is chirally controlled and is not a *S*p phosphorothioate internucleotidic linkage. In certain embodiments, no or no more than 1, 2, 3, 4, or 5 internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are *R*p phosphorothioate internucleotidic linkage. In certain embodiments, at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, or 32, or about 50%-100% (e.g., about or at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) of internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are each independently chirally controlled and a *S*p internucleotidic linkage. In certain embodiments, at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, or 32, or about 50%-100% (e.g., about or at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) of phosphorothioate internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) are each independently chirally controlled and are *S*p. In certain embodiments, each phosphorothioate internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) is chirally controlled. In certain embodiments, each phosphorothioate internucleotidic linkages 5' to a nucleoside opposite to a target nucleoside (e.g., a target adenosine) is *S*p.

Production of Oligonucleotides and Compositions

Various methods can be utilized for production of oligonucleotides and compositions and can be utilized in accordance with the present disclosure. For example, traditional phosphoramidite chemistry can be utilized to prepare stereorandom oligonucleotides and compositions, and certain reagents and chirally controlled technologies can be utilized to prepare chirally controlled oligonucleotide compositions, e.g., as described in US 9394333, US 9744183, US 9605019, US 9598458, US 9982257, US 10160969, US 10479995, US 2020/0056173, US 2018/0216107, US 2019/0127733, US 10450568, US 2019/0077817, US 2019/0249173, US 2019/0375774, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, and/or WO 2020/191252, the reagents and methods of each of which is incorporated herein by reference.

In some embodiments, chirally controlled/stereoselective preparation of oligonucleotides and compositions thereof comprise utilization of a chiral auxiliary, e.g., as part of monomeric phosphoramidites. Examples of such chiral auxiliary reagents and

phosphoramidites are described in US 9394333, US 9744183, US 9605019, US 9598458, US 9982257, US 10160969, US 10479995, US 2020/0056173, US 2018/0216107, US 2019/0127733, US 10450568, US 2019/0077817, US 2019/0249173, US 2019/0375774, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, and/or WO 2020/191252, the chiral auxiliary reagents and phosphoramidites of each of which are independently incorporated herein by reference. In some embodiments, a chiral auxiliary is  or  (DPSE chiral auxiliaries). In some embodiments, a chiral auxiliary is  or  . In some embodiments, a chiral auxiliary is  or  . In some embodiments, a chiral auxiliary comprises $-SO_2R^{AU}$, wherein R^{AU} is an optionally substituted group selected from C_{1-20} aliphatic, C_{1-20} heteroaliphatic having 1-10 heteroatoms, C_{6-20} aryl, C_{6-20} arylaliphatic, C_{6-20} arylheteroaliphatic having 1-10 heteroatoms, 5-20 membered heteroaryl having 1-10 heteroatoms, and 3-20 membered heterocyclyl having 1-10 heteroatoms. In some embodiments, a chiral auxiliary is  or  . In some embodiments, R^{AU} is optionally substituted aryl. In some embodiments, R^{AU} is optionally substituted phenyl. In some embodiments, R^{AU} is optionally substituted C_{1-6} aliphatic. In some embodiments, a chiral auxiliary is  or  (PSM chiral auxiliaries). In some embodiments, utilization of such chiral auxiliaries, e.g., preparation, phosphoramidites comprising such chiral auxiliaries, intermediate oligonucleotides comprising such auxiliaries (which auxiliaries are typically bonded to linkage phosphorus through −O− of −OH, and −NH− are optionally capped, e.g., by −C(O)R), protection, removal, etc., is described in US 9394333, US 9744183, US 9605019, US 9598458, US 9982257, US 10160969, US 10479995, US 2020/0056173, US 2018/0216107, US 2019/0127733, US 10450568, US 2019/0077817, US 2019/0249173, US 2019/0375774, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, and/or WO 2020/191252 and incorporated herein by reference.

In some embodiments, chirally controlled preparation technologies, including oligonucleotide synthesis cycles, reagents and conditions are described in US 9394333, US 9744183, US 9605019, US 9598458, US 9982257, US 10160969, US 10479995, US 2020/0056173, US 2018/0216107, US 2019/0127733, US 10450568, US 2019/0077817, US 2019/0249173, US 2019/0375774, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, and/or WO 2020/191252, the oligonucleotide synthesis methods, cycles, reagents and conditions of each of which are independently incorporated herein by reference.

Once synthesized, ds oligonucleotides targeting INHBE and compositions are typically further purified. Suitable purification technologies are widely known and practiced by those skilled in the art, including but not limited to those described in US 9394333, US 9744183, US 9605019, US 9598458, US 9982257, US 10160969, US 10479995, US 2020/0056173, US 2018/0216107, US 2019/0127733, US 10450568, US 2019/0077817, US 2019/0249173, US 2019/0375774, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, and/or WO 2020/191252, the purification technologies of each of which are independently incorporated herein by reference.

In some embodiments, a cycle comprises or consists of coupling, capping, modification and deblocking. In some embodiments, a cycle comprises or consists of coupling, capping, modification, capping and deblocking. These steps are typically performed in the order they are listed, but in some embodiments, as appreciated by those skilled in the art, the order of certain steps, e.g., capping and modification, may be altered. If desired, one or more steps may be repeated to improve conversion, yield and/or purity as those skilled in the art often perform in syntheses. For example, in some embodiments, coupling may be repeated; in some embodiments, modification (e.g., oxidation to install =O, sulfurization to install =S, etc.) may be repeated; in some embodiments, coupling is repeated after modification which can convert a P(III) linkage to a P(V) linkage which can be more stable under certain circumstances, and coupling is routinely followed by modification to convert newly formed P(III) linkages to P(V) linkages. In some embodiments, when steps are repeated, different conditions may be employed (e.g., concentration, temperature, reagent, time, etc.).

In some embodiments, oligonucleotides are linked to a solid support. In some embodiments, a solid support is a support for oligonucleotide synthesis. In some embodiments, a solid support comprises glass. In some embodiments, a solid support is CPG (controlled pore

glass). In some embodiments, a solid support is polymer. In some embodiments, a solid support is polystyrene. In some embodiments, the solid support is Highly Crosslinked Polystyrene (HCP). In some embodiments, the solid support is hybrid support of Controlled Pore Glass (CPG) and Highly Cross-linked Polystyrene (HCP). In some embodiments, a solid support is a metal foam. In some embodiments, a solid support is a resin. In some embodiments, oligonucleotides are cleaved from a solid support.

Technologies for formulating provided oligonucleotides and/or preparing pharmaceutical compositions, e.g., for administration to subjects via various routes, are readily available in the art and can be utilized in accordance with the present disclosure, e.g., those described in US 9394333, US 9744183, US 9605019, US 9598458, US 9982257, US 10160969, US 10479995, US 2020/0056173, US 2018/0216107, US 2019/0127733, US 10450568, US 2019/0077817, US 2019/0249173, US 2019/0375774, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, and/or WO 2020/191252.

Metabolites and Shortened Versions of Oligonucleotides

In some embodiments, a ds oligonucleotide targeting INHBE corresponds to a metabolite produced by cleavage (e.g., enzymatic cleavage by a nuclease) of a longer oligonucleotide, e.g., a longer ds oligonucleotide targeting INHBE. In some embodiments, the present disclosure pertains to a ds oligonucleotide targeting INHBE which corresponds to a portion, or fragment of a ds oligonucleotide targeting INHBE disclosed herein.

In some embodiments, the present disclosure pertains to an oligonucleotide which corresponds to a metabolite of a ds oligonucleotide targeting INHBE disclosed herein. In some embodiments, the present disclosure pertains to an oligonucleotide which is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or more bases shorter than an oligonucleotide disclosed herein. In some embodiments, the present disclosure pertains to an oligonucleotide which has a base sequence which is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or more bases shorter than that of an oligonucleotide disclosed herein.

In some embodiments, a metabolite is designated as 3'-N-#, or 5'-N-#, wherein the # indicates the number of bases removed, and the 3' or 5' indicates which end of the molecule from which the bases were deleted. For example, 3'-N-1 indicates a fragment or metabolite wherein 1 base was removed from the 3' end.

In some embodiments, the present disclosure perhaps to an oligonucleotide which

corresponds to a fragment or metabolite of an oligonucleotide disclosed herein, wherein the fragment or metabolite can be described as corresponding to 3'-N-1, 3'-N-2, 3'-N-3, 3'-N-4, 3'-N-5, 3'-N-6, 3'-N-7, 3'-N-8, 3'-N-9, 3'-N-10, 3'-N-11, 3'-N-12, 5'-N-1, 5'-N-2, 5'-N-3, 5'-N-4, 5'-N-5, 5'-N-6, 5'-N-7, 5'-N-8, 5'-N-9, 5'-N-10, 5'-N-11, or 5'-N-12 of an oligonucleotide described herein, wherein each T may be independently replaced with U and vice versa.

In some embodiments, the present disclosure pertains to an oligonucleotide which corresponds to a metabolite of an oligonucleotide, wherein the metabolite is truncated on the 5' and/or 3' end relative to the oligonucleotide disclosed herein, wherein each T may be independently replaced with U and vice versa. In some embodiments, the present disclosure pertains to an which corresponds to a metabolite of an oligonucleotide, wherein the metabolite is truncated on both the 5' and 3' end relative to the oligonucleotide disclosed herein, wherein each T may be independently replaced with U and vice versa. In some embodiments, the present disclosure pertains to an oligonucleotide which is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or more total bases shorter on the 5' and/or 3' end than an oligonucleotide disclosed herein. In some embodiments, the present disclosure pertains to an oligonucleotide which has a base sequence which is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or more bases total shorter on the 5' and/or 3' end than that of an oligonucleotide disclosed herein, wherein each T may be independently replaced with U and vice versa.

In some embodiments, the present disclosure pertains to an oligonucleotide which is a product of a cleavage of an oligonucleotide disclosed herein cleaved at a natural phosphate linkage. In some embodiments, the present disclosure pertains to an oligonucleotide which is a product of a cleavage of an oligonucleotide disclosed herein cleaved at a *R*p phosphorothioate internucleotidic linkage.

Various technologies can be utilized to identify, characterize and/or assess metabolites and/or shortened ds oligonucleotides targeting INHBE in accordance with the present disclosure, for example, those described in US 10479995, US 2020/0056173, US 2018/0216107, US 2019/0127733, US 10450568, US 2019/0249173, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2019/032607, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, and/or WO 2020/191252.

Characterization and Assessment

In some embodiments, properties and/or activities of ds oligonucleotides targeting INHBE and compositions thereof can be characterized and/or assessed using various

technologies available to those skilled in the art, e.g., biochemical assays (e.g., RNase H assays), cell based assays, animal models, clinical trials, etc.

In some embodiments, a method of identifying and/or characterizing an oligonucleotide composition, e.g., a ds oligonucleotide targeting INHBE composition, comprises steps of:

providing at least one composition comprising a plurality of oligonucleotides; and

assessing delivery relative to a reference composition.

In some embodiments, the present disclosure provides a method of identifying and/or characterizing an oligonucleotide composition, e.g., a ds oligonucleotide targeting INHBE composition, comprises steps of:

providing at least one composition comprising a plurality of oligonucleotides; and

assessing cellular uptake relative to a reference composition.

In some embodiments, the present disclosure provides a method of identifying and/or characterizing an oligonucleotide composition, e.g., a ds oligonucleotide targeting INHBE composition, comprises steps of:

providing at least one composition comprising a plurality of oligonucleotides; and

assessing reduction of transcripts of a target gene and/or a product encoded thereby relative to a reference composition.

In some embodiments, the present disclosure provides a method of identifying and/or characterizing an oligonucleotide composition, e.g., a ds oligonucleotide targeting INHBE composition, comprises steps of:

providing at least one composition comprising a plurality of oligonucleotides; and

assessing reduction of tau levels, its aggregation and/or spreading relative to a reference composition.

In some embodiments, properties and/or activities of oligonucleotides, e.g., ds oligonucleotides targeting INHBE, and compositions thereof are compared to reference oligonucleotides and compositions thereof, respectively.

In some embodiments, a reference oligonucleotide composition is a stereorandom oligonucleotide composition. In some embodiments, a reference oligonucleotide composition is a stereorandom composition of oligonucleotides of which all internucleotidic linkages are phosphorothioate. In some embodiments, a reference oligonucleotide composition is a DNA oligonucleotide composition with all phosphate linkages. In some embodiments, a reference oligonucleotide composition is otherwise identical to a provided chirally controlled oligonucleotide composition except that it is not chirally controlled. In some embodiments, a reference oligonucleotide composition is otherwise identical to a provided chirally controlled

oligonucleotide composition except that it has a different pattern of stereochemistry. In some embodiments, a reference oligonucleotide composition is similar to a provided oligonucleotide composition except that it has a different modification of one or more sugar, base, and/or internucleotidic linkage, or pattern of modifications. In some embodiments, an oligonucleotide composition is stereorandom and a reference oligonucleotide composition is also stereorandom, but they differ in regards to sugar and/or base modification(s) or patterns thereof.

In some embodiments, a reference composition is a composition of oligonucleotides having the same base sequence and the same chemical modifications. In some embodiments, a reference composition is a composition of oligonucleotides having the same base sequence and the same pattern of chemical modifications. In some embodiments, a reference composition is a non-chirally controlled (or stereorandom) composition of oligonucleotides having the same base sequence and chemical modifications. In some embodiments, a reference composition is a non-chirally controlled (or stereorandom) composition of oligonucleotides of the same constitution but is otherwise identical to a provided chirally controlled oligonucleotide composition.

In some embodiments, a reference oligonucleotide composition is of oligonucleotides having a different base sequence. In some embodiments, a reference oligonucleotide composition is of oligonucleotides that do not target INHBE (e.g., as negative control for certain assays).

In some embodiments, a reference composition is a composition of oligonucleotides having the same base sequence but different chemical modifications, including but not limited to chemical modifications described herein. In some embodiments, a reference composition is a composition of oligonucleotides having the same base sequence but different patterns of internucleotidic linkages and/or stereochemistry of internucleotidic linkages and/or chemical modifications.

Various methods are known in the art for detection of gene products, the expression, level and/or activity of which may be altered after introduction or administration of a provided oligonucleotide. For example, transcripts and their knockdown can be detected and quantified with qPCR, and protein levels can be determined via Western blot.

In some embodiments, assessment of efficacy of oligonucleotides can be performed in biochemical assays or in vitro in cells. In some embodiments, ds oligonucleotides targeting INHBE can be introduced to cells via various methods available to those skilled in the art, e.g., gymnotic delivery, transfection, lipofection, etc.

In some embodiments, the efficacy of a putative ds oligonucleotide targeting INHBE

can be tested in vitro.

In some embodiments, the efficacy of a putative ds oligonucleotide targeting INHBE can be tested in vitro using any known method of testing the expression, level and/or activity of a INHBE gene or gene product thereof.

In some embodiments, an animal model administered a ds oligonucleotide targeting INHBE can be evaluated for safety and/or efficacy.

In some embodiments, the effect(s) of administration of an oligonucleotide to an animal can be evaluated, including any effects on behavior, inflammation, and toxicity. In some embodiments, following dosing, animals can be observed for signs of toxicity including trouble grooming, lack of food consumption, and any other signs of lethargy.

In some embodiments, following administration of a ds oligonucleotide targeting INHBE to an animal, the animal can be sacrificed and analysis of tissues or cells can be performed to determine changes in INHBE, or other biochemical or other changes. In some embodiments, following necropsy, liver, heart, lung, kidney, and spleen can be collected, fixed, and processed for histopathological evaluation (standard light microscopic examination of hematoxylin and eosin-stained tissue slides).

In some embodiments, following administration of a ds oligonucleotide targeting INHBE to an animal, behavioral changes can be monitored or assessed. In some embodiments, such an assessment can be performed using a technique described in the scientific literature.

Various effects of testing in animals described herein can also be monitored in human subjects or patients following administration of a ds oligonucleotide targeting INHBE.

In addition, the efficacy of a ds oligonucleotide targeting INHBE in a human subject can be measured by evaluating, after administration of the oligonucleotide, any of various parameters known in the art, including but not limited to a reduction in a symptom of ****.

In some embodiments, following human treatment with an oligonucleotide, or contacting a cell or tissue in vitro with an oligonucleotide, cells and/or tissues are collected for analysis.

In some embodiments, in various cells and/or tissues, target nucleic acid levels can be quantitated by methods available in the art, many of which can be accomplished with commercially available kits and materials. Such methods include, e.g., Northern blot analysis, competitive polymerase chain reaction (PCR), quantitative real-time PCR, etc. RNA analysis can be performed on total cellular RNA or poly(A)+ mRNA. Probes and primers are designed to hybridize to a nucleic acid to be detected. Methods for designing real-time PCR probes and primers are well known and widely practiced in the art. For example, to detect and quantify

INHBE RNA, an example method comprises isolation of total RNA (e.g., including mRNA) from a cell or animal treated with an oligonucleotide or a composition and subjecting the RNA to reverse transcription and/or quantitative real-time PCR, for example, as described herein, or in: Moon et al. 2012 Cell Metab. 15: 240-246.

In some embodiments, protein levels can be evaluated or quantitated in various methods known in the art, e.g., enzyme-linked immunosorbent assay (ELISA), Western blot analysis (immunoblotting), immunocytochemistry, fluorescence-activated cell sorting (FACS), immunohistochemistry, immunoprecipitation, protein activity assays (for example, caspase activity assays), and quantitative protein assays. Antibodies useful for the detection of mouse, rat, monkey, and human proteins are commercially available or can be generated if needed. For example, various INHBE antibodies have been reported,.

Various technologies are available and/or known in the art for detecting levels of oligonucleotides or other nucleic acids. Such technologies are useful for detecting ds oligonucleotides targeting INHBE when administered to assess, e.g., delivery, cell uptake, stability, distribution, etc.

In some embodiments, selection criteria are used to evaluate the data resulting from various assays and to select particularly desirable oligonucleotides, e.g., desirable ds oligonucleotides targeting INHBE, with certain properties and activities. In some embodiments, selection criteria include an IC_{50} of less than about 10 nM, less than about 5 nM or less than about 1 nM. In some embodiments, selection criteria for a stability assay include at least 50% stability [at least 50% of an oligonucleotide is still remaining and/or detectable] at Day 1. In some embodiments, selection criteria for a stability assay include at least 50% stability at Day 2. In some embodiments, selection criteria for a stability assay include at least 50% stability at Day 3. In some embodiments, selection criteria for a stability assay include at least 50% stability at Day 4. In some embodiments, selection criteria for a stability assay include at least 50% stability at Day 5. In some embodiments, selection criteria for a stability assay include at least 80% [at least 80% of the oligonucleotide remains] at Day 5.

In some embodiments, efficacy of a ds oligonucleotide targeting INHBE is assessed directly or indirectly by monitoring, measuring or detecting a change in a condition, disorder, or disease or a biological pathway associated with INHBE.

In some embodiments, efficacy of a ds oligonucleotide targeting INHBE is assessed directly or indirectly by monitoring, measuring or detecting a change in a response to be affected by INHBE knockdown.

In some embodiments, a provided oligonucleotide (e.g., a ds oligonucleotide targeting

INHBE) can by analyzed by a sequence analysis to determine what other genes [e.g., genes which are not a target gene (e.g., INHBE)] have a sequence which is complementary to the base sequence of the provided oligonucleotide (e.g., the ds oligonucleotide targeting INHBE) or which have 0, 1, 2 or more mismatches from the base sequence of the provided oligonucleotide (e.g., the ds oligonucleotide targeting INHBE). Knockdown, if any, by the oligonucleotide of these potential off-targets can be determined to evaluate potential off-target effects of an oligonucleotide (e.g., a ds oligonucleotide targeting INHBE). In some embodiments, an off-target effect is also termed an unintended effect and/or related to hybridization to a bystander (non-target) sequence or gene.

Oligonucleotides which have been evaluated and tested for efficacy in knocking down INHBE have various uses, e.g., in treatment or prevention of a INHBE-associated condition, disorder, or disease or a symptom thereof.

In some embodiments, a ds oligonucleotide targeting INHBE which has been evaluated and tested for its ability to provide a particular biological effect (e.g., reduction of level, expression and/or activity of a INHBE target gene or a gene product thereof) can be used to treat, ameliorate and/or prevent a INHBE-associated condition, disorder, or disease.

Treatment of INHBE-Associated Conditions, disorders, or diseases

In some embodiments, the present disclosure provides a ds oligonucleotide targeting INHBE, which targets INHBE and directs target-specific knockdown of INHBE. In some embodiments, the present disclosure provides methods for preventing and/or treating INHBE-associated conditions, disorders, or diseases using provided ds oligonucleotides targeting INHBE and compositions thereof. In some embodiments, the present disclosure provides oligonucleotides and compositions thereof for use as medicaments, e.g., for INHBE-associated conditions, disorders, or diseases. In some embodiments, the present disclosure provides oligonucleotides and compositions thereof for use in the treatment of INHBE-associated conditions, disorders, or diseases. In some embodiments, the present disclosure provides oligonucleotides and compositions thereof for the manufacture of medicaments for the treatment of INHBE-associated conditions, disorders, or diseases.

In some embodiments, the present disclosure provides a method for treating and/or ameliorating one or more symptoms associated with an INHBE-associated condition, disorder, or disease in a mammal in need thereof, the method comprising administering to the mammal a therapeutically effective amount of a ds oligonucleotide targeting INHBE or a composition thereof. In some embodiments, the present disclosure provides a method for reducing

susceptibility to an INHBE-associated condition, disorder, or disease in a mammal in need thereof, the method comprising: administering to the mammal a therapeutically effective amount of a ds oligonucleotide targeting INHBE or a composition thereof. In some embodiments, the present disclosure provides a method for preventing or delaying the onset of an INHBE-associated condition, disorder, or disease in a mammal in need thereof, the method comprising: administering to the mammal a therapeutically effective amount of a ds oligonucleotide targeting INHBE or a composition thereof. In some embodiments, the present disclosure provides a method for treating and/or ameliorating one or more symptoms associated with an INHBE-associated condition, disorder, or disease in a mammal in need thereof, the method comprising: administering to the mammal a therapeutically effective amount of a nucleic acid-lipid particle comprising a ds oligonucleotide targeting INHBE. In some embodiments, the present disclosure provides a method for reducing susceptibility to an INHBE-associated condition, disorder, or disease in a mammal in need thereof, the method comprising: administering to the mammal a therapeutically effective amount of a nucleic acid-lipid particle comprising a ds oligonucleotide targeting INHBE. In some embodiments, the present disclosure provides a method for preventing or delaying the onset of an INHBE-associated condition, disorder, or disease in a mammal in need thereof, the method comprising: administering to the mammal a therapeutically effective amount of a nucleic acid-lipid particle comprising a ds oligonucleotide targeting INHBE. In some embodiments, a mammal is a human. In some embodiments, a mammal is susceptible to, afflicted with and/or suffering from an INHBE-associated condition, disorder, or disease. In some embodiments, an INHBE-associated condition, disorder, or disease includes, but is not limited to, metabolic disorders, e.g., metabolic syndrome, and related diseases, e.g., obesity, cardiovascular disease, diabetes, and hypertension.

In some embodiments, provided oligonucleotides and compositions are useful for preventing and/or treating metabolic syndromes such as heart diseases, type 2 and type 1 diabetes, kidney diseases, and obesity etc. In some embodiments, the present disclosure provides methods for preventing and/or treating metabolic disorders, e.g., metabolic syndrome, and related diseases, e.g., obesity, cardiovascular disease, diabetes, and hypertension, comprising administering to a subject susceptible to or suffering therefrom a therapeutically effective amount of a ds oligonucleotide targeting INHBE or a composition as described herein.

In some embodiments, the provided ds oligonucleotides targeting INHBE and compositions may be optionally utilized in combination with one or more other therapeutic agents. In certain embodiments, the provided ds oligonucleotides and compositions thereof are

used in combination with one or more of the following:.

Administration of Oligonucleotides and Compositions

Many delivery methods, regimen, etc. can be utilized in accordance with the present disclosure for administering provided ds oligonucleotides and compositions thereof (typically pharmaceutical compositions for therapeutic purposes), including various technologies known in the art.

In some embodiments, an oligonucleotide composition, e.g., a ds oligonucleotide targeting INHBE composition, is administered at a dose and/or frequency lower than that of an otherwise comparable reference oligonucleotide composition and has comparable or improved effects. In some embodiments, a chirally controlled oligonucleotide composition is administered at a dose and/or frequency lower than that of a comparable, otherwise identical stereorandom reference oligonucleotide composition and with comparable or improved effects, e.g., in improving the knockdown of the target transcript.

In some embodiments, the present disclosure recognizes that properties and activities, e.g., knockdown activity, stability, toxicity, etc. of oligonucleotides and compositions thereof can be modulated and optimized by chemical modifications and/or stereochemistry. In some embodiments, the present disclosure provides methods for optimizing oligonucleotide properties and/or activities through chemical modifications and/or stereochemistry. In some embodiments, the present disclosure provides oligonucleotides and compositions thereof with improved properties and/or activities. Without wishing to be bound by any theory, due to, e.g., their better activity, stability, delivery, distribution, toxicity, pharmacokinetic, pharmacodynamics and/or efficacy profiles, Applicant notes that provided oligonucleotides and compositions thereof in some embodiments can be administered at lower dosage and/or reduced frequency to achieve comparable or better efficacy, and in some embodiments can be administered at higher dosage and/or increased frequency to provide enhanced effects.

In some embodiments, the present disclosure provides, in a method of administering an oligonucleotide composition comprising a plurality of oligonucleotides sharing a common base sequence, the improvement comprising administering an oligonucleotide comprising a plurality of oligonucleotides that is characterized by improved delivery relative to a reference oligonucleotide composition of the same common base sequence.

In some embodiments, provided oligonucleotides, compositions and methods provide improved delivery. In some embodiments, provided oligonucleotides, compositions and methods provide improved cytoplasmatic delivery. In some embodiments, improved delivery

is to a population of cells. In some embodiments, improved delivery is to a tissue. In some embodiments, improved delivery is to an organ. In some embodiments, improved delivery is to an organism, e.g., a patient or subject. Example structural elements (e.g., chemical modifications, stereochemistry, combinations thereof, etc.), oligonucleotides, compositions and methods that provide improved delivery are extensively described in the present disclosure.

Various dosing regimens can be utilized to administer oligonucleotides and compositions of the present disclosure. In some embodiments, multiple unit doses are administered, separated by periods of time. In some embodiments, a given composition has a recommended dosing regimen, which may involve one or more doses. In some embodiments, a dosing regimen comprises a plurality of doses each of which are separated from one another by a time period of the same length; in some embodiments, a dosing regimen comprises a plurality of doses and at least two different time periods separating individual doses. In some embodiments, all doses within a dosing regimen are of the same unit dose amount. In some embodiments, different doses within a dosing regimen are of different amounts. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount different from the first dose amount. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second (or subsequent) dose amount that is the same as or different from the first dose (or another prior dose) amount. In some embodiments, a chirally controlled oligonucleotide composition is administered according to a dosing regimen that differs from that utilized for a non-chirally controlled (e.g., stereorandom) oligonucleotide composition of the same sequence, and/or of a different chirally controlled oligonucleotide composition of the same sequence. In some embodiments, a chirally controlled oligonucleotide composition is administered according to a dosing regimen that is reduced as compared with that of a chirally uncontrolled (e.g., stereorandom) oligonucleotide composition of the same sequence in that it achieves a lower level of total exposure over a given unit of time, involves one or more lower unit doses, and/or includes a smaller number of doses over a given unit of time. In some embodiments, a chirally uncontrolled oligonucleotide is administered according to a dosing regimen that extends for a longer period of time than does that of a chirally uncontrolled (e.g., stereorandom) oligonucleotide composition of the same sequence Without wishing to be limited by theory, Applicant notes that in some embodiments, the shorter dosing regimen, and/or longer time periods between doses, may be due to the improved stability, bioavailability, and/or efficacy of a chirally controlled oligonucleotide composition. In some embodiments, with their improved delivery (and other properties), provided compositions can

be administered in lower dosages and/or with lower frequency to achieve biological effects, for example, clinical efficacy.

Pharmaceutical Compositions

When used as therapeutics, a provided ds oligonucleotide, e.g., a ds oligonucleotide targeting INHBE, or oligonucleotide composition thereof is typically administered as a pharmaceutical composition. In some embodiments, the present disclosure provides pharmaceutical compositions comprising a provided compound, e.g., an oligonucleotide, or a pharmaceutically acceptable salt thereof, and a pharmaceutical carrier. In some embodiments, for therapeutic and clinical purposes, oligonucleotides of the present disclosure are provided as pharmaceutical compositions. As appreciated by those skilled in the art, oligonucleotides of the present disclosure can be provided in their acid, base or salt forms. In some embodiments, oligonucleotides can be in acid forms, e.g., for natural phosphate linkages, in the form of −OP(O)(OH)O−; for phosphorothioate internucleotidic linkages, in the form of −OP(O)(SH)O−; etc. In some embodiments, ds oligonucleotides targeting INHBE can be in salt forms, e.g., for natural phosphate linkages, in the form of −OP(O)(ONa)O− in sodium salts; for phosphorothioate internucleotidic linkages, in the form of −OP(O)(SNa)O− in sodium salts; etc. Unless otherwise noted, oligonucleotides of the present disclosure can exist in acid, base and/or salt forms.

In some embodiments, a pharmaceutical composition is a liquid composition. In some embodiments, a pharmaceutical composition is provided by dissolving a solid oligonucleotide composition, or diluting a concentrated oligonucleotide composition, using a suitable solvent, e.g., water or a pharmaceutically acceptable buffer. In some embodiments, liquid compositions comprise anionic forms of provided oligonucleotides and one or more cations. In some embodiments, liquid compositions have pH values in the weak acidic, about neutral, or basic range. In some embodiments, pH of a liquid composition is about a physiological pH, e.g., about 7.4.

In some embodiments, a provided oligonucleotide is formulated for administration to and/or contact with a body cell and/or tissue expressing its target. For example, in some embodiments, a provided ds oligonucleotide targeting INHBE is formulated for administration to a body cell and/or tissue expressing INHBE. In some embodiments, such a body cell and/or tissue are a neuron or a cell and/or tissue of the central nervous system. In some embodiments, broad distribution of oligonucleotides and compositions may be achieved with intraparenchymal administration, intrathecal administration, or intracerebroventricular

administration.

In some embodiments, the pharmaceutical composition is formulated for intravenous injection, oral administration, buccal administration, inhalation, nasal administration, topical administration, ophthalmic administration or otic administration. In some embodiments, the pharmaceutical composition is a tablet, a pill, a capsule, a liquid, an inhalant, a nasal spray solution, a suppository, a suspension, a gel, a colloid, a dispersion, a suspension, a solution, an emulsion, an ointment, a lotion, an eye drop or an ear drop.

In some embodiments, the present disclosure provides a pharmaceutical composition comprising chirally controlled oligonucleotide or composition thereof, in admixture with a pharmaceutically acceptable inactive ingredient (e.g., a pharmaceutically acceptable excipient, a pharmaceutically acceptable carrier, etc.). In some embodiments, the present disclosure provides a pharmaceutical composition delivering chirally controlled oligonucleotide or composition thereof, in admixture with a pharmaceutically acceptable inactive ingredient (e.g., a pharmaceutically acceptable excipient, a pharmaceutically acceptable carrier, etc.). One of skill in the art will recognize that the pharmaceutical compositions include pharmaceutically acceptable salts of provided oligonucleotide or compositions. In some embodiments, a pharmaceutical composition is a chirally controlled oligonucleotide composition. In some embodiments, a pharmaceutical composition is a stereopure oligonucleotide composition.

In some embodiments, the present disclosure provides salts of oligonucleotides and pharmaceutical compositions thereof. In some embodiments, a salt is a pharmaceutically acceptable salt. In some embodiments, a pharmaceutical composition comprises an oligonucleotide, optionally in its salt form, and a sodium salt. In some embodiments, a pharmaceutical composition comprises an oligonucleotide, optionally in its salt form, and sodium chloride. In some embodiments, each hydrogen ion of an oligonucleotide that may be donated to a base (e.g., under conditions of an aqueous solution, a pharmaceutical composition, etc.) is replaced by a non-H^+ cation. For example, in some embodiments, a pharmaceutically acceptable salt of an oligonucleotide is an all-metal ion salt, wherein each hydrogen ion (for example, of −OH, −SH, etc.) of each internucleotidic linkage (e.g., a natural phosphate linkage, a phosphorothioate internucleotidic linkage, etc.) is replaced by a metal ion. Various suitable metal salts for pharmaceutical compositions are widely known in the art and can be utilized in accordance with the present disclosure. In some embodiments, a pharmaceutically acceptable salt is a sodium salt. In some embodiments, a pharmaceutically acceptable salt is magnesium salt. In some embodiments, a pharmaceutically acceptable salt is a calcium salt. In some embodiments, a pharmaceutically acceptable salt is a potassium salt. In some embodiments, a

pharmaceutically acceptable salt is an ammonium salt (cation $N(R)_4^+$). In some embodiments, a pharmaceutically acceptable salt comprises one and no more than one types of cation. In some embodiments, a pharmaceutically acceptable salt comprises two or more types of cation. In some embodiments, a cation is Li^+, Na^+, K^+, Mg^{2+} or Ca^{2+}. In some embodiments, a pharmaceutically acceptable salt is an all-sodium salt. In some embodiments, a pharmaceutically acceptable salt is an all-sodium salt, wherein each internucleotidic linkage which is a natural phosphate linkage (acid form −O−P(O)(OH)−O−), if any, exists as its sodium salt form (−O−P(O)(ONa)−O−), and each internucleotidic linkage which is a phosphorothioate internucleotidic linkage (acid form −O−P(O)(SH)−O−), if any, exists as its sodium salt form (−O−P(O)(SNa)−O−).

Various technologies for delivering nucleic acids and/or oligonucleotides are known in the art can be utilized in accordance with the present disclosure. For example, a variety of supramolecular nanocarriers can be used to deliver nucleic acids. Example nanocarriers include, but are not limited to liposomes, cationic polymer complexes and various polymeric compounds. Complexation of nucleic acids with various polycations is another approach for intracellular delivery; this includes use of PEGylated polycations, polyethyleneamine (PEI) complexes, cationic block co-polymers, and dendrimers. Several cationic nanocarriers, including PEI and polyamidoamine dendrimers help to release contents from endosomes. Other approaches include use of polymeric nanoparticles, microspheres, liposomes, dendrimers, biodegradable polymers, conjugates, prodrugs, inorganic colloids such as sulfur or iron, antibodies, implants, biodegradable implants, biodegradable microspheres, osmotically controlled implants, lipid nanoparticles, emulsions, oily solutions, aqueous solutions, biodegradable polymers, poly(lactide-coglycolic acid), poly(lactic acid), liquid depot, polymer micelles, quantum dots and lipoplexes. In some embodiments, an oligonucleotide is conjugated to another molecule.

In therapeutic and/or diagnostic applications, compounds, e.g., oligonucleotides, of the disclosure can be formulated for a variety of modes of administration, including systemic and topical or localized administration. Techniques and formulations generally may be found in Remington, The Science and Practice of Pharmacy (20th ed. 2000).

Pharmaceutically acceptable salts for basic moieties are generally well known to those of ordinary skill in the art, and may include, e.g., acetate, benzenesulfonate, besylate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, carnsylate, carbonate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide,

isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, or teoclate. Other pharmaceutically acceptable salts may be found in, for example, Remington, The Science and Practice of Pharmacy (20th ed. 2000). Preferred pharmaceutically acceptable salts include, for example, acetate, benzoate, bromide, carbonate, citrate, gluconate, hydrobromide, hydrochloride, maleate, mesylate, napsylate, pamoate (embonate), phosphate, salicylate, succinate, sulfate, or tartrate.

In some embodiments, ds oligonucleotides targeting INHBE are formulated in pharmaceutical compositions described in WO 2005/060697, WO 2011/076807 or WO 2014/136086.

Depending on the specific conditions, disorders, or diseases being treated, provided agents, e.g., oligonucleotides, may be formulated into liquid or solid dosage forms and administered systemically or locally. Provided oligonucleotides may be delivered, for example, in a timed- or sustained- low release form as is known to those skilled in the art. Techniques for formulation and administration may be found in Remington, The Science and Practice of Pharmacy (20th ed. 2000). Suitable routes may include oral, buccal, by inhalation spray, sublingual, rectal, transdermal, vaginal, transmucosal, nasal or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intra-articullar, intra-sternal, intra-synovial, intra-hepatic, intralesional, intracranial, intraperitoneal, intranasal, or intraocular injections or another mode of delivery.

For injection, provided agents, e.g., oligonucleotides may be formulated and diluted in aqueous solutions, such as in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For such transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulations. Such penetrants are generally known in the art and can be utilized in accordance with the present disclosure.

Use of pharmaceutically acceptable carriers to formulate compounds, e.g., provided oligonucleotides, for the practice of the disclosure into dosages suitable for various mods of administration is well known in the art. With proper choice of carrier and suitable manufacturing practice, compositions of the present disclosure, e.g., those formulated as solutions, may be administered via various routes, e.g., parenterally, such as by intravenous injection.

In some embodiments, a composition comprising a ds oligonucleotide targeting INHBE further comprises any or all of: calcium chloride dihydrate, magnesium chloride hexahydrate, potassium chloride, sodium chloride, sodium phosphate dibasic anhydrous, sodium phosphate, monobasic dihydrate, and/or water for Injection. In some embodiments, a composition further comprises any or all of: calcium chloride dihydrate (0.21 mg) USP, magnesium chloride hexahydrate (0.16 mg) USP, potassium chloride (0.22 mg) USP, sodium chloride (8.77 mg) USP, sodium phosphate dibasic anhydrous (0.10 mg) USP, sodium phosphate monobasic dihydrate (0.05 m g) USP, and Water for Injection USP.

In some embodiments, a composition comprising an oligonucleotide further comprises any or all of: cholesterol, (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino) butanoate(DLin-MC3-DMA), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), alpha-(3'-{[1,2-di(myristyloxy)propanoxy] carbonylamino}propyl)-omega-methoxy, polyoxyethylene(PEG2000-C-DMG), potassium phosphate monobasic anhydrous NF, sodium chloride, sodium phosphate dibasic heptahydrate, and Water for Injection. In some embodiments, the pH of a composition comprising a ds oligonucleotide targeting INHBE is ~7.0. In some embodiments, a composition comprising an oligonucleotide further comprises any or all of: 6.2 mg cholesterol USP, 13.0 mg (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino) butanoate(DLin-MC3-DMA), 3.3 mg 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1.6 mg α-(3'-{[1,2-di(myristyloxy)propanoxy] carbonylamino}propyl)-ω-methoxy, polyoxyethylene(PEG2000-C-DMG), 0.2 mg potassium phosphate monobasic anhydrous NF, 8.8 mg sodium chloride USP, 2.3 mg sodium phosphate dibasic heptahydrate USP, and Water for Injection USP, in an approximately 1 mL total volume.

Provided compounds, e.g., oligonucleotides, can be formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. In some embodiments, such carriers enable provided oligonucleotides to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and the like, for, e.g., oral ingestion by a subject (e.g., patient) to be treated.

For nasal or inhalation delivery, provided compounds, e.g., oligonucleotides, may be formulated by methods known to those of skill in the art, and may include, e.g., examples of solubilizing, diluting, or dispersing substances such as saline, preservatives, such as benzyl alcohol, absorption promoters, and fluorocarbons.

In certain embodiments, parenteral administration is by injection, by, e.g., a syringe, a pump, etc. In certain embodiments, an injection is a bolus injection. In certain embodiments,

an injection is administered directly to a tissue or location, such as striatum, caudate, cortex, hippocampus and/or cerebellum.

In certain embodiments, methods of specifically localizing provided compounds, e.g., oligonucleotides, such as by bolus injection, may decrease median effective concentration (EC50) by a factor of 20, 25, 30, 35, 40, 45 or 50. In certain embodiments, a targeted tissue is brain tissue. In certain embodiments, a targeted tissue is striatal tissue. In certain embodiments, decreasing EC50 is desirable because it reduces the dose required to achieve a pharmacological result in a patient in need thereof.

In certain embodiments, a provided oligonucleotide is delivered by injection or infusion once every week, every two weeks, every month, every two months, every 90 days, every 3 months, every 6 months, twice a year or once a year.

Pharmaceutical compositions suitable for use in the present disclosure include compositions wherein the active ingredients, e.g., oligonucleotides, are contained in effective amounts to achieve their intended purposes. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

In addition to active ingredients, pharmaceutical compositions may contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of an active compound into preparations which can be used pharmaceutically. Preparations formulated for oral administration may be in the form of tablets, dragees, capsules, or solutions.

In some embodiments, pharmaceutical compositions for oral use can be obtained by combining an active compound with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethyl-cellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone). If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

In some embodiments, dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol (PEG), and/or titanium dioxide,

lacquer solutions, and suitable organic solvents or solvent mixtures. Dye-stuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol. Push-fit capsules can contain active ingredients, e.g., oligonucleotides, in admixture with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, active compounds, e.g., oligonucleotides, may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols (PEGs). In addition, stabilizers may be added.

In some embodiments, a provided composition comprises a lipid. In some embodiments, a lipid is conjugated to an active compound, e.g., an oligonucleotide. In some embodiments, a lipid is not conjugated to an active compound. In some embodiments, a lipid comprises a C_{10}-C_{40} linear, saturated or partially unsaturated, aliphatic chain. In some embodiments, a lipid comprises a C_{10}-C_{40} linear, saturated or partially unsaturated, aliphatic chain, optionally substituted with one or more C_{1-4} aliphatic group. In some embodiments, the lipid is selected from the group consisting of lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, alpha-linolenic acid, gamma-linolenic acid, docosahexaenoic acid (cis-DHA), turbinaric acid and dilinoleyl alcohol. In some embodiments, an active compound is a provided oligonucleotide. In some embodiments, a composition comprises a lipid and an active compound, and further comprises another component which is another lipid or a targeting compound or moiety. In some embodiments, a lipid is an amino lipid; an amphipathic lipid; an anionic lipid; an apolipoprotein; a cationic lipid; a low molecular weight cationic lipid; a cationic lipid such as CLinDMA and DLinDMA; an ionizable cationic lipid; a cloaking component; a helper lipid; a lipopeptide; a neutral lipid; a neutral zwitterionic lipid; a hydrophobic small molecule; a hydrophobic vitamin; a PEG-lipid; an uncharged lipid modified with one or more hydrophilic polymers; phospholipid; a phospholipid such as 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine; a stealth lipid; a sterol; a cholesterol; a targeting lipid; or another lipid described herein or reported in the art suitable for pharmaceutical uses. In some embodiments, a composition comprises a lipid and a portion of another lipid capable of mediating at least one function of another lipid. In some embodiments, a targeting compound or moiety is capable of targeting a compound (e.g., an oligonucleotide) to a particular cell or tissue or subset of cells or tissues. In some embodiments, a targeting moiety is designed to take advantage of cell- or tissue-specific expression of particular targets, receptors, proteins, or

another subcellular component. In some embodiments, a targeting moiety is a ligand (e.g., a small molecule, antibody, peptide, protein, carbohydrate, aptamer, etc.) that targets a composition to a cell or tissue, and/or binds to a target, receptor, protein, or another subcellular component.

Certain example lipids for delivery of an active compound, e.g., an oligonucleotide, allow (e.g., do not prevent or interfere with) the function of an active compound. In some embodiments, a lipid is lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, alpha-linolenic acid, gamma-linolenic acid, docosahexaenoic acid (cis-DHA), turbinaric acid or dilinoleyl alcohol.

As described in the present disclosure, lipid conjugation, such as conjugation with fatty acids, may improve one or more properties of oligonucleotides.

In some embodiments, a composition for delivery of an active compound, e.g., an oligonucleotide, is capable of targeting an active compound to particular cells or tissues as desired. In some embodiments, a composition for delivery of an active compound is capable of targeting an active compound to a muscle cell or tissue. In some embodiments, the present disclosure provides compositions and methods related to delivery of active compounds, wherein the compositions comprise an active compound and a lipid. In various embodiments to a muscle cell or tissue, a lipid is selected from lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, alpha-linolenic acid, gamma-linolenic acid, docosahexaenoic acid (cis-DHA), turbinaric acid and dilinoleyl alcohol.

In some embodiments, a ds oligonucleotide targeting INHBE is delivered via a composition comprising any one or more of, or a method of delivery involving the use of any one or more of: transferrin receptor-targeted nanoparticle; cationic liposome-based delivery strategy; cationic liposome; polymeric nanoparticle; viral carrier; retrovirus; adeno-associated virus; stable nucleic acid lipid particle; polymer; cell-penetrating peptide; lipid; dendrimer; neutral lipid; cholesterol; lipid-like molecule; fusogenic lipid; hydrophilic molecule; polyethylene glycol (PEG) or a derivative thereof; shielding lipid; PEGylated lipid; PEG-C-DMSO; PEG-C-DMSA; DSPC; ionizable lipid; a guanidinium-based cholesterol derivative; ion-coated nanoparticle; metal-ion coated nanoparticle; manganese ion-coated nanoparticle; angubindin-1; nanogel; incorporation of the INHBE targeting ds oligonucleotide into a branched nucleic acid structure; and/or incorporation of the INHBE targeting ds oligonucleotide into a branched nucleic acid structure comprising 2, 3, 4 or more oligonucleotides.

In some embodiments, a composition comprising an oligonucleotide is lyophilized. In

some embodiments, a composition comprising an oligonucleotide is lyophilized, and the lyophilized oligonucleotide is in a vial. In some embodiments, the vial is back filled with nitrogen. In some embodiments, the lyophilized oligonucleotide composition is reconstituted prior to administration. In some embodiments, the lyophilized oligonucleotide composition is reconstituted with a sodium chloride solution prior to administration. In some embodiments, the lyophilized oligonucleotide composition is reconstituted with a 0.9% sodium chloride solution prior to administration. In some embodiments, reconstitution occurs at the clinical site for administration. In some embodiments, in a lyophilized composition, an oligonucleotide composition is chirally controlled or comprises at least one chirally controlled internucleotidic linkage and/or the ds oligonucleotide targets INHBE.

Other features of certain embodiments will become apparent in the course of the following descriptions of exemplary embodiments, which are given for illustration and are not intended to be limiting thereof.

EXEMPLIFICATION

Certain examples of provided technologies (compounds (oligonucleotides, reagents, etc.), compositions, methods (methods of preparation, use, assessment, etc.), are described below.

EXAMPLE 1. Oligonucleotide Synthesis

Various technologies for preparing oligonucleotides and oligonucleotide compositions (both stereorandom and chirally controlled) are known and can be utilized in accordance with the present disclosure, including, for example, those in US 9394333, US 9744183, US 9605019, US 9598458, US 9982257, US 10160969, US 10479995, US 2020/0056173, US 2018/0216107, US 2019/0127733, US 10450568, US 2019/0077817, US 2019/0249173, US 2019/0375774, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, and/or WO 2021/071858, the methods and reagents of each of which are incorporated herein by reference. Stereorandom and chirally controlled guide strand sequences were prepared utilizing the synthetic procedures as exemplified in above mentioned disclosures. Respective passenger strands were designed to have covalently linked GalNAc moiety as delivery vehicle at either end of sequences. Oligonucleotides with 5'-GalNAc modifications were synthesized by coupling C6-amino modifier linker at the 5'-end of sequence. Oligonucleotides with 3'-GalNAc moiety as delivery

vehicle were synthesized by utilizing 3'-C6 amino modified support. The single strand was cleaved from CPG by using deprotection condition as exemplified in earlier disclosures. The resulting amino group containing crude oligonucleotide was purified by ion exchange chromatography on AKTA pure system using a sodium chloride gradient. Desired product was desalted and further used for conjugation with GalNAc acid. After conjugation reaction was found to be complete the material was further purified by ion exchange chromatography and desalted to achieve desired material. For introduction of PN linkages in guide and passenger strands, specific PN coupling cycles were introduced at desired positions in oligonucleotide sequence utilizing the conditions as exemplified in WO2019/200185.

In certain embodiments, oligonucleotides were prepared using suitable chiral auxiliaries, e.g., DPSE and PSM chiral auxiliaries. Various oligonucleotides, e.g., those in **Table 1**, and compositions thereof, were prepared in accordance with the present disclosure.

Various technologies can be utilized to assess properties and/or activities of provided oligonucleotides and compositions thereof. Some such technologies are described in this Example. Those skilled in the art appreciate that many other technologies can be readily utilized. As demonstrated herein, provided oligonucleotides and compositions, among other things, can be highly active, e.g., in reducing levels of their target nucleic acids.

Abbreviation

1X reagent: TEA-3HF : TEA : H_2O : DMSO = 5.0 : 1.8 : 15.5 : 77.7 (v/v/v/v)

ADIH: 2-azido-1,3-dimethylimidazolium hexafluorophosphate

CMIMT: *N*-cyanomethylimidazolium triflate

CPG: controlled pore glass

DCM: dichloromethane, CH_2Cl_2

DIPEA: diisopropylethylamine

DMSO: dimethylsulfoxide

DMTr: 4,4′-dimethoxytrityl

GalNAc: *N*-acetylgalactosamine

HF: hydrogen fluoride

HATU: 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate

IBN: isobutyronitrile

MeCN: acetonitrile

MeIm: *N*-methylimidazole

TCA: trichloroacetic acid

TEA: triethylamine

XH: xanthane hydride

General procedure for the synthesis of chiral-oligos (25 μmol scale):

The automated solid-phase synthesis of chiral-oligos was performed according to the cycles shown in Table 16 (regular amidite cycle, for PO linkages), Table 17 (regular amidite cycle, for stereo-random PS linkages), Table 18 (DPSE amidite cycle, for chiral PS linkages), and Table 19 (PSM amidite cycle, for chiral PN linkages).

Table 2. Regular Amidite Synthetic Cycle for PO linkages

step	operation	reagents and solvent	volume	waiting time
1	detritylation	3% TCA / DCM	10 mL	65 s
2	coupling	0.2M monomer / 20% IBN-MeCN 0.5M CMIMT / MeCN	0.5 mL 1.0 mL	8 min
3	oxidation	50mM I_2 / pyridine-H_2O (9:1, v/v)	2.0 mL	1 min
4	cap-2	20% Ac_2O, 30% 2,6-lutidine / MeCN 20% MeIm / MeCN	1.0 mL 1.0 mL	45 s

Table 3. Regular Amidite Synthetic Cycle for stereo-random PS linkages

step	operation	reagents and solvent	volume	waiting time
1	detritylation	3% TCA / DCM	10 mL	65 s
2	coupling	0.2M monomer / 20% IBN-MeCN 0.5M CMIMT / MeCN	0.5 mL 1.0 mL	8 min
3	sulfurization	0.2M XH / pyridine	2.0 mL	6 min
4	cap-2	20% Ac_2O, 30% 2,6-lutidine / MeCN 20% MeIm / MeCN	1.0 mL 1.0 mL	45 s

Table 4. DPSE Amidite Synthetic Cycle for chiral PS linkages

step	operation	reagents and solvent	volume	waiting time
1	detritylation	3% TCA / DCM	10 mL	65 s
2	coupling	0.2M monomer / 20% IBN-MeCN 0.5M CMIMT / MeCN	0.5 mL 1.0 mL	8 min
3	cap-1	20% Ac_2O, 30% 2,6-lutidine / MeCN	2.0 mL	2 min
4	sulfurization	0.2M XH / pyridine	2.0 mL	6 min
5	cap-2	20% Ac_2O, 30% 2,6-lutidine / MeCN 20% MeIm / MeCN	1.0 mL 1.0 mL	45 s

Table 5. PSM Amidite Synthetic Cycle for chiral PN linkages

step	operation	reagents and solvent	volume	waiting time
1	detritylation	3% TCA / DCM	10 mL	65 s
2	coupling	0.2M monomer / 20% IBN-MeCN 0.5M CMIMT / MeCN	0.5 mL 1.0 mL	8 min
3	cap-1	20% Ac_2O, 30% 2,6-lutidine / MeCN	2.0 mL	2 min
4	imidation	0.5M ADIH reagent / MeCN	2.0 mL	6 min
5	cap-2	20% Ac_2O, 30% 2,6-lutidine / MeCN 20% MeIm / MeCN	1.0 mL 1.0 mL	45 s

1. In some embodiments, preparations include one or more DPSE and/or PSM cycles

General procedure for the C&D conditions (25 μmol scale):

After completion of the synthesis, the CPG solid support was dried and transferred into 50 mL plastic tube. The CPG was treated with 1X reagent (2.5 mL; 100 μL/umol) for 3 h at 28°C, then added conc. NH_3 (5.0 mL; 200 μL/umol) for 24 h at 37°C. The reaction mixture was cooled to room temperature and the CPG was separated by membrane filtration, washed with 15 mL of H_2O. The crude material (filtrate) was analyzed by LTQ and RP-UPLC.

General procedure for the GalNAc conjugation conditions (1 μmol scale):

Into a plastic tube, tri-GalNAc (2.0 eq.), HATU (1.9 eq.), and DIPEA (10 eq.) were dissolved in anhydrous MeCN (0.5 mL). The mixture was stirred for 10 min at room temperature, then the mixture was added into the amino-oligo (1 μmol) in H_2O (1 mL) and stirred for 1 h at 37 °C. The reaction was monitored by LC-MS and RP-UPLC. After the reaction was completed, the resultant GalNAc-conjugated oligo was treated with conc. NH_3 (2 mL) for 1 h at 37 °C. The solution was concentrated under vacuum to remove MeCN and conc. NH_3. The residue was then dissolved in H_2O (10 mL) for reversed phase purification.

In addition, or alternativatly to, the methods described above, the synthesis and deprotection of steropure oligonucleotide sequences containing 5'-Phosphonate can be performed as follows.

Abbreviation:

ETT: 5-(Ethylthio)-1H-tetrazole

CMIMT: *N*-cyanomethylimidazolium triflate

ADIH: 2-azido-1,3-dimethylimidazolium hexafluorophosphate

CPG: controlled pore glass

DCM: dichloromethane, CH_2Cl_2

ACN: acetonitrile

IBN: isobutyronitrile

DMSO: Dimethyl sulfoxide

MeIm: *N*-methylimidazole

TCA: trichloroacetic acid

TEA: triethylamine

TEA-3HF: triethylamine trihydrofluoride

DS1 reagent: TEA-3HF : TEA : H_2O : DMSO = 5.0 : 7.0 : 14.7 : 73.3 (v/v/v/v)

TMSI: Trimethylsilyl iodide

XH: xanthane hydride

Ac_2O: acetic anhydride

Vped5m: 5-(E)-vinylphosphonate-5-deoxy-5methyl

General procedure for the synthesis of chiral-oligos (25 μmol scale):

The automated solid-phase synthesis of chiral-oligos was performed according to the cycles shown in Table 1 (regular amidite cycle, for PO linkages), Table 2 (DPSE amidite cycle using 2'-deoxy-5'-phosphonate nucleosides, for chiral PS linkages), Table 3 (PSM amidite cycle using 2'-O-methyl and 2'-O-methoxyethyl nucleosides, for chiral PS linkages), Table 4 (PSM amidite cycle, for chiral PN linkages). All the amidites were dissolved into the appropriate solvents (Acetonitrile or 20% isobutyronitrile in 80% acetonitrile), dried at least for 2 h under 4Å molecular sieves and then was used in the synthetic cycle. After the last coupling of 5'-phosponate amidite, the column was washed with 20% DEA in acetonitrile.

Table 6. Regular Amidite Synthetic Cycle for PO linkages

step	operation	reagents and solvent	volume	waiting time
1	detritylation	3% TCA / DCM	10 mL	65 s
2	coupling	0.2M monomer / 20% IBN-MeCN 0.5M ETT / MeCN	0.5 mL 1.0 mL	8 min
3	oxidation	50mM I_2 / pyridine-H_2O (9:1, v/v)	2.0 mL	1 min
4	cap-2	20% Ac_2O, 30% 2,6-lutidine / MeCN 20% MeIm / MeCN	1.0 mL 1.0 mL	45 s

Table 7. DPSE Amidite Synthetic Cycle for chiral PS linkages

step	operation	reagents and solvent	volume	waiting time
1	detritylation	3% TCA / DCM	10 mL	65 s
2	coupling	0.2M monomer / 20% IBN-MeCN 0.5M CMIMT / MeCN	0.5 mL 1.0 mL	8 min
3	cap-1	20% Ac_2O, 30% 2,6-lutidine / MeCN	2.0 mL	2 min

4	sulfurization	0.2M XH / pyridine	2.0 mL	6 min
5	cap-2	20% Ac_2O, 30% 2,6-lutidine / MeCN 20% MeIm / MeCN	1.0 mL 1.0 mL	45 s

Table 8. PSM Amidite Synthetic Cycle for chiral PS linkages

step	operation	reagents and solvent	volume	waiting time
1	detritylation	3% TCA / DCM	10 mL	65 s
2	coupling	0.2M monomer / 20% IBN-MeCN 0.5M CMIMT / MeCN	0.5 mL 1.0 mL	8 min
3	cap-1	20% Ac_2O, 30% 2,6-lutidine / MeCN	2.0 mL	2 min
4	sulfurization	0.2M XH / pyridine	2.0 mL	6 min
5	cap-2	20% Ac_2O, 30% 2,6-lutidine / MeCN 20% MeIm / MeCN	1.0 mL 1.0 mL	45 s

Table 9. PSM Amidite Synthetic Cycle for chiral PN linkages (n001)

step	operation	reagents and solvent	volume	waiting time
1	detritylation	3% TCA / DCM	10 mL	65 s
2	coupling	0.2M monomer / 20% IBN-MeCN 0.5M CMIMT / MeCN	0.5 mL 1.0 mL	8 min
3	Imidation	0.5M ADIH / MeCN	2.0 mL	6 min
4	cap-2	20% Ac_2O, 30% 2,6-lutidine / MeCN 20% MeIm / MeCN	1.0 mL 1.0 mL	45 s

General procedure for the 5′-phosphonate deprotection conditions (25 µmole):

To prepare TMSI solution for 5'-phosphonate deprotection, pyridine (0.5 mL) was added to DCM (23.9 mL) and the resulting solution was cooled in ice-bath for 15 minutes. After that TMSI reagent (0.6 mL) was added to the mixture to get a bright yellow solution (total volume 25.0 mL). TMSI quenching solution (50 mL) was prepared by adding 2-Dodecane thiol (12.0 mL) and TEA (18.0 mL) in acetonitrile (18.0 mL).

After completion of the synthesis, the CPG solid support was dried and transferred into 50 mL plastic tube. Minimum amount of DCM was added to 5'-Phosphonate containing oligonucleotide on CPG and the CPG was vortexed to get a homogenous slurry. To this homogenous slurry, the TMSI solution (10.0 mL) was added slowly and mixed well. After the addition of total TMSI solution the color of the reaction mixture turns yellow indicating excess of TMSI solution. The resulting reaction mixture was stirred for 30 minutes at room temperature. After 30 min. the support was promptly washed using excess of acetonitrile followed by addition of quenching solution (10.0 mL) and this process was repeated three times (Total quenching volume 30.0 mL). The total time of exposure was limited to 20 min. The CPG was rinsed thoroughly using acetonitrile and drying under vacuum. Afterwards, CPG was subjected to standard cleavage and deprotection condition.

General procedure for the C&D conditions (25 µmol scale):

After completion of the synthesis and 5'-phosphonate deprotection, the CPG solid support was dried and transferred into 50 mL plastic tube. The CPG was treated with DS1 reagent (2.5 mL; 100 uL/umol) for 3 h at 27 °C, then added conc. NH_3 (5.0 mL; 200 umol/umol) for 24 h at 37 °C. The reaction mixture was cooled to room temperature and the CPG was separated by membrane filtration, washed with 15 mL of H_2O. The crude material (filtrate) was analyzed by LTQ and RP-UPLC.

EXAMPLE 2. Provided Oligonucleotides and Compositions Are Active in vitro in Human Primary Hepatocytes

Various siRNAs for human INHBE were designed and constructed. A number of siRNAs were tested *in vitro* in human or NHP primary hepatocytes at one or a range of concentrations. Example protocol for *in vitro* determination of siRNA activity in human or NHP primary hepatocytes: For determination of siRNAs activity, siRNAs at specific

concentration were gymnotically delivered to primary hepatocytes plated at 96-well plates, with 10,000 cells/well. Following 48 hours treatment, total RNA was extracted using SV96 Total RNA Isolation kit (Promega). cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad). For human INHBE mRNA, the following qPCR assay were utilized: Thermofisher Taqman qPCR assay ID Hs00368884_g1. For non-human primate (NHP) INHBE mRNA, the following qPCR assay were utilized: Thermofisher Taqman qPCR assay ID Mf02820386_g1. Human hSFRS9 was used as normalizer (Forward 5' TGGAATATGCCCTGCGTAAA 3', Reverse 5' TGGTGCTTCTCTCAGGATAAAC 3', Probe 5'/5HEX/TGGATGACA/Zen/CCAAATTCCGCTCTCA/3IABkFQ/3'. mRNA knockdown levels were calculated as %mRNA remaining relative to mock treatment.

Table 10 shows % human INHBE mRNA remaining at 10 nM siRNA treatment in primary human hepatocyte relative to human SFRS9 control. N = 2. N.D.: Not determined.

	10nM		
siRNA	% remaining mRNA (hINHBE/hSFRS9)-1	% remaining mRNA (hINHBE/hSFRS9)-2	Mean
DSR-0103433	108.81	95.21	102.01
DSR-0103434	95.82	88.48	92.15
DSR-0103435	89.94	130.23	110.09
DSR-0103436	96.87	93.72	95.29
DSR-0103437	91.41	92.59	92.00
DSR-0103438	83.18	76.71	79.94
DSR-0103439	78.41	79.41	78.91
DSR-0103440	73.29	82.83	78.06
DSR-0103441	94.22	73.93	84.07
DSR-0103442	58.10	69.18	63.64
DSR-0103443	78.70	110.93	94.81
DSR-0103444	77.79	62.27	70.03
DSR-0103445	107.25	102.61	104.93
DSR-0103446	90.73	128.66	109.69
DSR-0103447	88.82	86.35	87.59
DSR-0103448	83.80	87.75	85.78
DSR-0103449	102.57	82.48	92.52

DSR-0103450	85.72	90.09	87.91
DSR-0103451	97.12	107.62	102.37
DSR-0103452	104.29	93.90	99.09
DSR-0103453	103.90	96.36	100.13
DSR-0103454	89.82	102.29	96.06
DSR-0103455	88.67	102.72	95.69
DSR-0103456	80.46	83.74	82.10
DSR-0103457	112.59	77.62	95.10
DSR-0103458	96.50	90.70	93.60
DSR-0103459	88.95	113.26	101.10
DSR-0103460	92.32	111.53	101.93
DSR-0103461	95.38	87.33	91.36
DSR-0103462	97.82	91.14	94.48
DSR-0103463	108.16	89.18	98.67
DSR-0103464	82.73	74.01	78.37
DSR-0103465	109.98	97.61	103.79
DSR-0103466	92.87	93.74	93.31
DSR-0103467	108.80	100.65	104.73
DSR-0103468	105.96	118.19	112.07
DSR-0103469	92.56	94.56	93.56
DSR-0103470	81.09	95.40	88.25
DSR-0103471	90.39	88.53	89.46
DSR-0103472	75.04	69.61	72.33
DSR-0103473	125.90	87.09	106.49
DSR-0103474	54.91	65.70	60.31
DSR-0103475	88.01	90.45	89.23
DSR-0103476	62.40	58.39	60.40
DSR-0103477	87.17	82.43	84.80
DSR-0103478	99.44	101.21	100.32
DSR-0103479	101.81	82.87	92.34
DSR-0103480	76.27	80.14	78.20
DSR-0103481	67.55	54.83	61.19
DSR-0103482	69.83	77.55	73.69
DSR-0103483	73.63	68.42	71.02
DSR-0103484	71.74	60.35	66.04
DSR-0103485	58.19	55.12	56.65
DSR-0103486	74.76	75.05	74.90
DSR-0103487	100.05	87.07	93.56
DSR-0103488	84.18	82.28	83.23
DSR-0103489	101.24	74.45	87.84
DSR-0103490	74.22	85.00	79.61
DSR-0103491	117.66	88.55	103.10
DSR-0103492	111.66	87.00	99.33
DSR-0103493	85.14	84.09	84.61
DSR-0103494	87.73	99.83	93.78

DSR-0103495	103.89	77.21	90.55
DSR-0103496	94.33	87.21	90.77
DSR-0103497	106.19	92.66	99.43
DSR-0103498	93.19	99.60	96.39
DSR-0103499	96.67	84.18	90.42
DSR-0103500	92.22	83.17	87.70
DSR-0103501	77.89	78.75	78.32
DSR-0103502	73.37	78.66	76.02
DSR-0103503	96.25	79.94	88.10
DSR-0103504	73.36	67.57	70.46
DSR-0103505	103.68	80.43	92.05
DSR-0103506	91.61	89.41	90.51
DSR-0103507	94.55	86.48	90.52
DSR-0103508	100.60	105.69	103.15
DSR-0103509	88.66	92.32	90.49
DSR-0103510	111.03	88.64	99.84
DSR-0103511	100.22	95.51	97.86
DSR-0103512	81.05	91.90	86.47
DSR-0103513	182.41	94.77	138.59
DSR-0103514	66.51	71.52	69.01
DSR-0103515	99.64	102.22	100.93
DSR-0103516	107.47	100.04	103.76
DSR-0103517	78.82	80.80	79.81
DSR-0103518	79.14	79.08	79.11
DSR-0103519	96.29	81.33	88.81
DSR-0103520	83.96	85.34	84.65
DSR-0103521	142.80	91.86	117.33
DSR-0103522	63.62	63.70	63.66
DSR-0103523	75.92	72.07	73.99
DSR-0103524	104.51	0.87	52.69
DSR-0103525	82.17	78.96	80.57
DSR-0103526	101.57	101.15	101.36
DSR-0103527	74.74	79.18	76.96
DSR-0103528	84.98	101.61	93.30
DSR-0103529	92.38	106.45	99.42
DSR-0103530	105.76	100.80	103.28
DSR-0103531	83.64	118.01	100.83
DSR-0103532	83.13	128.13	105.63
DSR-0103533	78.49	323.50	201.00
DSR-0103534	83.96	105.02	94.49
DSR-0103535	98.38	111.43	104.90
DSR-0103536	82.68	108.08	95.38
DSR-0103537	107.81	135.57	121.69
DSR-0103538	93.16	79.36	86.26
DSR-0103539	81.69	109.36	95.53

DSR-0103540	79.47	91.02	85.25
DSR-0103541	89.63	114.36	101.99
DSR-0103542	89.12	108.17	98.65
DSR-0103543	104.20	110.76	107.48
DSR-0103544	84.76	95.20	89.98
DSR-0103545	96.15	116.95	106.55
DSR-0103546	49.88	54.69	52.29
DSR-0103547	77.68	77.26	77.47
DSR-0103548	76.56	104.77	90.66
DSR-0103549	84.08	106.64	95.36
DSR-0103550	84.69	92.71	88.70
DSR-0103551	87.76	100.74	94.25
DSR-0103552	88.50	91.85	90.17
DSR-0103553	89.87	103.71	96.79
DSR-0103554	98.81	100.18	99.49
DSR-0103555	88.21	96.10	92.15
DSR-0103556	80.71	98.13	89.42
DSR-0103557	74.98	106.14	90.56
DSR-0103558	76.53	95.26	85.90
DSR-0103559	86.11	94.43	90.27
DSR-0103560	69.67	72.25	70.96
DSR-0103561	94.72	105.15	99.93
DSR-0103562	78.08	71.26	74.67
DSR-0103563	42.78	44.65	43.71
DSR-0103564	54.71	57.47	56.09
DSR-0103565	83.74	94.79	89.26
DSR-0103566	89.15	98.29	93.72
DSR-0103567	93.99	87.03	90.51
DSR-0103568	89.12	86.76	87.94
DSR-0103569	97.91	111.27	104.59
DSR-0103570	96.53	87.09	91.81
DSR-0103571	102.75	101.16	101.96
DSR-0103572	92.71	93.18	92.94
DSR-0103573	85.86	95.39	90.62
DSR-0103574	85.62	97.78	91.70
DSR-0103575	88.44	100.78	94.61
DSR-0103576	75.60	94.20	84.90
DSR-0103577	122.70	114.11	118.41
DSR-0103578	88.08	76.24	82.16
DSR-0103579	93.43	87.72	90.57
DSR-0103580	78.16	90.00	84.08
DSR-0103581	81.92	98.83	90.37
DSR-0103582	31.70	31.67	31.68
DSR-0103583	70.67	71.97	71.32
DSR-0103584	67.89	65.15	66.52

DSR-0103585	68.74	116.28	92.51
DSR-0103586	93.24	86.63	89.94
DSR-0103587	92.41	88.61	90.51
DSR-0103588	62.63	66.08	64.35
DSR-0103589	72.06	87.42	79.74
DSR-0103590	94.80	93.77	94.29
DSR-0103591	84.27	78.96	81.62
DSR-0103592	79.01	93.62	86.31
DSR-0103593	63.04	68.76	65.90
DSR-0103594	91.22	87.26	89.24
DSR-0103595	86.06	91.78	88.92
DSR-0103596	81.28	97.16	89.22
DSR-0103597	78.43	94.88	86.65
DSR-0103598	77.85	79.87	78.86
DSR-0103599	91.79	133.18	112.49
DSR-0103600	90.24	104.00	97.12
DSR-0103601	61.49	68.65	65.07
DSR-0103602	85.98	84.00	84.99
DSR-0103603	98.00	92.83	95.41
DSR-0103604	60.52	68.37	64.44
DSR-0103605	49.64	67.14	58.39
DSR-0103606	72.14	81.85	77.00
DSR-0103607	95.72	116.77	106.24
DSR-0103608	67.88	97.48	82.68
DSR-0103609	79.46	88.33	83.89
DSR-0103610	100.45	85.43	92.94
DSR-0103611	89.82	91.72	90.77
DSR-0103612	83.84	106.44	95.14
DSR-0103613	82.06	78.24	80.15
DSR-0103614	125.70	132.72	129.21
DSR-0103615	43.77	58.06	50.91
DSR-0103616	71.06	98.26	84.66
DSR-0103617	66.79	137.94	102.36
DSR-0103618	109.04	121.47	115.26
DSR-0103619	130.39	33.43	81.91
DSR-0103620	64.64	32.44	48.54
DSR-0103621	52.31	21.93	37.12
DSR-0103622	85.67	37.28	61.48
DSR-0103623	85.06	39.50	62.28
DSR-0103624	91.14	45.07	68.10
DSR-0103625	84.73	39.97	62.35
DSR-0103626	75.39	37.55	56.47
DSR-0103627	94.83	25.45	60.14
DSR-0103628	80.34	35.30	57.82
DSR-0103629	67.65	22.31	44.98

DSR-0103630	54.00	20.58	37.29
DSR-0103631	51.27	18.71	34.99
DSR-0103632	85.56	32.96	59.26
DSR-0103633	52.15	20.49	36.32
DSR-0103634	65.04	32.44	48.74
DSR-0103635	127.55	34.11	80.83
DSR-0103636	86.41	37.16	61.78
DSR-0103637	49.13	14.87	32.00
DSR-0103638	25.63	19.94	22.78
DSR-0103639	33.20	12.31	22.76
DSR-0103640	97.78	31.36	64.57
DSR-0103641	99.32	35.53	67.43
DSR-0103642	90.37	32.68	61.52
DSR-0103643	98.79	37.42	68.10
DSR-0103644	99.02	40.12	69.57
DSR-0103645	114.11	35.78	74.94
DSR-0103646	103.34	63.32	83.33
DSR-0103647	92.34	39.04	65.69
DSR-0103648	107.78	42.38	75.08
DSR-0103649	98.68	40.71	69.70
DSR-0103650	79.64	40.77	60.20
DSR-0103651	123.84	31.30	77.57
DSR-0103652	57.45	28.84	43.14
DSR-0103653	93.88	39.58	66.73
DSR-0103654	103.67	36.95	70.31
DSR-0103655	86.12	34.99	60.56
DSR-0103656	57.79	26.37	42.08
DSR-0103657	98.91	37.90	68.41
DSR-0103658	78.43	38.00	58.22
DSR-0103659	106.20	28.48	67.34
DSR-0103660	98.32	36.55	67.43
DSR-0103661	84.32	33.70	59.01
DSR-0103662	98.35	46.37	72.36
DSR-0103663	103.57	33.21	68.39
DSR-0103664	121.88	44.76	83.32
DSR-0103665	91.02	39.77	65.39
DSR-0103666	80.85	37.88	59.37
DSR-0103667	102.14	29.50	65.82
DSR-0103668	93.04	38.47	65.75
DSR-0103669	85.18	33.19	59.19
DSR-0103670	99.11	45.02	72.07
DSR-0103671	83.40	29.51	56.45
DSR-0103672	99.78	44.84	72.31
DSR-0103673	84.88	39.96	62.42
DSR-0103674	83.29	34.01	58.65

DSR-0103675	99.22	29.34	64.28
DSR-0103676	64.38	23.73	44.05
DSR-0103677	51.87	24.82	38.35
DSR-0103678	70.56	35.53	53.04
DSR-0103679	79.19	32.90	56.04
DSR-0103680	103.63	46.59	75.11
DSR-0103681	98.95	35.54	67.25
DSR-0103682	95.93	43.35	69.64
DSR-0103683	111.14	41.92	76.53
DSR-0103684	67.35	22.54	44.94
DSR-0103685	87.97	36.12	62.04
DSR-0103686	74.84	32.95	53.89
DSR-0103687	81.79	33.64	57.72
DSR-0103688	74.17	32.59	53.38
DSR-0103689	90.01	45.48	67.74
DSR-0103690	65.87	25.32	45.60
DSR-0103691	69.30	20.54	44.92
DSR-0103692	39.94	15.41	27.67
DSR-0103693	70.06	29.35	49.71
DSR-0103694	69.30	24.83	47.06
DSR-0103695	43.59	14.69	29.14
DSR-0103696	78.91	31.55	55.23
DSR-0103697	52.11	27.05	39.58
DSR-0103698	41.79	16.15	28.97
DSR-0103699	68.66	25.37	47.02
DSR-0103700	58.64	25.97	42.31
DSR-0103701	80.77	35.14	57.95
DSR-0103702	73.89	41.99	57.94
DSR-0103703	48.04	17.70	32.87
DSR-0103704	82.37	29.66	56.01
DSR-0103705	62.43	27.04	44.74
DSR-0103706	51.27	30.14	40.70
DSR-0103707	119.74	36.93	78.34
DSR-0103708	113.84	31.53	72.68
DSR-0103709	71.60	41.56	56.58
DSR-0103710	89.21	49.08	69.15
DSR-0103711	39.94	15.34	27.64

Table 11 shows % human INHBE mRNA remaining at 100 nM siRNA treatment in primary human hepatocyte relative to human SFRS9 control. N = 2. N.D.: Not determined.

	100nM

siRNA	% remaining mRNA (hINHBE/hSFRS9)-1	% remaining mRNA (hINHBE/hSFRS9)-2	Mean
DSR-0103433	110.73	82.72	96.73
DSR-0103434	137.42	92.93	115.17
DSR-0103435	105.88	101.06	103.47
DSR-0103436	108.07	67.65	87.86
DSR-0103437	115.07	95.03	105.05
DSR-0103438	87.34	69.46	78.40
DSR-0103439	102.53	104.96	103.74
DSR-0103440	104.30	89.55	96.93
DSR-0103441	69.66	71.45	70.56
DSR-0103442	62.41	53.19	57.80
DSR-0103443	99.38	81.03	90.20
DSR-0103444	81.38	67.74	74.56
DSR-0103445	117.88	108.91	113.40
DSR-0103446	141.60	104.66	123.13
DSR-0103447	96.87	109.97	103.42
DSR-0103448	110.97	109.69	110.33
DSR-0103449	80.97	84.72	82.85
DSR-0103450	88.01	73.20	80.60
DSR-0103451	98.22	94.69	96.46
DSR-0103452	98.90	87.77	93.33
DSR-0103453	111.88	95.05	103.46
DSR-0103454	93.03	102.82	97.93
DSR-0103455	112.76	78.28	95.52
DSR-0103456	87.62	82.22	84.92
DSR-0103457	64.41	66.18	65.29
DSR-0103458	120.03	82.41	101.22
DSR-0103459	117.19	108.96	113.07
DSR-0103460	112.70	104.34	108.52
DSR-0103461	116.97	99.39	108.18
DSR-0103462	113.63	113.80	113.71
DSR-0103463	107.26	87.10	97.18
DSR-0103464	101.47	82.25	91.86
DSR-0103465	99.13	107.45	103.29
DSR-0103466	92.89	76.16	84.53
DSR-0103467	124.76	96.58	110.67
DSR-0103468	108.49	90.70	99.59
DSR-0103469	107.66	77.62	92.64
DSR-0103470	88.76	97.19	92.97
DSR-0103471	112.81	66.25	89.53
DSR-0103472	87.33	73.83	80.58

DSR-0103473	78.56	70.70	74.63
DSR-0103474	42.19	30.09	36.14
DSR-0103475	86.90	64.97	75.93
DSR-0103476	36.48	28.63	32.56
DSR-0103477	99.42	77.27	88.35
DSR-0103478	85.51	70.49	78.00
DSR-0103479	97.91	66.79	82.35
DSR-0103480	91.92	82.32	87.12
DSR-0103481	13.44	13.88	13.66
DSR-0103482	43.35	37.97	40.66
DSR-0103483	52.25	41.93	47.09
DSR-0103484	33.49	35.97	34.73
DSR-0103485	17.08	13.47	15.28
DSR-0103486	72.16	60.50	66.33
DSR-0103487	102.19	77.59	89.89
DSR-0103488	81.55	72.36	76.96
DSR-0103489	43.46	41.91	42.68
DSR-0103490	45.20	38.32	41.76
DSR-0103491	115.17	97.50	106.34
DSR-0103492	74.35	55.20	64.77
DSR-0103493	83.49	100.62	92.05
DSR-0103494	86.32	90.20	88.26
DSR-0103495	110.31	83.39	96.85
DSR-0103496	96.81	80.86	88.83
DSR-0103497	92.11	84.79	88.45
DSR-0103498	107.22	92.83	100.02
DSR-0103499	82.11	72.65	77.38
DSR-0103500	68.88	68.23	68.56
DSR-0103501	75.01	79.08	77.04
DSR-0103502	45.47	46.16	45.81
DSR-0103503	95.27	86.08	90.68
DSR-0103504	71.30	65.01	68.15
DSR-0103505	60.39	70.80	65.59
DSR-0103506	144.48	111.36	127.92
DSR-0103507	108.81	93.29	101.05
DSR-0103508	97.43	105.91	101.67
DSR-0103509	100.80	104.84	102.82
DSR-0103510	109.38	92.77	101.08
DSR-0103511	121.39	113.00	117.20
DSR-0103512	105.01	96.49	100.75
DSR-0103513	101.92	104.67	103.29
DSR-0103514	51.21	44.96	48.08
DSR-0103515	107.41	91.36	99.38
DSR-0103516	103.94	88.75	96.34
DSR-0103517	73.83	78.76	76.29

DSR-0103518	51.82	52.69	52.26
DSR-0103519	87.95	72.77	80.36
DSR-0103520	85.97	89.87	87.92
DSR-0103521	108.12	105.13	106.62
DSR-0103522	43.82	32.00	37.91
DSR-0103523	59.74	50.91	55.32
DSR-0103524	94.58	76.42	85.50
DSR-0103525	63.95	51.87	57.91
DSR-0103526	83.70	77.22	80.46
DSR-0103527	42.45	48.29	45.37
DSR-0103528	80.77	88.84	84.80
DSR-0103529	65.24	58.30	61.77
DSR-0103530	92.65	111.86	102.26
DSR-0103531	70.34	94.33	82.34
DSR-0103532	85.35	105.47	95.41
DSR-0103533	93.92	484.95	289.43
DSR-0103534	90.70	99.09	94.89
DSR-0103535	95.17	107.19	101.18
DSR-0103536	82.76	120.80	101.78
DSR-0103537	116.77	111.43	114.10
DSR-0103538	80.24	102.21	91.22
DSR-0103539	87.13	138.02	112.58
DSR-0103540	68.12	65.90	67.01
DSR-0103541	95.95	119.10	107.52
DSR-0103542	73.72	96.26	84.99
DSR-0103543	92.97	114.85	103.91
DSR-0103544	91.32	107.87	99.60
DSR-0103545	76.49	92.23	84.36
DSR-0103546	33.84	40.85	37.35
DSR-0103547	50.86	57.72	54.29
DSR-0103548	70.29	82.37	76.33
DSR-0103549	70.73	92.46	81.60
DSR-0103550	90.63	110.48	100.55
DSR-0103551	74.68	86.07	80.38
DSR-0103552	84.42	79.73	82.08
DSR-0103553	99.03	124.69	111.86
DSR-0103554	100.25	107.26	103.75
DSR-0103555	95.90	114.78	105.34
DSR-0103556	102.11	92.49	97.30
DSR-0103557	93.23	108.24	100.74
DSR-0103558	92.44	98.00	95.22
DSR-0103559	80.82	97.15	88.98
DSR-0103560	61.94	57.05	59.50
DSR-0103561	106.36	112.87	109.62
DSR-0103562	58.69	72.83	65.76

DSR-0103563	22.94	27.30	25.12
DSR-0103564	38.46	45.67	42.07
DSR-0103565	75.45	98.72	87.08
DSR-0103566	82.37	81.62	81.99
DSR-0103567	87.90	115.00	101.45
DSR-0103568	90.96	90.14	90.55
DSR-0103569	105.33	102.98	104.15
DSR-0103570	76.34	82.35	79.34
DSR-0103571	99.34	120.34	109.84
DSR-0103572	87.12	92.76	89.94
DSR-0103573	81.00	90.83	85.91
DSR-0103574	92.86	95.20	94.03
DSR-0103575	102.63	102.44	102.53
DSR-0103576	97.56	101.50	99.53
DSR-0103577	116.96	111.51	114.24
DSR-0103578	77.14	91.94	84.54
DSR-0103579	101.25	97.83	99.54
DSR-0103580	88.42	95.09	91.75
DSR-0103581	95.90	93.03	94.46
DSR-0103582	13.77	13.91	13.84
DSR-0103583	49.23	51.10	50.17
DSR-0103584	51.33	50.78	51.06
DSR-0103585	71.84	75.20	73.52
DSR-0103586	78.26	92.46	85.36
DSR-0103587	84.86	92.37	88.62
DSR-0103588	57.32	65.63	61.47
DSR-0103589	73.00	91.18	82.09
DSR-0103590	91.93	94.00	92.97
DSR-0103591	67.40	79.65	73.52
DSR-0103592	74.30	77.94	76.12
DSR-0103593	36.27	41.76	39.02
DSR-0103594	71.29	86.32	78.80
DSR-0103595	85.81	92.16	88.98
DSR-0103596	74.66	79.40	77.03
DSR-0103597	78.90	78.27	78.59
DSR-0103598	78.66	76.81	77.74
DSR-0103599	118.81	111.83	115.32
DSR-0103600	81.39	84.58	82.98
DSR-0103601	46.51	59.01	52.76
DSR-0103602	83.76	87.36	85.56
DSR-0103603	86.37	96.44	91.40
DSR-0103604	61.20	72.09	66.64
DSR-0103605	44.95	43.19	44.07
DSR-0103606	66.89	66.12	66.51
DSR-0103607	89.20	85.05	87.13

DSR-0103608	60.65	56.14	58.40
DSR-0103609	54.84	50.20	52.52
DSR-0103610	78.91	72.79	75.85
DSR-0103611	85.19	85.67	85.43
DSR-0103612	101.61	112.16	106.89
DSR-0103613	85.61	85.70	85.66
DSR-0103614	72.29	83.79	78.04
DSR-0103615	28.70	21.51	25.11
DSR-0103616	45.62	43.15	44.39
DSR-0103617	58.72	59.73	59.22
DSR-0103618	93.43	110.56	102.00
DSR-0103619	80.67	64.58	72.63
DSR-0103620	33.73	24.75	29.24
DSR-0103621	25.13	18.61	21.87
DSR-0103622	61.27	46.37	53.82
DSR-0103623	51.19	43.73	47.46
DSR-0103624	84.35	59.40	71.88
DSR-0103625	58.41	49.12	53.77
DSR-0103626	70.65	55.12	62.88
DSR-0103627	46.65	32.23	39.44
DSR-0103628	63.47	40.89	52.18
DSR-0103629	33.59	25.94	29.77
DSR-0103630	24.18	17.45	20.82
DSR-0103631	24.50	18.90	21.70
DSR-0103632	37.83	29.14	33.49
DSR-0103633	25.80	20.04	22.92
DSR-0103634	34.71	27.60	31.16
DSR-0103635	79.99	55.94	67.96
DSR-0103636	63.58	48.86	56.22
DSR-0103637	18.78	14.85	16.81
DSR-0103638	13.73	9.25	11.49
DSR-0103639	20.03	13.35	16.69
DSR-0103640	59.21	46.45	52.83
DSR-0103641	63.15	55.75	59.45
DSR-0103642	76.82	52.95	64.89
DSR-0103643	82.26	70.42	76.34
DSR-0103644	85.27	67.08	76.18
DSR-0103645	88.93	69.31	79.12
DSR-0103646	89.54	75.43	82.48
DSR-0103647	77.73	63.61	70.67
DSR-0103648	95.48	67.32	81.40
DSR-0103649	91.31	72.30	81.80
DSR-0103650	86.92	65.07	75.99
DSR-0103651	83.21	62.86	73.03
DSR-0103652	46.97	29.92	38.45

DSR-0103653	63.71	53.70	58.71
DSR-0103654	61.80	50.74	56.27
DSR-0103655	75.08	66.76	70.92
DSR-0103656	34.21	28.16	31.18
DSR-0103657	77.77	52.77	65.27
DSR-0103658	76.61	57.58	67.09
DSR-0103659	53.80	42.38	48.09
DSR-0103660	75.46	51.29	63.37
DSR-0103661	59.46	55.74	57.60
DSR-0103662	97.09	75.54	86.32
DSR-0103663	98.71	64.55	81.63
DSR-0103664	87.04	63.93	75.48
DSR-0103665	83.96	61.91	72.93
DSR-0103666	56.32	48.06	52.19
DSR-0103667	73.18	60.99	67.08
DSR-0103668	85.73	64.20	74.97
DSR-0103669	74.56	50.80	62.68
DSR-0103670	106.73	76.18	91.45
DSR-0103671	76.16	56.35	66.25
DSR-0103672	89.78	73.70	81.74
DSR-0103673	86.53	73.55	80.04
DSR-0103674	50.22	40.41	45.31
DSR-0103675	62.74	42.73	52.73
DSR-0103676	45.30	32.20	38.75
DSR-0103677	40.07	30.56	35.32
DSR-0103678	52.53	42.20	47.36
DSR-0103679	71.02	54.20	62.61
DSR-0103680	78.47	61.34	69.90
DSR-0103681	73.53	66.12	69.82
DSR-0103682	93.87	79.13	86.50
DSR-0103683	88.36	60.69	74.53
DSR-0103684	41.84	32.98	37.41
DSR-0103685	71.15	56.09	63.62
DSR-0103686	60.13	44.41	52.27
DSR-0103687	71.08	54.20	62.64
DSR-0103688	52.04	46.68	49.36
DSR-0103689	66.03	58.22	62.13
DSR-0103690	39.77	34.24	37.01
DSR-0103691	39.10	25.49	32.29
DSR-0103692	28.05	20.07	24.06
DSR-0103693	37.59	34.29	35.94
DSR-0103694	40.99	30.59	35.79
DSR-0103695	23.83	19.16	21.50
DSR-0103696	59.04	43.99	51.52
DSR-0103697	35.74	37.25	36.50

DSR-0103698	26.95	23.72	25.34
DSR-0103699	37.13	28.04	32.59
DSR-0103700	46.41	30.82	38.61
DSR-0103701	74.23	64.89	69.56
DSR-0103702	50.53	38.57	44.55
DSR-0103703	28.37	23.82	26.10
DSR-0103704	56.50	43.33	49.91
DSR-0103705	52.00	43.05	47.52
DSR-0103706	67.35	59.73	63.54
DSR-0103707	93.89	60.28	77.09
DSR-0103708	75.66	50.16	62.91
DSR-0103709	75.78	51.08	63.43
DSR-0103710	61.34	56.99	59.16
DSR-0103711	21.59	16.66	19.12

Table 12 shows % human INHBE mRNA remaining at 150, 50 and 15nM siRNA treatment in primary human hepatocyte relative to human SFRS9 control. N = 2. N.D.: Not determined.

	150nM			50nM		
siRNA	% remaining mRNA (hINHBE/hSFRS9)-1	% remaining mRNA (hINHBE/hSFRS9)-2	Mean	% remaining mRNA (hINHBE/hSFRS 9)-1	% remaining mRNA (hINHBE/hSFR S9)-2	Mean
DSR-0102657	90.27	79.70	84.98	110.75	92.33	101.54
DSR-0104067	14.88	13.41	14.15	23.16	18.05	20.60
DSR-0104068	9.81	9.73	9.77	12.77	12.63	12.70
DSR-0104069	17.97	20.51	19.24	20.62	21.57	21.09
DSR-0104070	23.33	24.16	23.75	24.70	25.13	24.91
DSR-0104071	15.46	14.17	14.81	25.79	19.39	22.59
DSR-0104072	10.03	10.65	10.34	13.52	13.71	13.62
DSR-0104073	28.94	32.98	30.96	31.12	31.83	31.48
DSR-0104074	10.14	14.86	12.50	16.42	18.68	17.55
DSR-0104075	12.26	18.07	15.16	14.09	15.94	15.01
DSR-0104076	30.45	33.58	32.01	26.71	30.13	28.42
DSR-0104077	17.52	17.41	17.47	22.37	18.49	20.43
DSR-0104078	20.87	27.33	24.10	27.35	25.76	26.55

DSR-0104079	24.86	22.83	23.85	27.59	20.76	24.17
DSR-0104080	38.93	42.85	40.89	45.14	43.24	44.19
DSR-0104081	16.05	20.36	18.21	16.35	18.71	17.53
DSR-0104082	22.14	23.22	22.68	22.46	24.08	23.27
DSR-0104083	10.78	14.44	12.61	16.32	15.40	15.86
DSR-0104084	21.89	33.28	27.58	27.94	31.38	29.66
DSR-0104085	18.57	21.65	20.11	23.14	21.91	22.53
DSR-0104086	12.86	12.44	12.65	17.28	12.02	14.65
DSR-0104087	15.27	19.56	17.42	23.71	19.28	21.49
DSR-0104088	36.95	68.68	52.82	40.42	41.91	41.16
DSR-0104089	46.23	67.04	56.63	62.25	58.91	60.58
DSR-0104090	29.87	38.00	33.93	39.04	31.24	35.14
DSR-0104091	16.32	19.85	18.08	22.42	17.71	20.06
DSR-0104092	16.72	25.82	21.27	28.88	22.80	25.84
DSR-0104093	22.63	20.68	21.66	24.71	31.06	27.88
DSR-0104094	23.85	21.81	22.83	24.55	22.70	23.62
DSR-0104095	44.01	44.01	44.01	53.39	40.65	47.02
DSR-0104096	27.47	32.15	29.81	33.34	28.24	30.79
DSR-0104097	18.94	22.28	20.61	21.78	18.75	20.27
DSR-0104098	35.50	34.01	34.75	45.29	41.61	43.45
DSR-0104099	8.05	10.59	9.32	13.24	10.31	11.78
DSR-0104100	34.00	46.93	40.46	49.73	42.49	46.11
DSR-0104101	33.88	33.85	33.87	40.43	48.05	44.24
DSR-0104102	21.35	18.69	20.02	24.55	19.85	22.20
DSR-0104103	29.62	26.40	28.01	34.28	30.40	32.34

siRNA	15nM		
	% remaining mRNA (hINHBE/hSFRS9)-1	% remaining mRNA (hINHBE/hSFRS9)-2	Mean
DSR-0102657	93.46	85.51	89.48

DSR-0104067	30.18	28.67	29.43
DSR-0104068	20.33	17.14	18.73
DSR-0104069	30.87	21.09	25.98
DSR-0104070	38.79	36.83	37.81
DSR-0104071	37.08	46.95	42.02
DSR-0104072	27.48	30.05	28.77
DSR-0104073	42.28	45.90	44.09
DSR-0104074	21.61	24.28	22.95
DSR-0104075	18.38	23.06	20.72
DSR-0104076	29.14	90.07	59.61
DSR-0104077	26.62	24.11	25.36
DSR-0104078	34.36	36.20	35.28
DSR-0104079	25.17	39.65	32.41
DSR-0104080	58.16	55.34	56.75
DSR-0104081	27.98	24.69	26.33
DSR-0104082	26.67	25.32	25.99
DSR-0104083	25.63	22.79	24.21
DSR-0104084	40.12	43.66	41.89
DSR-0104085	22.17	21.32	21.75
DSR-0104086	21.41	17.63	19.52
DSR-0104087	31.71	27.09	29.40
DSR-0104088	56.88	44.28	50.58
DSR-0104089	56.05	58.48	57.26
DSR-0104090	40.30	43.89	42.09
DSR-0104091	25.47	29.65	27.56
DSR-0104092	31.98	38.20	35.09
DSR-0104093	25.24	25.45	25.35
DSR-0104094	36.91	27.25	32.08
DSR-0104095	38.55	38.38	38.46

DSR-0104096	39.02	29.02	34.02
DSR-0104097	20.48	23.19	21.84
DSR-0104098	53.12	45.17	49.15
DSR-0104099	15.79	14.79	15.29
DSR-0104100	66.76	50.57	58.66
DSR-0104101	44.14	38.94	41.54
DSR-0104102	27.23	25.48	26.35
DSR-0104103	32.43	30.82	31.62

Table 13 IC50 of knocking down human INHBE mRNA in primary human hepatocyte.

siRNA	IC50(nM)	95% CI
DSR-0104069	0.47	0.23 to 0.94
DSR-0104072	1.75	0.90 to 3.41
DSR-0104074	1.01	0.46 to 2.20
DSR-0104075	0.41	0.15 to 1.07
DSR-0104077	0.93	0.51 to 1.74
DSR-0104081	0.56	0.25 to 1.25
DSR-0104071	2.73	0.86 to 7.50
DSR-0104083	0.48	0.24 to 0.97
DSR-0104086	1.64	0.80 to 3.39
DSR-0104091	3.74	2.18 to 6.39
DSR-0104097	2.01	0.96 to 4.17
DSR-0104099	2.50	0.49 to 8.71
DSR-0104102	2.42	1.56 to 3.74
DSR-0104068	0.93	0.57 to 1.51

Table 14 IC50 of knocking down human INHBE mRNA in primary human hepatocyte, based on the same experimental protocol but carried out as an independent experiment.

siRNA	IC50(nM)	95% CI
DSR-0104159	1.17	0.43 to 3.59
DSR-0104291	0.97	0.47 to 2.02
DSR-0104293	0.64	0.28 to 1.50

Table 15 IC50 of knocking down non-human primate (NHP) INHBE mRNA in primary NHP hepatocyte.

siRNA	IC50(nM)	95% CI
DSR-0104069	1.26	N.D. to 9.53
DSR-0104075	1.77	0.65 to 4.53
DSR-0104077	1.95	0.38 to 8.43
DSR-0104102	3.14	0.95 to 10.25
DSR-0104099	3.93	1.02 to 12.44
DSR-0104083	4.31	1.558 to 10.88
DSR-0104068	4.73	1.52 to 12.86
DSR-0104071	8.47	2.94 to 24.42
DSR-0104072	8.51	4.04 to 18.33
DSR-0104091	11.32	3.70 to 35.90

Table 16 IC50 of knocking down human INHBE mRNA in primary human hepatocyte.

siRNA	IC50(nM)	95% CI
DSR-0103633	2.11	1.05 to 4.28
DSR-0104083	0.42	0.26 to 0.67
DSR-0103563	0.92	0.32 to 2.86
DSR-0104074	0.59	0.26 to 1.37
DSR-0103615	4.84	2.93 to 7.94
DSR-0104077	1.44	0.88 to 2.33
DSR-0103476	3.99	1.60 to 9.48
DSR-0104070	1.31	0.80 to 2.15
DSR-0103693	4.40	1.54 to 11.63
DSR-0104092	3.76	2.30 to 6.17
DSR-0103605	5.40	2.96 to 9.79
DSR-0104076	2.44	1.11 to 5.26
DSR-0103629	5.17	2.91 to 9.08
DSR-0104080	12.36	3.16 to 49.95
DSR-0103677	4.13	1.95 to 8.67
DSR-0104089	5.44	1.03 to 29.44
DSR-0103474	4.95	1.17 to 15.97
DSR-0104069	1.04	0.59 to 1.82
DSR-0104067	1.76	0.93 to 3.24

DSR-0104068	0.99	0.44 to 2.13
DSR-0103582	1.49	0.71 to 3.15
DSR-0104075	1.13	0.54 to 2.45
DSR-0103631	1.97	1.09 to 3.63
DSR-0104082	1.12	0.19 to 8.64

EXAMPLE 3. Provided Oligonucleotides and Compositions Are Active in vitro in Mouse Primary Hepatocytes

Various siRNAs for mouse INHBE were designed and constructed. A number of siRNAs were tested *in vitro* in mouse primary hepatocytes at one or a range of concentrations. Example protocol for *in vitro* determination of siRNA activity in mouse primary hepatocytes: For determination of siRNAs activity, siRNAs at specific concentration were gymnotically delivered to primary hepatocytes plated at 96-well plates, with 10,000 cells/well. Following 48 hours treatment, total RNA was extracted using SV96 Total RNA Isolation kit (Promega). cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad). For mouse INHBE mRNA, the following qPCR assay were utilized: Thermofisher Taqman qPCR assay ID Mm03023993_m1. Mouse HPRT was used as normalizer (Forward 5'CAAACTTTGCTTTCCCTGGTT3', Reverse 5'TGGCCTGTATCCAACACTTC3', Probe 5'/5HEX/ACCAGCAAG/Zen/CTTGCAACCTTAACC/3IABkFQ/3'. mRNA knockdown levels were calculated as %mRNA remaining relative to mock treatment.

Table 17 shows % mouse INHBE mRNA remaining at 150 or 50 nM siRNA treatment in primary mouse hepatocyte relative to mouse HPRT control. N = 2. N.D.: Not determined

	150nM			50nM		
siRNA	% remaining mRNA (mINHBE/mHPRT)-1	% remaining mRNA (mINHBE/mHPRT)-2	Mean	% remaining mRNA (mINHBE/mHPRT)-1	% remaining mRNA (mINHBE/mHPRT)-2	Mean
DSR-0103591	76.53	66.56	71.55	93.99	64.75	79.37
DSR-0103582	52.54	34.11	43.32	35.22	35.32	35.27
DSR-0103552	49.13	72.16	60.65	66.45	57.91	62.18

DSR-0103696	68.99	72.38	70.69	78.50	49.13	63.82
DSR-0103590	99.50	97.95	98.72	108.34	90.39	99.36
DSR-0103581	100.13	82.73	91.43	90.31	112.06	101.18
DSR-0103540	100.03	105.83	102.93	110.04	97.25	103.64
DSR-0103611	121.55	136.29	128.92	118.81	133.02	125.91
DSR-0103589	115.89	101.77	108.83	113.10	83.92	98.51
DSR-0103579	115.56	133.44	124.50	109.93	121.60	115.76
DSR-0103497	98.29	84.48	91.39	132.53	118.54	125.54
DSR-0103610	118.46	153.24	135.85	116.89	148.07	132.48
DSR-0103588	100.77	113.10	106.93	101.11	132.64	116.88
DSR-0103578	93.59	108.54	101.07	97.68	119.92	108.80
DSR-0103477	113.15	91.42	102.28	99.91	112.87	106.39
DSR-0103609	139.66	136.36	138.01	154.50	149.45	151.97
DSR-0103587	123.18	117.82	120.50	124.83	137.93	131.38
DSR-0103560	94.13	92.58	93.36	117.23	111.81	114.52
DSR-0103475	102.48	90.25	96.37	135.63	127.10	131.36
DSR-0103608	100.76	110.86	105.81	84.64	130.44	107.54
DSR-0103586	94.27	111.91	103.09	99.79	119.07	109.43
DSR-0103559	92.77	106.17	99.47	91.79	112.54	102.17
DSR-0103474	48.30	52.30	50.30	68.40	80.17	74.29
DSR-0103607	104.34	110.80	107.57	115.73	118.41	117.07
DSR-0103585	87.39	115.33	101.36	90.95	117.42	104.19
DSR-0103558	114.55	125.03	119.79	112.18	120.35	116.27
DSR-0103466	96.70	95.74	96.22	121.03	125.31	123.17
DSR-0103606	58.62	75.32	66.97	65.63	74.83	70.23
DSR-0103584	57.24	62.28	59.76	55.50	63.07	59.28
DSR-0103557	75.84	82.60	79.22	70.48	86.73	78.60
DSR-0103465	57.89	83.44	70.66	71.46	87.29	79.37

Table 18 IC50 of knocking down mouse INHBE mRNA in primary mouse hepatocyte.

siRNA	IC50(nM)	95% CI
DSR-0104067	7.98	2.63 to 23.06
DSR-0104068	3.56	2.00 to 6.28

Table 19 IC50 of knocking down mouse INHBE mRNA in primary mouse hepatocyte.

siRNA	IC50(nM)	95% CI
DSR-0104068	3.63	2.10 to 6.23
DSR-0104108	2.02	0.46 to 8.22

EXAMPLE 4. Provided Oligonucleotides and Compositions Are Active *in vivo*

In vivo determination of mouse INHBE siRNA activity: All animal procedures were performed under IACUC guidelines. To evaluate the potency and liver exposure of provided oligonucleotides and compositions, male 8-10 weeks of age C57BL/6 mice were dose at 3 or 10 mg/kg at desired oligonucleotide concentration on Day 0 by subcutaneous administration. Animals were euthanized on Day 7 (at fed state) or Day 14 (after overnight fasting) by CO_2 asphyxiation followed by thoracotomy and terminal blood collection. After cardiac perfusion with PBS, liver samples were harvested and flash-frozen in dry ice. Liver total RNA was extracted using SV96 Total RNA Isolation kit (Promega), after tissue lysis with TRIzol and bromochloropropane. cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad).). For mouse INHBE mRNA, the following qPCR assay were utilized: Thermofisher Taqman qPCR assay ID Mm03023993_m1. Mouse HPRT was used as normalizer (Forward 5'CAAACTTTGCTTTCCCTGGTT3', Reverse 5'TGGCCTGTATCCAACACTTC3', Probe 5'/5HEX/ACCAGCAAG/Zen/CTTGCAACCTTAACC/3IABkFQ/3' K. Oligonucleotide accumulation in liver was determined by hybrid ELISA. Serum lipid profile was measured at Charles River Laboratories.

Ago2 immunoprecipitation assay: Tissues were lysed in lysis buffer 50 mM Tris-HCl at pH 7.5, 200mM NaCl, 0.5% Triton X-100, 2 mM EDTA, 1 mg/mL heparin) with protease inhibitor (Sigma-Aldrich). Lysate concentration was measured with a protein BCA kit (Pierce BCA protein assay kit or Bradford protein assay kit). Anti-Ago2 antibody was purchased from Wako Chemicals. Control mouse IgG was from eBioscience. Dynabeads

(Invitrogen) were used to precipitate antibodies. Ago2-associated siRNA and endogenous miR122 were measured by Stem-Loop RT followed by TaqMan PCR analysis using Taqman miRNA and siRNA assay kit (Thermo fisher) based on manufacturer's methods.

Table 20 shows % mouse INHBE mRNA remaining relative to PBS control in the Liver 7 days and 14 days post dosing. N = 5. N.D.: Not determined.

Week 1							
		DSR-0102657		DSR-0104067			
PBS		10mg/kg		3 mg/kg		10 mg/kg	
Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA
1	78.96	6	145.41	11	96.44	16	64.73
2	151.40	7	204.85	12	141.39	17	40.71
3	105.01	8	121.18	13	134.21	18	71.65
4	111.93	9	153.95	14	94.45	19	60.36
5	52.69	10	169.11	15	167.85	20	63.73
Mean	100.00	Mean	158.90	Mean	126.87	Mean	60.23
Week 1				week 2			
DSR-0104068						DSR-0102657	
3 mg/kg		10 mg/kg		PBS		10 mg/kg	
Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA
21	75.54	26	64.40	31	159.07	36	111.12
22	70.47	27	73.66	32	106.96	37	122.28
23	106.24	28	58.27	33	85.36	38	194.87
24	75.49	29	51.75	34	71.55	39	136.48
25	83.30	30	34.82	35	77.06	40	113.31
Mean	82.21	Mean	56.58	Mean	100.00	Mean	135.61
Week 2							
DSR-0104067				DSR-0104068			
3 mg/kg		10 mg/kg		3 mg/kg		10 mg/kg	

Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA
41	77.07	46	101.96	51	34.77	56	38.03
42	73.13	47	101.19	52	90.01	57	23.90
43	144.72	48	63.20	53	90.52	58	49.16
44	79.24	49	95.98	54	48.19	59	49.74
45	76.95	50	83.41	55	130.80	60	74.66
Mean	90.22	Mean	89.15	Mean	78.86	Mean	47.10

Table 21 Ago2 loading of guide strand relative to miR-122 in 10mg/kg treated mouse cohort 7 days and 14 days post dose. N=3

	Day 7				
	Ct: mINHBE/Ago2	Ct: miR-122/Ago2	Ct: mINHBE/IgG	Ct: miR-122/IgG	Relative mINHBE/miR-122
PBS-1	27.56	18.14	27.42	27.21	0.0016885
PBS-2	27.53	17.53	27.05	27.21	0.000874
PBS-3	27.12	19.66	27.4	26.94	0.0078125
DSR-0104067-1	18.73	18.74	26.46	28.36	0.2698071
DSR-0104067-2	18.42	18.16	26.64	28.45	0.2381595
DSR-0104067-3	19.00	17.59	26.79	27.92	0.1719427
DSR-0104068-1	17.36	18.12	26.23	29.45	0.1817466
DSR-0104068-2	16.60	18.31	25.91	29.84	0.2146414
DSR-0104068-3	16.39	18.19	26.23	30.17	0.2268798
			Day 14		
PBS-4	26.75	19.05	27.38	29.92	0.0008269
PBS-5	26.95	20.05	27.24	30.57	0.0008327
PBS-6	27.49	20.87	27.17	31.16	0.0006398
DSR-0104067-4	20.22	19.12	26.57	28.13	0.1582196
DSR-0104067-5	18.03	17.37	26.55	27.63	0.2993697
DSR-0104067-6	19.12	17.71	27.21	27.77	0.255253
DSR-0104068-4	17.7	18.11	25.94	28.04	0.3099269

DSR-0104068-5	16.95	17.85	25.8	28.04	0.3950207
DSR-0104068-6	17.02	18.1	25.8	27.44	0.6783022

Table 22 shows accumulation of antisense strand in liver tissue. N = 5. N.D.: Not determined.

Week 1							
		DSR-0102657		DSR-0104067			
PBS		10mg/kg		3 mg/kg		10 mg/kg	
Animal No.	Antisense strand (µg/g of tissue)	Animal No.	Antisense strand (µg/g of tissue)	Animal No.	Antisense strand (µg/g of tissue)	Animal No.	Antisense strand (µg/g of tissue)
1	0.00	6	2.55	11	1.44	16	3.80
2	0.00	7	2.86	12	1.10	17	4.17
3	0.00	8	2.69	13	1.31	18	4.09
4	0.00	9	2.67	14	1.52	19	3.37
5	0.00	10	2.82	15	1.30	20	3.64
Mean	0.00	Mean	2.72	Mean	1.33	Mean	3.81
Week 1				Week 2			
	DSR-0104068					DSR-0102657	
3 mg/kg		10 mg/kg		PBS		10 mg/kg	
Animal No.	Antisense strand (µg/g of tissue)	Animal No.	Antisense strand (µg/g of tissue)	Animal No.	Antisense strand (µg/g of tissue)	Animal No.	Antisense strand (µg/g of tissue)
21	4.70	26	8.05	31	0.00	36	2.46
22	5.70	27	8.65	32	0.00	37	2.89
23	5.45	28	9.73	33	0.00	38	2.64
24	6.13	29	9.25	34	0.00	39	3.22
25	5.92	30	9.25	35	0.00	40	2.93
Mean	5.58	Mean	8.99	Mean	0.00	Mean	2.83
Week 2							
DSR-0104067					DSR-0104068		
3 mg/kg		10 mg/kg		3 mg/kg		10 mg/kg	
Animal No.	Antisense strand (µg/g of tissue)	Animal No.	Antisense strand (µg/g of tissue)	Animal No.	Antisense strand (µg/g of tissue)	Animal No.	Antisense strand (µg/g of tissue)

41	0.52	46	2.08	51	4.85	56	8.42
42	0.57	47	1.81	52	5.83	57	9.31
43	0.76	48	1.53	53	5.58	58	8.69
44	0.96	49	2.00	54	6.23	59	8.12
45	0.71	50	2.10	55	5.92	60	7.98
Mean	0.70	Mean	1.91	Mean	5.68	Mean	8.50

EXAMPLE 5. Provided Oligonucleotides and Compositions Are Active *in vivo*

In vivo determination of mouse INHBE siRNA activity and efficacy: All animal procedures were performed under IACUC guidelines. To evaluate the efficacy of provided oligonucleotides and compositions, male DIO C57BL/6 mice were purchased from The Jackson Laboratory. When arriving, these mice were 13-weeks old and have been maintained on high fat diet for 7 weeks. Mice on chow diet at the same age were used as control. After arriving, mice were maintained on the same diet. After acclimation, mice on HFD were randomized based on body weight. Starting from Day 0, mice were dosed with PBS or desired oligonucleotide at 10 mg/kg every week by subcutaneous administration. Animals were euthanized on Day 35 or Day 56 after overnight fasting by CO_2 asphyxiation followed by thoracotomy and terminal blood collection. After cardiac perfusion with PBS, liver samples were harvested and flash-frozen in dry ice. Liver total RNA was extracted using SV96 Total RNA Isolation kit (Promega), after tissue lysis with TRIzol and bromochloropropane. cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad). For mouse INHBE mRNA, the following qPCR assay were utilized: Thermofisher Taqman qPCR assay ID Mm03023993_m1. Mouse HPRT was used as normalizer (Forward 5'CAAACTTTGCTTTCCCTGGTT3', Reverse 5'TGGCCTGTATCCAACACTTC3', Probe 5'/5HEX/ACCAGCAAG/Zen/CTTGCAACCTTAACC/3IABkFQ/3'. Serum lipid profile was measured at Charles River Laboratories. Fat mass changes were measured in mesenteric white adipose tissue (mesWAT), epididymal white adipose tissue (epiWAT), inguinal white adipose tissue (ingWAT), and interscapular brown adipose tissue (iBAT).

Table 23 shows mouse weekly pre-dosing body weight

		Body weight (g)					
Animal no	Test Article/ Diet	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35
1	PBS/ chow diet	28.3	30	29.3	29.9	30.9	30
2	PBS/ chow diet	28.4	29.3	28.9	29.8	30.4	30.8
3	PBS/ chow diet	30.4	31	30.9	31	32.2	31.9
4	PBS/ chow diet	29.2	29.2	29.9	29.8	31.2	31.4
5	PBS/ chow diet	29.3	30.8	30.4	30.6	31.5	31.6
6	PBS/ chow diet	29.3	29.4	28.9	29.4	31.1	32.1
7	PBS/ chow diet	28.6	29.7	29.3	29	31.1	31
8	PBS/ chow diet	29.1	29.7	29.4	30.2	31.5	31.9
9	PBS/ HFD	37.7	39.4	41.6	44.5	46.2	48.1
10	PBS/ HFD	35	35.3	36.7	39.3	41.1	43.8
11	PBS/ HFD	40.8	43.1	44.5	47	48.2	50.3
12	PBS/ HFD	35.6	37.8	39	41.4	42.5	44.2
13	PBS/ HFD	40.8	42.4	44.4	46.4	47	48.6
14	PBS/ HFD	43.2	44.1	44.5	48.7	50.6	52.5
15	PBS/ HFD	43.6	44.7	46.2	48.6	48.7	50.9
16	PBS/ HFD	33.3	33.8	35	36.2	37.8	39.6
17	DSR-0102657/HFD	41.2	41.3	41.4	42.4	44.3	46.5
18	DSR-0102657/HFD	42.1	43.7	44.9	46.5	47.7	49.4
19	DSR-0102657/HFD	43.4	44.7	45.4	48.4	48.7	50.7
20	DSR-0102657/HFD	35.9	33.9	34.9	35.5	35.1	34.8
21	DSR-0102657/HFD	31.8	31.4	31	31.7	33.1	35
22	DSR-0102657/HFD	34.5	36.6	36.5	38.2	39.8	40.9
23	DSR-0102657/HFD	40	39.3	39.4	42	44.7	45.7
24	DSR-0102657/HFD	39.1	39.4	40.1	41.8	41.8	41.8
25	DSR-0104068/HFD	42.2	42.3	41.4	41.1	42.1	43.4
26	DSR-0104068/HFD	37.9	37	36	35.8	35.9	36.7
27	DSR-0104068/HFD	35.9	37.3	37.3	37.8	38.9	40.3
28	DSR-0104068/HFD	33.7	35	35.4	35.5	36.7	37.8
29	DSR-0104068/HFD	36.6	37.5	38.1	38.2	38.5	39.9
30	DSR-0104068/HFD	41.4	41.2	41.1	40.7	40.5	40.9
31	DSR-0104068/HFD	38.8	38.9	38	37.4	36.1	37.2
32	DSR-0104068/HFD	40.5	41.4	39.2	38.2	39	40.7

Table 24 shows % mouse INHBE mRNA remaining relative to PBS control in the liver on day 35.

PBS/ chow diet		PBS/ HFD		DSR-0102657		DSR-0104068	
Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA

1	132.55	9	97.08	17	131.31	25	51.49
2	70.01	10	114.66	18	140.25	26	41.10
3	99.38	11	121.73	19	128.88	27	43.72
4	95.24	12	93.73	20	80.24	28	43.90
5	131.64	13	84.69	21	168.69	29	40.67
6	108.26	14	119.39	22	116.06	30	45.65
7	60.70	15	140.03	23	119.99	31	25.25
8	102.22	16	100.98	24	123.34	32	39.23
Mean	100.00	Mean	109.03	Mean	126.09	Mean	41.38

Table 25 shows liver weight in grams on day 35.

PBS/ chow diet		PBS/ HFD		DSR-0102657		DSR-0104068	
Animal no	Liver weigh (g)	Animal no	Liver weigh (g)	Animal no	Liver weigh (g)	Animal no	Liver weigh (g)
1	0.96	9	1.52	17	1.16	25	2.86
2	1.04	10	1.27	18	1.27	26	1.8
3	1.15	11	2.05	19	1.46	27	2.1
4	1.1	12	1.44	20	1.12	28	1.78
5	1.13	13	1.54	21	1.12	29	1.75
6	1.19	14	2.08	22	1.04	30	2.48
7	1.1	15	2.18	23	1.02	31	1.9
8	1.08	16	1.12	24	1.06	32	2.3
Mean	1.09	Mean	1.65	Mean	1.16	Mean	2.12

Table 26 shows epiWAT weight in grams on day 35.

PBS/ chow diet		PBS/ HFD		DSR-0102657		DSR-0104068	
Animal no	epiWAT weigh (g)	Animal no	epiWAT weigh (g)	Animal no	epiWAT weigh (g)	Animal no	epiWAT weigh (g)
1	0.73	9	2.08	17	2.28	25	1.09
2	0.81	10	2.25	18	2.14	26	1.03
3	0.63	11	2.32	19	2.09	27	1.61
4	0.49	12	2.31	20	0.72	28	1.68
5	0.87	13	1.72	21	1.01	29	1.58
6	0.74	14	2.19	22	2.12	30	1.21
7	0.73	15	1.82	23	2.26	31	1.26
8	1.01	16	2.23	24	2.27	32	1.47

Mean	0.75	Mean	2.12	Mean	1.86	Mean	1.37

Table 27 shows ingWAT weight in grams on day 35.

PBS/ chow diet		PBS/ HFD		DSR-0102657		DSR-0104068	
Animal no	ingWAT weigh (g)	Animal no	ingWAT weigh (g)	Animal no	ingWAT weigh (g)	Animal no	ingWAT weigh (g)
1	0.22	9	0.88	17	1.31	25	0.65
2	0.22	10	1.03	18	1.1	26	0.57
3	0.15	11	1.02	19	1.11	27	0.49
4	0.18	12	0.75	20	0.26	28	0.64
5	0.2	13	0.95	21	0.27	29	0.48
6	0.24	14	1.19	22	0.53	30	0.66
7	0.23	15	1.23	23	1.26	31	0.44
8	0.19	16	0.72	24	1.04	32	0.84
Mean	0.20	Mean	0.97	Mean	0.86	Mean	0.60

Table 28 shows mesWAT weight in grams on day 35.

PBS/ chow diet		PBS/ HFD		DSR-0102657		DSR-0104068	
Animal no	mesWAT weigh (g)	Animal no	mesWAT weigh (g)	Animal no	mesWAT weigh (g)	Animal no	mesWAT weigh (g)
1	0.19	9	1.01	17	1.62	25	0.59
2	0.22	10	0.86	18	1.65	26	0.48
3	0.17	11	1.34	19	2.04	27	0.42
4	0.12	12	0.87	20	0.25	28	0.53
5	0.22	13	1.46	21	0.27	29	0.43
6	0.25	14	1.3	22	0.71	30	0.42
7	0.22	15	1.47	23	1.18	31	0.41
8	0.33	16	0.49	24	0.74	32	0.55
Mean	0.22	Mean	1.10	Mean	1.06	Mean	0.48

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Table 29 shows iBAT weight in grams on day 35.

PBS/ chow diet	PBS/ HFD	DSR-0102657	DSR-0104068

Animal no	iBATweigh (g)	Animal no	iBAT weigh (g)	Animal no	iBATweigh (g)	Animal no	iBAT weigh (g)
1	0.14	9	0.15	17	0.25	25	0.19
2	0.15	10	0.14	18	0.28	26	0.18
3	0.12	11	0.22	19	0.29	27	0.16
4	0.09	12	0.16	20	0.1	28	0.18
5	0.14	13	0.22	21	0.13	29	0.17
6	0.15	14	0.21	22	0.13	30	0.2
7	0.13	15	0.2	23	0.23	31	0.16
8	0.1	16	0.12	24	0.16	32	0.19
Mean	0.13	Mean	0.18	Mean	0.20	Mean	0.18

Table 30 shows serum cholesterol level on day 35.

PBS/ chow diet		PBS/ HFD		DSR-0102657		DSR-0104068	
Animal no	serum total cholesterol (mg/dL)	Animal no	serum total cholesterol (mg/dL)	Animal no	serum total cholesterol (mg/dL)	Animal no	serum total cholesterol (mg/dL)
1	143	9	190	17	174	25	255
2	175	10	200	18	172	26	207
3	154	11	231	19	229	27	187
4	142	12	190	20	130	28	216
5	137	13	164	21	131	29	158
6	157	14	287	22	135	30	280
7	144	15	248	23	162	31	232
8	189	16	209	24	139	32	226
Mean	155.13	Mean	214.88	Mean	159.00	Mean	220.13

Table 31 shows serum HDL level on day 35.

PBS/ chow diet		PBS/ HFD		DSR-0102657		DSR-0104068	
Animal no	serum HDL (mg/dL)	Animal no	serum HDL (mg/dL)	Animal no	serum HDL (mg/dL)	Animal no	serum HDL (mg/dL)
1	64	9	65	17	57	25	70
2	72	10	65	18	57	26	66
3	69	11	65	19	63	27	69
4	66	12	67	20	60	28	68
5	53	13	49	21	57	29	61
6	66	14	77	22	56	30	81

7	67	15	67	23	58	31	75
8	72	16	70	24	54	32	66
Mean	66.13	Mean	65.63	Mean	57.75	Mean	69.50

Table 32 shows serum LDL level on day 35.

PBS/ chow diet		PBS/ HFD		DSR-0102657		DSR-0104068	
Animal no	serum LDL (mg/dL)	Animal no	serum LDL (mg/dL)	Animal no	serum LDL (mg/dL)	Animal no	serum LDL (mg/dL)
1	15	9	24	17	40	25	54
2	25	10	29	18	40	26	36
3	16	11	36	19	59	27	28
4	18	12	25	20	15	28	41
5	20	13	24	21	15	29	22
6	21	14	50	22	19	30	59
7	14	15	39	23	38	31	46
8	27	16	31	24	25	32	48
Mean	19.50	Mean	32.25	Mean	31.38	Mean	41.75

Table 33 shows serum TG level on day 35.

PBS/ chow diet		PBS/ HFD		DSR-0102657		DSR-0104068	
Animal no	serum TG (mg/dL)	Animal no	serum TG (mg/dL)	Animal no	serum TG (mg/dL)	Animal no	serum TG (mg/dL)
1	116	9	147	17	146	25	151
2	147	10	161	18	154	26	168
3	118	11	127	19	200	27	146
4	148	12	177	20	125	28	153
5	205	13	104	21	210	29	138
6	203	14	133	22	173	30	146
7	156	15	125	23	167	31	153
8	126	16	168	24	156	32	134
Mean	152.38	Mean	142.75	Mean	166.38	Mean	148.63

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Table 34 shows mouse weekly pre-dosing body weight.

		Body weight (g)					
Animal no	Test Article/ Diet	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35
33	PBS/ chow diet	27.6	29.1	30.1	30.4	31.1	31.5
34	PBS/ chow diet	28.9	29.5	30.4	30.2	30.1	31.1
35	PBS/ chow diet	28.0	29.4	29.9	31.5	32.4	32.0
36	PBS/ chow diet	27.6	29.3	30.4	30.6	31.2	31.7

37	PBS/ chow diet	30.4	31.8	32.2	32.5	33.1	34.8
38	PBS/ chow diet	28.3	29.9	30.3	30.3	30.3	31.3
39	PBS/ chow diet	29.6	30.3	30.9	31.5	34.4	33.8
40	PBS/ chow diet	30.0	31.7	32.1	32.3	32.8	33.9
41	PBS/ HFD	35.3	35.6	37.5	38.1	38.2	39.1
42	PBS/ HFD	41.7	43.2	44.4	45.0	45.5	45.5
43	PBS/ HFD	37.1	37.6	39.5	41.5	42.8	44.0
44	PBS/ HFD	32.4	34.3	36.0	36.6	37.1	39.3
45	PBS/ HFD	39.7	40.0	40.6	41.1	42.8	45
46	PBS/ HFD	40.5	40.9	41.4	43.7	45.3	46.8
47	PBS/ HFD	43.0	43.5	45.5	46.7	47.7	49.1
48	PBS/ HFD	42.5	42.5	43.1	45.0	46.5	47.0
49	DSR-0102657/HFD	34.2	34.9	35.8	37.0	37.8	37.7
50	DSR-0102657/HFD	40.7	37.7	38.7	41.1	42.4	43.9
51	DSR-0102657/HFD	34.7	33.9	34.8	35.7	37.5	37.3
52	DSR-0102657/HFD	38.7	38.4	39.7	40.9	41.0	42.3
53	DSR-0102657/HFD	37.4	38.1	39.4	40.1	40.8	44.2
54	DSR-0102657/HFD	38.4	37.4	37.9	39.5	41.1	42.7
55	DSR-0102657/HFD	39.6	40.3	42.1	44.0	44.8	46.0
56	DSR-0102657/HFD	43.4	45.0	45.5	47.7	49.1	50.5
57	DSR-0104068/HFD	39.1	39.6	38.7	37.4	37.7	38.9
58	DSR-0104068/HFD	37.0	36.6	35.6	35.4	35.8	36.9
59	DSR-0104068/HFD	34.8	36.1	35.9	35.7	36.6	37.4
60	DSR-0104068/HFD	32.7	33.0	34.2	35.1	36.3	37.3
61	DSR-0104068/HFD	37.4	37.3	36.1	36.4	37.3	37.8
62	DSR-0104068/HFD	42.9	42.4	42.6	42.8	43.1	44.6
63	DSR-0104068/HFD	41.3	41.2	40.2	39.8	40.5	41.5
64	DSR-0104068/HFD	37.2	37.6	36.5	35.7	35.5	35.9

		Body weight (g)		
Animal no	Test Article/ Diet	Day 42	Day 49	Day 56
33	PBS/ chow diet	32.1	32.2	32.1
34	PBS/ chow diet	31.3	31.8	32.7
35	PBS/ chow diet	33.9	34.4	35.3
36	PBS/ chow diet	32.0	32.7	32.2
37	PBS/ chow diet	35.2	36.7	36.0
38	PBS/ chow diet	32.9	33.1	31.7
39	PBS/ chow diet	32.8	33.8	33.5
40	PBS/ chow diet	33.3	34.3	33.9
41	PBS/ HFD	40.2	42.0	42.4
42	PBS/ HFD	45.4	47.4	47.5
43	PBS/ HFD	44.6	44.9	45.9
44	PBS/ HFD	40.4	42.1	41.7
45	PBS/ HFD	44.8	45.7	45.9

46	PBS/ HFD	46.7	47.9	48.1
47	PBS/ HFD	49.6	50.4	51.0
48	PBS/ HFD	48.3	49.4	49.4
49	DSR-0102657/HFD	37.8	39.7	40.1
50	DSR-0102657/HFD	44.9	46.6	47.2
51	DSR-0102657/HFD	37.6	39.4	39.9
52	DSR-0102657/HFD	43.8	44.6	44.7
53	DSR-0102657/HFD	46.0	48.5	48.3
54	DSR-0102657/HFD	43.5	45.1	45.7
55	DSR-0102657/HFD	47.3	47.5	47.1
56	DSR-0102657/HFD	51.5	51.9	52.5
57	DSR-0104068/HFD	39.5	39.6	39.0
58	DSR-0104068/HFD	37.6	38.6	38.6
59	DSR-0104068/HFD	38.5	38.7	38.1
60	DSR-0104068/HFD	38.6	38.5	38.9
61	DSR-0104068/HFD	38.8	39.5	39.9
62	DSR-0104068/HFD	45.6	46.1	45.6
63	DSR-0104068/HFD	42.3	42.4	41.4
64	DSR-0104068/HFD	35.8	35.5	34.9

Table 35 shows % mouse INHBE mRNA remaining relative to PBS control in the liver after 8 weekly siRNA treatment in DIO mice.

PBS/ chow diet		PBS/ HFD		DSR-0102657		DSR-0104068	
Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA
33	113.37	41	120.70	49	94.36	57	31.24
34	144.26	42	94.35	50	79.78	58	40.58
35	87.79	43	101.75	51	121.59	59	49.64
36	63.86	44	134.37	52	120.31	60	32.12
37	83.02	45	155.66	53	237.44	61	41.32
38	83.82	46	127.09	54	208.13	62	26.89
39	108.01	47	124.70	55	205.72	63	33.65
40	115.86	48	126.66	56	176.51	64	35.98
Mean	100.00	Mean	123.16	Mean	155.48	Mean	36.43

Table 36 shows liver weight in grams on day 56.

PBS/ chow diet	PBS/ HFD	DSR-0102657	DSR-0104068

Animal no	Liver weigh (g)	Animal no	Liver weigh (g)	Animal no	Liver weigh (g)	Animal no	Liver weigh (g)
33	1.1	41	1.12	49	1.01	57	2.44
34	1.13	42	1.87	50	1.18	58	2.49
35	1.34	43	1.55	51	0.9	59	2.35
36	1.16	44	1.09	52	1.08	60	2.08
37	1.15	45	1.04	53	1.04	61	2.29
38	1.12	46	1.95	54	1.01	62	3.73
39	N.D.	47	2.39	55	1.48	63	3.1
40	1.24	48	1.95	56	1.42	64	1.75
Mean	1.18	Mean	1.62	Mean	1.14	Mean	2.53

Table 37 shows epiWAT weight in grams on day 56.

PBS/ chow diet		PBS/ HFD		DSR-0102657		DSR-0104068	
Animal no	epiWAT weigh (g)	Animal no	epiWAT weigh (g)	Animal no	epiWAT weigh (g)	Animal no	epiWAT weigh (g)
1	1.26	9	2.42	17	2.41	25	1.36
2	1.1	10	1.95	18	2.32	26	1.24
3	1.39	11	2.24	19	2.14	27	1.52
4	1.1	12	2.69	20	2.3	28	1.36
5	1.64	13	2.43	21	2.11	29	1.26
6	1.13	14	2.21	22	2.67	30	1.61
7	1.21	15	2.1	23	2.04	31	1.32
8	1.13	16	1.93	24	2.1	32	1.08
Mean	1.25	Mean	2.25	Mean	2.26	Mean	1.34

Table 38 shows ingWAT weight in grams on day 56.

PBS/ chow diet		PBS/ HFD		DSR-0102657		DSR-0104068	
Animal no	ingWAT weigh (g)	Animal no	ingWAT weigh (g)	Animal no	ingWAT weigh (g)	Animal no	ingWAT weigh (g)
1	0.19	9	0.92	17	0.61	25	0.57
2	0.22	10	1.31	18	1.25	26	0.64
3	0.31	11	1.21	19	1.01	27	0.54
4	0.2	12	0.6	20	0.91	28	0.45
5	0.36	13	0.7	21	0.77	29	0.52
6	0.31	14	1.36	22	1.25	30	1.04
7	0.31	15	1.47	23	1.25	31	0.83
8	0.28	16	1.5	24	1.29	32	0.39
Mean	0.27	Mean	1.13	Mean	1.04	Mean	0.62

5

Table 39 shows mesWAT weight in grams on day 56.

PBS/ chow diet		PBS/ HFD		DSR-0102657		DSR-0104068	
Animal no	mesWAT weigh (g)	Animal no	mesWAT weigh (g)	Animal no	mesWAT weigh (g)	Animal no	mesWAT weigh (g)
1	0.31	9	0.66	17	0.6	25	0.47
2	0.25	10	1.26	18	1.47	26	0.36
3	0.42	11	1.45	19	0.69	27	0.43
4	0.27	12	0.57	20	1.01	28	0.41
5	0.44	13	0.74	21	1.12	29	0.42
6	0.3	14	1.27	22	0.91	30	0.89
7	0.37	15	1.47	23	1.66	31	0.63
8	0.34	16	1.69	24	1.52	32	0.36
Mean	0.34	Mean	1.14	Mean	1.12	Mean	0.50

Table 40 shows iBAT weight in grams on day 56.

PBS/ chow diet		PBS/ HFD		DSR-0102657		DSR-0104068	
Animal no	iBAT weigh (g)	Animal no	iBAT weigh (g)	Animal no	iBAT weigh (g)	Animal no	iBAT weigh (g)
1	0.11	9	0.11	17	0.08	25	0.10
2	0.07	10	0.17	18	0.16	26	0.15
3	0.13	11	0.17	19	0.16	27	0.13
4	0.14	12	0.12	20	0.19	28	0.14
5	0.13	13	0.14	21	0.23	29	0.10
6	0.13	14	0.13	22	0.19	30	0.22
7	0.10	15	0.18	23	0.19	31	0.13
8	0.08	16	0.19	24	0.26	32	0.10
Mean	0.11	Mean	0.15	Mean	0.18	Mean	0.13

EXAMPLE 6. Provided Oligonucleotides and Compositions Are Active *in vivo*

In vivo determination of mouse INHBE siRNA activity: All animal experiments were performed at Biomedical Research Models, Ins. Dba Biomere (Worcester, MA) under an approved protocol and in compliance with Biomere's Institutional Animal Care and Use Committee guidelines for care and use of animals. Mice were on a 12-hour light-dark cycle. Food (LabDiet 5R58) and water were available ad libitum. Housing rooms were maintained at 20-26°C and relative humidity was 30-70%. The animals in this experiment were C57BL/6j males, between 24-30 weeks of age. The mice were dosed at 10mg/kg with either DSR-0104108 or DSR-0104212 on Day 0 by subcutaneous administration. There were 8 mice per group per necropsy timepoint. Animals were euthanized after overnight fasting on Day 14, Day 28, or Day 56 by CO2 asphyxiation followed by thoracotomy and terminal blood collection. After cardiac perfusion with PBS, liver punches were harvested and flash-frozen on dry ice,

and the remaining liver was flash frozen in foil using liquid nitrogen. Liver total RNA was extracted using SV96 Total RNA Isolation kit (Promega), after tissue lysis with TRIzol and bromochloropropane. cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad). For mouse INHBE mRNA, the following qPCR assay was utilized: Thermofisher Taqman qPCR assay ID Mm03023993_m1. Mouse HPRT was used as normalizer (Forward 5'CAAACTTTGCTTTCCCTGGTT3', Reverse 5'TGGCCTGTATCCAACACTTC3', Probe 5'/5HEX/ACCAGCAAG/Zen/CTTGCAACCTTAACC/3IABkFQ/3' K. Oligonucleotide accumulation in liver was determined by hybrid ELISA.

Table 41a. Example Double Stranded Oligonucleotides Targeting INHBE.

ID	GUIDE SEQUENCE	PASSENGER SEQUENCE
DSR-0104108	**SSR-0108095**	**SSR-0108001**

Table 41b. Examples of Guide Sequences Targeting INHBE

GUIDE SEQUENCE	HELM	BASE SEQUENCE
SSR-0108095	**RNA1{p.[Rm5d5m](U)[Ssp].[fl2r](A)[Rsp].m(A)[n001S].[fl2r](G)p.m(A)p.[fl2r](C)p.m(G)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](G)p.m(A)p.m(A)p.[fl2r](U)p.m(G)p.[fl2r](G)p.m(A)p.m(A)p.m(G)p.m(G)p.m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0**	**UAAGACGGCAGAAUGGAAGGAUU**

Table 41c. Examples of Passenger Sequences Targeting INHBE

GUIDE SEQUENCE	HELM	BASE SEQUENCE
SSR-0108001	RNA1{p.m(U)[Ssp].m(C)p.m(C)p.m(U)p.m(U)p.m(C)p.[fl2r](C)p.m(A)p.[fl2r](U)p.[fl2r](U)p.[fl2r](C)p.m(U)p.m(G)p.m(C)p.m(C)p.m(G)p.m(U)p.m(C)p.m(U)p.m(U)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	UCCUUCCAUUCUGCCGUCUUA

Table 42 shows % mouse INHBE mRNA remaining relative to PBS control in the liver 14, 28, and 56 days post dosing. N = 8. N.D.: Not determined.

Week 2	
	DSR-0104108
PBS	10mg/kg

Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA
1	69.82	9	29.72
2	102.33	10	24.66
3	60.69	11	36.65
4	178.55	12	32.65
5	88.39	13	11.59
6	99.20	14	25.66
7	113.69	15	26.99
8	87.34	16	24.99
Mean	100.00	Mean	26.61
		DSR-0104108	
PBS		10mg/kg	
Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA
25	88.05	33	51.82
26	146.57	34	36.42
27	84.93	35	115.81
28	139.75	36	99.45
29	97.49	37	44.56
30	110.55	38	35.06
31	81.42	39	26.52
32	51.22	40	46.96
Mean	100.00	Mean	57.08
		DSR-0104108	
PBS		10mg/kg	
Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA
49	120.14	57	41.17
50	88.30	58	53.31
51	140.01	59	47.15
52	106.66	60	56.29
53	117.59	61	38.87
54	68.51	62	25.51
55	87.98	63	39.12
56	70.81	64	29.89

Mean	100.00	Mean	41.41

EXAMPLE 7. Provided Oligonucleotides and Compositions Are Active *in vivo*

In vivo determination of mouse INHBE siRNA activity: All animal experiments were performed at Biomedical Research Models, Ins. Dba Biomere (Worcester, MA) under an approved protocol and in compliance with Biomere's Institutional Animal Care and Use Committee guidelines for care and use of animals. Mice were on a 12-hour light-dark cycle. Food (either Research Diet D12492i or Lab Diet 5R58) and water were available ad libitum. Housing rooms were maintained at 20-26°C and relative humidity was 30-70%. The animals in this experiment were either diet induced obesity C57BL/6Ntac or normal C57BL/6NTac males, between 14-16 weeks of age. The mice were dosed with DSR-0104108 at 1, 3, or 10 mg/kg on Day 0 by subcutaneous administration. There were 8 mice per group per necropsy timepoint. Food consumption and body weights were captured twice a week. Animals were euthanized after overnight fasting on Day 14, Day 28, or Day 84 by CO2 asphyxiation followed by thoracotomy and terminal blood collection. After cardiac perfusion with PBS, liver, white adipose tissues (epididymal, inguinal, and mesenteric), and intrascapular brown adipose tissues were collected and weighed. Liver punches were harvested and flash-frozen on dry ice, and the remaining liver was flash frozen in foil using liquid nitrogen. White adipose tissue and intra-scapular brown adipose tissues were collected and flash frozen on dry ice. Liver total RNA was extracted using SV96 Total RNA Isolation kit (Promega), after tissue lysis with TRIzol and bromochloropropane. cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad).). For mouse INHBE mRNA, the following qPCR assay were utilized: Thermofisher Taqman qPCR assay ID Mm03023993_m1. Mouse HPRT was used as normalizer (Forward 5'CAAACTTTGCTTTCCCTGGTT3', Reverse 5'TGGCCTGTATCCAACACTTC3', Probe 5'/5HEX/ACCAGCAAG/Zen/CTTGCAACCTTAACC/3IABkFQ/3' K. Oligonucleotide accumulation in liver was determined by hybrid ELISA. In preclinical mouse models, the INHBE GalNAc-siRNA of the present disclosure has demonstrated highly potent (ED50 < 1mg/kg) and durable silencing following one, low-single-digit dose, supporting every-six-month or annual subcutaneous dosing in humans.

Table 43 shows % mouse INHBE mRNA remaining relative to PBS control 14, 28, 84 days post dosing in the liver of diet induced obesity mice. N = 8. N.D.: Not determined.

Week 2							
		DSR-0104108					
PBS		1mg/kg		3 mg/kg		10 mg/kg	
Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA
97	94.27	105	31.24	113	24.56	121	28.73
98	101.45	106	33.57	114	27.59	122	25.29
99	107.23	107	39.34	115	25.70	123	24.83
100	111.11	108	31.65	116	28.48	124	32.76
101	103.54	109	36.96	117	29.74	125	24.35
102	93.67	110	41.47	118	26.14	126	24.16
103	89.56	111	37.70	119	37.27	127	25.90
104	99.19	112	53.70	120	31.70	128	24.34
Mean	100.00	Mean	38.20	Mean	28.90	Mean	26.30
Week 4							
		DSR-0104108					
PBS		1mg/kg		3 mg/kg		10 mg/kg	
Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA
129	216.02	137	74.60	145	26.15	153	24.49
130	104.45	138	34.93	146	27.53	154	35.86
131	70.85	139	77.40	147	27.47	155	22.15
132	88.28	140	49.15	148	42.85	156	29.37
133	61.42	141	32.46	149	28.09	157	21.98
134	86.48	142	49.94	150	29.74	158	20.54
135	95.04	143	46.73	151	28.90	159	24.67
136	77.46	144	43.88	152	18.42	160	22.27
Mean	100.00	Mean	51.14	Mean	28.64	Mean	25.17
Week 12							
		DSR-0104108					
PBS		1mg/kg		3 mg/kg		10 mg/kg	
Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA	Animal no	%mRNA remaining of mINHBE mRNA
161	118.82	169	90.89	177	96.11	185	108.63
162	109.05	170	94.91	178	78.51	186	94.17

163	89.21	171	62.80	179	78.97	187	72.76
164	93.84	172	93.35	180	92.66	188	114.71
165	93.43	173	95.62	181	100.81	189	81.47
166	86.96	174	90.92	182	67.89	190	91.10
167	107.49	175	72.32	183	122.21	191	100.41
168	101.20	176	115.92	184	137.70	192	73.29
Mean	100.00	Mean	89.59	Mean	96.86	Mean	92.07

****

While various embodiments have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the functions and/or obtaining the results and/or one or more of the advantages described in the present disclosure, and each of such variations and/or modifications is deemed to be included. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be example and that the actual parameters, dimensions, materials, and/or configurations may depend upon the specific application or applications for which the teachings of the present disclosure is/are used. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the embodiments of the present disclosure. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto, claimed technologies may be practiced otherwise than as specifically described and claimed. In addition, any combination of two or more features, systems, articles, materials, kits, and/or methods, if such features, systems, articles, materials, kits, and/or methods are not mutually inconsistent, is included within the scope of the present disclosure.

CLAIMS

What is claimed is:

1. A composition comprising a double-stranded RNAi (dsRNAi) agent capable of directing INHBE (Inhibin subunit βE)-specific RNA interference to induce lipolysis while preserving muscle mass, the dsRNAi agent comprising a guide strand and a passenger strand, wherein:

e) the guide strand is complementary or substantially complementary to an INHBE target RNA sequence;

f) the guide strand comprises:

i. a non-negatively charged internucleotidic linkage in the *S*p configuration between the +3 nucleotide relative to the 5' terminal nucleotide and the immediately downstream (+4) nucleotide;

ii. a non-negatively charged internucleotidic linkage in the *R*p configuration between the +10 nucleotide and the immediately downstream (+11) nucleotide;

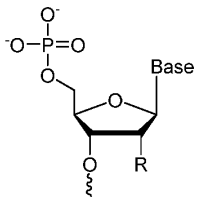
iii. phosphorothioate internucleotidic linkages in *S*p configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide; and/or

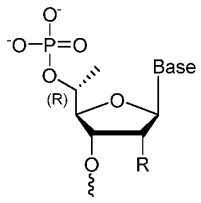
iv. phosphorothioate internucleotidic linkages in *R*p, *S*p, or alternating configurations between the 5' terminal (+1) nucleotide and the immediately downstream (+2) nucleotide and between the +2 nucleotide and the immediately downstream (+3) nucleotide;

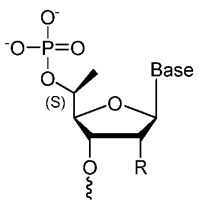
c) the guide strand further comprises a 5' phosphate modification;

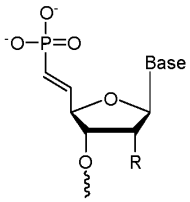
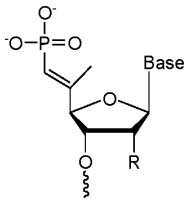
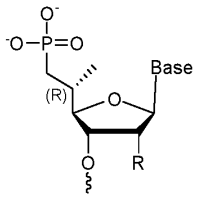
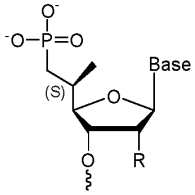
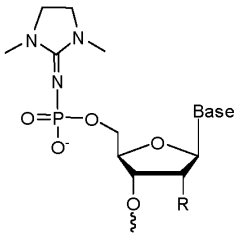
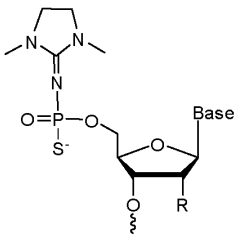
d) the passenger strand comprises one or more chiral internucleotidic linkages in *R*p or *S*p configuration; and

e) the guide strand and the passenger strand each independently has a length of 15-49 nucleotides. 2. The composition of claim 1, wherein the guide strand comprises a 5' phosphate modification selected from:

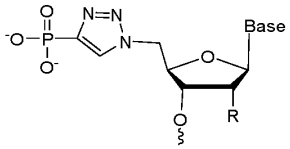






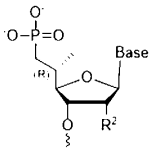
and



Base: A, C, G, T, U, abasic, and modified nucleobases;

R: H, OH, O-alkyl, F, MOE, LNA bridge to the 4' position, BNA bridge to the 4' position.

3. The composition of claim 2 wherein the guide strand comprises a 5' phosphate modification selected from 5' MeP modifications and 5' triazole-P modifications.

4. The double stranded oligonucleotide or composition of claim 14 wherein the 5' MeP modification is  .

4. The composition of claim 4, further comprising a backbone phosphorothioate chiral center in Sp configuration between the 5' terminal (+1) nucleotide and the immediately downstream

(+2) nucleotide, and a backbone phosphorothioate chiral center in the Rp configuration between the +2 nucleotide and the immediately downstream (+3) nucleotide.

5. The composition of claim 1, wherein the guide strand comprises one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide, and the passenger strand comprises one or more backbone chiral centers in Rp or Sp configuration.

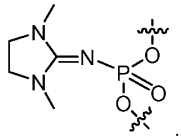
6. The composition of claim 1, wherein the guide strand comprises backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide, and the passenger strand comprises 0-n Rp, Sp, or stereorandom non-negatively charged internucleotidic linkages, where n is about 1 to 49 and one or more backbone chiral centers in Rp or Sp configuration.

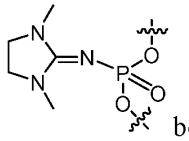
7. The composition of claim 1, wherein the guide strand comprises backbone phosphorothioate chiral centers in Rp, Sp, or alternating configurations between the 5' terminal (+1) nucleotide and the immediately downstream (+2) nucleotide and between the +2 nucleotide and the immediately downstream (+3) nucleotide, and the passenger strand comprises 0-n Rp, Sp, or stereorandom non-negatively charged internucleotidic linkages, where n is about 1 to 49 and one or more backbone chiral centers in Rp or Sp configuration.

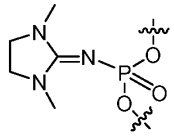
8. The composition of claim 1, wherein the guide strand comprises one or more backbone phosphorothioate chiral centers in Rp or Sp configuration upstream of backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide, and the passenger strand comprises 0-n Rp, Sp, or stereorandom non-negatively charged internucleotidic linkages, where n is about 1 to 49 and one or more backbone chiral centers in Rp or Sp configuration.

9. The composition of claim 1, wherein the guide strand comprises one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide, and the passenger strand comprises 0-n non-negatively charged internucleotidic linkages, where n is about 1 to 49 and one or more backbone chiral centers in Rp or Sp configuration.

10. The composition of any one of the preceding claims, wherein the Rp, Sp, or stereorandom non-negatively charged backbone internucleotidic linkages have neutral charge.

11. The composition of claim 10, wherein the neutral backbone internucleotidic linkages is  .

12. The composition of claim 11, wherein the guide strand comprises a linkage having the following structure  between the third (+3) and fourth (+4) nucleotides of the guide strand, between the tenth (+10) and eleventh (+11) nucleotides of the guide strand, or both.

13. The composition of claim 12, wherein the passenger strand comprises a linkage having the following structure  5' to the central nucleotide of the passenger strand, 3' to the central nucleotide of the passenger strand, or both.

14. The composition of claim 1, where the guide and passenger strands in the composition that independently share a common base sequence, a common pattern of base modification, a

common pattern of sugar modification, and/or a common pattern of internucleotidic linkages are at least 90% of all the guide and passenger strands in the composition.

15. The composition of any of the preceding claims, wherein the double stranded oligonucleotide comprises a carbohydrate moiety connected at a nucleoside, an internucleotidic linkage, optionally through a linker.

16. The composition of any of the preceding claims, wherein the double stranded oligonucleotide comprises a lipid moiety connected to the double stranded oligonucleotide at a nucleoside, an internucleotidic linkage, optionally through a linker.

17. The composition of any of the preceding claims, wherein one or both strands of the double stranded oligonucleotide comprises a target moiety connected at a nucleoside, an internucleotidic linkage, optionally through a linker.

18. The composition of any one of the preceding claims, wherein at least 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% of the internucleotidic linkages of the double stranded oligonucleotide are independently chiral internucleotidic linkages.

19. The composition of any one of the preceding claims, wherein at least 3%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% of the nucleotidic units of the double stranded oligonucleotide independently comprise a 2'-substitution.

20. The composition of any one of the preceding claims, wherein a 2'-substitution of the oligonucleotide is 2'-F.

21. The composition of any one of the preceding claims, wherein a 2'-substitution of the oligonucleotide is 2'-OR1.

22. The composition of any one of the preceding claims, wherein a 2'-substitution of the oligonucleotide is–L–, wherein L connects C2 and C4 of the sugar unit.

23. The composition of any one of the preceding claims, wherein at least 3%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% of the nucleotidic units of the double stranded oligonucleotide comprise no 2'-substitution.

24. The composition of any one of the preceding claims, wherein the guide strand comprises an INHBE target-binding sequence that is completely complementary to an INHBE target sequence, wherein the INHBE target-binding sequence has a length of at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 bases, wherein each base is optionally substituted adenine, cytosine, guanosine, thymine, or uracil.

25. The composition of any one of the preceding claims, wherein the INHBE target sequence comprises two SNPs.

26. The composition of any one of the preceding claims, wherein the INHBE target sequence comprises an allelic site and the INHBE target-binding sequence is completely complementary to the INHBE target sequence of a disease-associated allele but not that of an allele less associated with the disease.

27. The composition of any one of the preceding claims, wherein

the double stranded oligonucleotide comprises a guide strand that binds with a transcript of an INHBE target nucleic acid sequence for which a plurality of alleles exist within a population, each of which contains a specific nucleotide characteristic sequence element that defines the allele relative to other alleles of the same INHBE target nucleic acid sequence,

wherein the base sequence of the guide strand is or comprises a sequence that is complementary to the characteristic sequence element that defines a target allele, and

the guide strand being characterized in that, when it is contacted with a cell comprising transcripts of INHBE target nucleic acid sequence, it shows suppression of transcripts of the target allele, or a protein encoded thereby, at a level that is greater than a level of suppression observed for another allele of the same nucleic acid sequence.

28. The composition of claim 1, comprising DSR-0104068, DSR-0104099, DSR-0104072, DSR-0104075, DSR-0104083, DSR-0104091, DSR-0104071, or DSR-0104108.

29. A method for reducing level and/or activity of an INHBE transcript or a protein encoded thereby, comprising administering to a cell expressing the INHBE transcript a composition of any one of the preceding claims, wherein the guide strand of double stranded oligonucleotide or composition comprises a INHBE-binding sequence that is completely complementary to an INHBE target sequence in the transcript.

30. The method of claim 29 wherein the cell is a liver cell.

31. A method of treating a metabolic disorder, comprising administering a composition of any one of claims 1-28.

32. The method of claim 31, wherein the metabolic disorder is metabolic syndrome.

33. A method of treating obesity, comprising administering a composition of any one of claims 1-28.

34. A method of treating cardiovascular disease, comprising administering a composition of any one of claims 1-28.

35. A method of treating diabetes, comprising administering a composition of any one of claims 1-28.

36. A method of treating hypertension, comprising administering a composition of any one of claims 1-28.

37. The method of any one of claims 31-36, comprising administration of a second therapeutic.

38. The method of claim 37, wherein the second therapeutic is selected from the group consisting of: insulin; sulfonylurea; meglitinide; biguanide; thiazolidinedione; alpha-glucosidase inhibitor; SGLT2 inhibitor; DPP4 inhibitor; glucagon like peptide 1 receptor agonist (GLP-1RA); glucose-dependent insulinotropic polypeptide agonist (GIP RA); glucagon receptor agonist (Gcg RA); co-agonist of GLP-1R, GIP R, and/or Gcg R; HMG-CoA reductase inhibitor, statins; PCSK9 inhibitor; ApoC3 inhibitor; ANGPTL3 inhibitor; ATP citrate lyase (bempedoic acid), ezetimide; Lp(a) inhibitor, LPL activator, and combinations thereof.

39. The method of claim 38, wherein the composition of any one of claims 1-28 is administered concurrently with the second therapeutic.

40. The method of claim 39, wherein the composition of any one of claims 1-28 is administered sequentially with the second therapeutic.