Therefore, in the absence of any current treatment regimen which can restore immunological control of HBV in a large proportion of patients, there is a need for an effective treatment against HBV infection which can inhibit viral replication as well as restore immunological control in the majority of patients. Accordingly, there is a need in the art for alternative therapies and combination therapies for subjects infected with HBV and/or having an HBV-associated disease.

Summary ~~of the Invention~~

The present ~~invention~~disclosure provides iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a Hepatitis B virus (HBV) gene. The HBV gene may be within a cell, *e.g.,* a cell within a subject, such as a human.

The present ~~invention~~disclosure also provides methods and therapies for treating a subject having a disorder that would benefit from inhibiting or reducing the expression of an HBV gene, *e.g.,* an HBV infection and/or an HBV-associated disease, such as chronic Hepatitis B infection (CHB), cirrhosis, liver failure, and hepatocellular carcinoma (HCC), using iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of an HBV gene for inhibiting the expression of an HBV gene.

The RNAi agents of the ~~invention~~disclosure have been designed to target regions in the HBV genome that are conserved across all 8 serotypes of HBV. In addition, the RNAi agents of the ~~invention~~disclosure have been designed to inhibit all steps of the HBV life cycle, *e.g.,* replication, assembly, secretion of virus, and secretion of sub-viral antigens, by inhibiting expression of more than one HBV gene. In particular, since transcription of the HBV genome results in polycistronic, overlapping RNAs, an RNAi agent of the ~~invention~~disclosure targeting a single HBV gene results in significant inhibition of expression of most or all HBV transcripts. For example, because the HBV genome is transcribed into a single mRNA, an RNAi agent of the ~~invention~~disclosure targeting the S gene will result in inhibition of not only S gene expression but also the expression of the "downstream" reverse transcriptase gene. Furthermore, the RNAi agents of the ~~invention~~disclosure have been designed to inhibit HBV viral replication by targeting HBV structural genes, and the HBV X gene thereby permitting a subject's immune system to detect and respond to the presence of HBsAg to produce anti-HBV antibodies to clear an HBV infection. Without intending to be limited by theory, it is believed that a combination or sub-combination of the foregoing properties and the specific target sites and/or the specific modifications in these RNAi agents confer to the RNAi agents of the ~~invention~~disclosure improved efficacy, stability, safety, potency, and durability.

Accordingly, in one ~~aspect~~example, the present ~~invention~~disclosure provides double stranded RNAi agents for inhibiting expression of hepatitis B virus (HBV) in a cell. The double stranded RNAi agents include a sense strand and an antisense strand forming a double-stranded region,

wherein said sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1, and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2, wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In one ~~embodiment~~example, the one or more of the 3 nucleotide differences in the nucleotide sequence of the antisense strand is a nucleotide mismatch in the antisense strand.

In another ~~embodiment~~example, the one or more of the 3 nucleotide differences in the nucleotide sequence of the antisense strand is a nucleotide mismatch in the sense strand.

In one ~~embodiment~~example, all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand are modified nucleotides.

In one ~~embodiment~~example, the sense strand and the antisense strand comprise a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the sequences listed in any one of Tables 3, 4, 6, 7, 12, 13, 22, 23, 25, and 26.

In one ~~embodiment~~example, the at least one of said modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, and a nucleotide comprising a 5'-phosphate mimic.

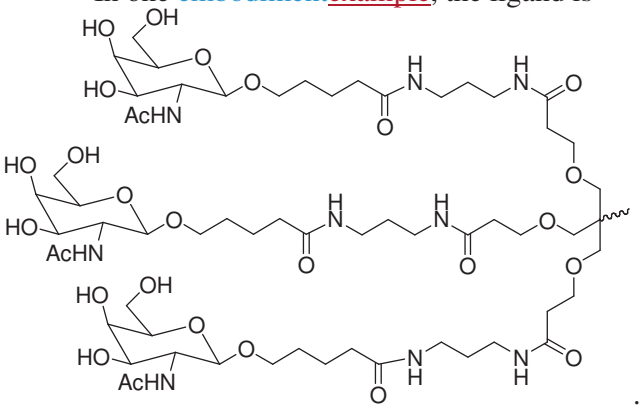
In one ~~embodiment~~example, the at least one strand comprises a 3' overhang of at least 1 nucleotide. In another ~~embodiment~~example, the at least one strand comprises a 3' overhang of at least 2 nucleotides.

In one ~~embodiment~~example, the double-stranded region is 15-30 nucleotide pairs in length. In another ~~embodiment~~example, the double-stranded region is 17-23 nucleotide pairs in length. In yet another ~~embodiment~~example, the double-stranded region is 17-25 nucleotide pairs in length. In one ~~embodiment~~example, the e double-stranded region is 23-27 nucleotide pairs in length. In another

~~embodiment~~example, the double-stranded region is 19-21 nucleotide pairs in length. In yet another ~~embodiment~~example, the double-stranded region is 21-23 nucleotide pairs in length.

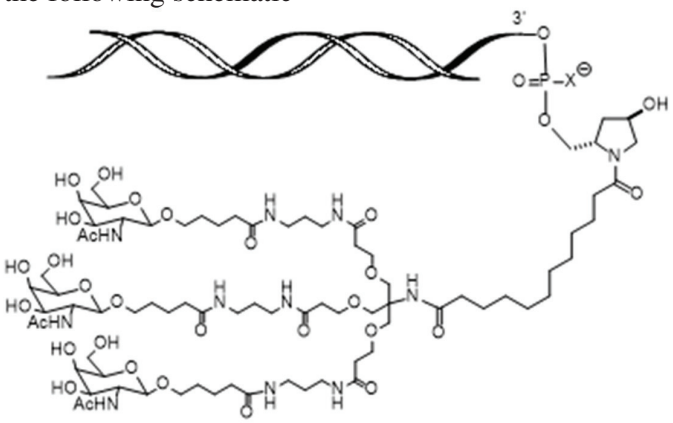
In one ~~embodiment~~example, each strand has 15-30 nucleotides. In another ~~embodiment~~example, each strand has 19-30 nucleotides.

In one ~~embodiment~~example, the ligand is



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In one ~~embodiment~~example, the RNAi agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

In one ~~embodiment~~example, the RNAi agent is selected from the group of RNAi agents listed in any one of Tables 3, 4, 6, 7, 12, 13, 22, 23, 25, and 26.

In one ~~aspect~~example, the present ~~invention~~disclosure provides double stranded RNAi agents for inhibiting expression of hepatitis B virus (HBV) in a cell. The double stranded RNAi agents include a sense strand and an antisense strand forming a double-stranded region, wherein said sense strand comprises 5'- UCGUGGUGGACUUCUCUCA -3' (SEQ ID NO:5), and said antisense strand comprises 5'- UGAGAGAAGUCCACCACGAUU -3' (SEQ ID NO:6), wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

The present ~~invention~~disclosure also provides RNAi agents comprising sense and antisense nucleotide sequences which are at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over their entire length to the foregoing sense and antisense nucleotide sequences.

In another ~~aspect~~example, the present ~~invention~~disclosure provides double stranded RNAi agents for inhibiting expression of hepatitis B virus (HBV) in a cell. The double stranded RNAi agents include a sense strand and an antisense strand forming a double-stranded region, wherein said sense strand comprises 5'- GUGCACUUCGCUUCACCUCUA -3' (SEQ ID NO:7), and said antisense strand comprises 5'- UAGAGGUGAAGCGAAGUGCACUU -3' (SEQ ID NO:8), wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker. The present ~~invention~~disclosure also provides RNAi agents comprising sense and antisense nucleotide sequences which are at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over their entire length to the foregoing sense and antisense nucleotide sequences.

In another ~~aspect~~example, the present ~~invention~~disclosure provides double stranded RNAi agents for inhibiting expression of hepatitis B virus (HBV) in a cell. The double stranded RNAi agents include a sense strand and an antisense strand forming a double-stranded region, wherein said sense strand comprises 5'- CGUGGUGGACUUCUCUCAAUU -3' (SEQ ID NO:9), and said antisense strand comprises 5'- AAUUGAGAGAAGUCCACCAGCAG -3' (SEQ ID NO:10), wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker. The present ~~invention~~disclosure also provides RNAi agents comprising sense and antisense nucleotide sequences which are at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over their entire length to the foregoing sense and antisense nucleotide sequences.

In another ~~aspect~~example, the present ~~invention~~disclosure provides double stranded RNAi agents for inhibiting expression of hepatitis B virus (HBV) in a cell. The double stranded RNAi agents include a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises 5'- CGUGGUGGUCUUCUCUAAAUU -3' (SEQ ID NO:37), and the antisense strand comprises 5'- AAUUGAGAGAAGUCCACCAGCUU -3' (SEQ ID NO:38), wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker. The present

~~invention~~disclosure also provides RNAi agents comprising sense and antisense nucleotide sequences which are at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over their entire length to the foregoing sense and antisense nucleotide sequences.

In another ~~aspect~~example, the present ~~invention~~disclosure provides double stranded RNAi agents for inhibiting expression of hepatitis B virus (HBV) in a cell. The double stranded RNAi agents include a sense strand and an antisense strand forming a double-stranded region, wherein said sense strand comprises 5'- GGUGGACUUCUCUCAAUUUUA -3' (SEQ ID NO:11), and said antisense strand comprises 5'- UAAAAUUGAGAGAAGUCCACCAC -3' (SEQ ID NO:12), wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker. The present ~~invention~~disclosure also provides RNAi agents comprising sense and antisense nucleotide sequences which are at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over their entire length to the foregoing sense and antisense nucleotide sequences.

In another ~~aspect~~example, the present ~~invention~~disclosure provides double stranded RNAi agents for inhibiting expression of hepatitis B virus (HBV) in a cell. The double stranded RNAi agents include a sense strand and an antisense strand forming a double-stranded region, wherein said sense strand comprises 5'- GUGUGCACUUCGCUUCACA -3' (SEQ ID NO:39), and said antisense strand comprises 5'- UGUGAAGCGAAGUGCACACUU -3' (SEQ ID NO:40), wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker. The present ~~invention~~disclosure also provides RNAi agents comprising sense and antisense nucleotide sequences which are at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over their entire length to the foregoing sense and antisense nucleotide sequences.

In one ~~embodiment~~example, all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand comprise a modification.

In one ~~embodiment~~example, at least one of said modified nucleotides is selected from the group consisting of a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified

nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, and a nucleotide comprising a 5'-phosphate mimic.

In one ~~embodiment~~example, the 5'-phosphate mimic is a 5'-vinyl phosphate (5'-VP).

In one ~~embodiment~~example, the sense strand comprises 5'-uscsguGfgUfGfGfacuucucuca – 3' (SEQ ID NO:13) and the antisense strand comprises 5'-usGfsagaGfaAfGfuccaCfcAfcgasusu – 3' (SEQ ID NO:14), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; and s is a phosphorothioate linkage.

In another ~~embodiment~~example, the sense strand comprises 5'-uscsguGfgUfGfGfacuucucuca – 3' (SEQ ID NO:15) and the antisense strand comprises 5'-PusGfsagaGfaAfGfuccaCfcAfcgasusu – 3' (SEQ ID NO:16), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; and s is a phosphorothioate linkage; and P is a 5'-phosphate or 5'phosphate mimic.

In one ~~embodiment~~example, the sense strand comprises 5'-gsusgcacUfuCfGfCfuucaccucua – 3' (SEQ ID NO:17) and the antisense strand comprises 5'-usAfsgagGfugaagcgAfaGfugcacsusu – 3' (SEQ ID NO:18), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; and s is a phosphorothioate linkage.

In another ~~embodiment~~example, the sense strand comprises 5'-gsusgcacUfuCfGfCfuucaccucua – 3' (SEQ ID NO:19) and the antisense strand comprises 5'-PusAfsgagGfugaagcgAfaGfugcacsusu – 3' (SEQ ID NO:20) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; and s is a phosphorothioate linkage; and P is a 5'-phosphate or 5'phosphate mimic.

In one ~~embodiment~~example, the sense strand comprises 5'-csgsugguGfgAfCfUfucucUfCfaauu – 3' (SEQ ID NO:21) and the antisense strand comprises 5'-asAfsuugAfgAfgAfaguCfcAfccagcsasg – 3' (SEQ ID NO:22), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; and s is a phosphorothioate linkage.

In another ~~embodiment~~example, the sense strand comprises 5'-csgsugguGfgAfCfUfucucUfCfaauu – 3' (SEQ ID NO:23) and the antisense strand comprises 5'-PasAfsuugAfgAfgAfaguCfcAfccagcsasg – 3' (SEQ ID NO:24) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are
2′-fluoro A, G, C or U; and s is a phosphorothioate linkage; and P is a 5'-phosphate or 5'phosphate mimic.

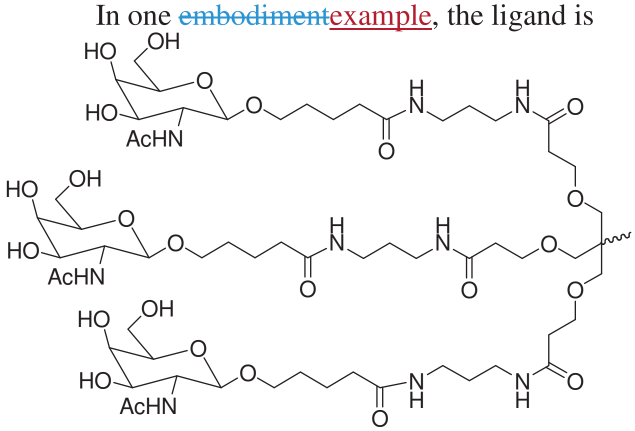
In another ~~embodiment~~example, the sense strand comprises 5’-csgsuggudGgucdTucucuaaauu – 3’ (SEQ ID NO:35) and the antisense strand comprises 5’- asdAsuugagagdAagudCcaccagcsusu – 3’ (SEQ ID NO:36), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; dA, dC, dG, and dT are deoxyribose A, C, G, and T; and s is a phosphorothioate linkage.

In one ~~embodiment~~example, the sense strand comprises 5’-gsgsuggaCfuUfCfUfcucaAfUfuuua – 3’ (SEQ ID NO:25) and the antisense strand comprises 5’- usAfsaaaUfuGfAfgagaAfgUfccaccsasc – 3’ (SEQ ID NO:26), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; and s is a phosphorothioate linkage.

In another ~~embodiment~~example, the sense strand comprises 5’-gsgsuggaCfuUfCfUfcucaAfUfuuua – 3’ (SEQ ID NO:27) and the antisense strand comprises 5’- PusAfsaaaUfuGfAfgagaAfgUfccaccsasc – 3’ (SEQ ID NO:28) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; and s is a phosphorothioate linkage; and P is a 5’-phosphate or 5’phosphate mimic.

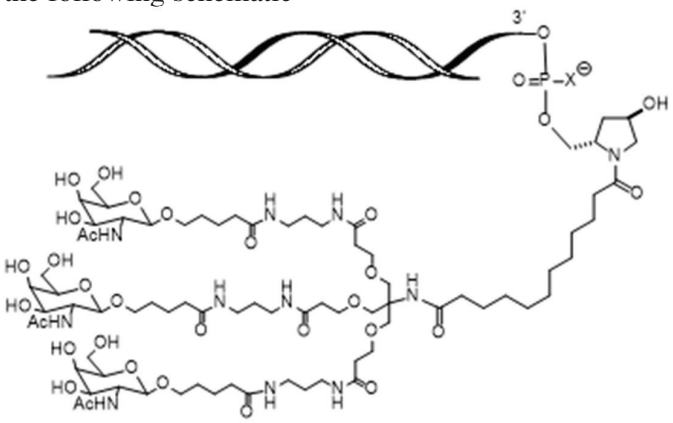
In another ~~embodiment~~example, the sense strand comprises 5’- gsusguGfcAfCfUfucgcuucaca -3’ (SEQ ID NO:41) and the antisense strand comprises 5’- usGfsugaAfgCfGfaaguGfcAfcacsusu -3’ (SEQ ID NO:42), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; and s is a phosphorothioate linkage.

In one ~~embodiment~~example, the ligand is



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In one ~~embodiment~~example, the RNAi agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

In one ~~embodiment~~example, the P is a 5'-phosphate mimic. In one ~~embodiment~~example, the 5'-phosphate mimic is a 5'-vinyl phosphate (5'-VP).

In another ~~aspect~~example, the present ~~invention~~disclosure provides compositions comprising two or more double stranded RNAi agents for inhibiting expression of hepatitis B virus (HBV) in a cell, wherein each double stranded RNAi agent independently comprises a sense strand and an antisense strand forming a double-stranded region, wherein each of said sense strands independently comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1, and each of said antisense strands independently comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2, wherein substantially all of the nucleotides of each of said sense strands and substantially all of the nucleotides of each of said antisense strands are independently modified nucleotides, wherein each of said sense strands are independently conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In one ~~embodiment~~example, the one or more of the 3 nucleotide differences in the nucleotide sequence of the antisense strand is a nucleotide mismatch in the antisense strand. In another ~~embodiment~~example, the one or more of the 3 nucleotide differences in the nucleotide sequence of the antisense strand is a nucleotide mismatch in the sense strand.

In one ~~embodiment~~example, all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand are modified nucleotides.

In one ~~embodiment~~example, the sense strand and said antisense strand comprise a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the sequences listed in any one of Tables 3, 4, 6, 7, 12, 13, 22, 23, 25, and 26.

In one ~~embodiment~~example, the at least one of said modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, and a nucleotide comprising a 5'-phosphate mimic.

In another ~~aspect~~example, the present ~~invention~~disclosure provides compositions for inhibiting expression of hepatitis B virus (HBV) in a cell, the composition comprising (a) a first double-stranded RNAi agent comprising a first sense strand and a first antisense strand forming a double-stranded region, wherein substantially all of the nucleotides of said first sense strand and substantially all of the nucleotides of the first antisense strand are modified nucleotides, wherein said first sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; and (b) a second double-stranded RNAi agent comprising a second sense strand and a second antisense strand forming a double-stranded region, wherein substantially all of the nucleotides of said second sense strand and substantially all of the nucleotides of said second antisense strand are modified nucleotides, wherein said second sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; wherein the first and second sense strands each independently comprise a sequence selected from the group consisting of
5'- UCGUGGUGGACUUCUCUCA -3' (SEQ IDNO:5),
5'- GUGCACUUCGCUUCACCUCUA -3' (SEQ IDNO:7),
5'- CGUGGUGGACUUCUCUCAAUU -3' (SEQ IDNO:9),
5'- CGUGGUGGUCUUCUCUAAAUU -3' (SEQ IDNO:37),
5'- GGUGGACUUCUCUCAAUUUUA -3' (SEQ IDNO:11), and
5'- GUGUGCACUUCGCUUCACA -3' (SEQ IDNO:39) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequences), and wherein the first and second antisense strands each independently comprise a sequence selected from the group consisting of
5'- UGAGAGAAGUCCACCACGAUU -3' (SEQ ID NO:6),
5'- UAGAGGUGAAGCGAAGUGCACUU -3' (SEQ ID NO:8),

5’- AAUUGAGAGAAGUCCACCAGCAG -3’ (SEQ ID NO:10),
5’- AAUUGAGAGAAGUCCACCAGCUU -3’ (SEQ ID NO:38),
5’- UAAAAUUGAGAGAAGUCCACCAC -3’ (SEQ ID NO:12), and
5’- UGUGAAGCGAAGUGCACACUU -3’ (SEQ ID NO:40) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequences).

In one ~~embodiment~~example, the first and second sense strand and/or all of the nucleotides of the first and second antisense strand comprise a modification.

In one ~~embodiment~~example, the at least one of said modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3’-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2’-amino-modified nucleotide, a 2’-O-allyl-modified nucleotide, 2’-C-alkyl-modified nucleotide, 2’-hydroxly-modified nucleotide, a 2’-methoxyethyl modified nucleotide, a 2’-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5’-phosphate, and a nucleotide comprising a 5’-phosphate mimic.

In one ~~embodiment~~example, the first and second RNAi agents are selected from the group consisting of:
5’-uscsguGfgUfGfGfacuucucuca – 3’ (SEQ ID NO:13)
5’-usGfsagaGfaAfGfuccaCfcAfcgasusu – 3’ (SEQ ID NO:14);
5’-uscsguGfgUfGfGfacuucucuca – 3’ (SEQ ID NO:15)
5’-PusGfsagaGfaAfGfuccaCfcAfcgasusu – 3’ (SEQ ID NO:16);
5’-gsusgcacUfuCfGfCfuucaccucua – 3’ (SEQ ID NO:17)
5’-usAfsgagGfugaagcgAfaGfugcacsusu – 3’ (SEQ ID NO:18);
5’-gsusgcacUfuCfGfCfuucaccucua – 3’ (SEQ ID NO:19)
5’-PusAfsgagGfugaagcgAfaGfugcacsusu – 3’ (SEQ ID NO:20);
5’-csgsugguGfgAfCfUfucucUfCfaauu – 3’ (SEQ ID NO:21)
5’-asAfsuugAfgAfgAfaguCfcAfccagcsasg – 3’ (SEQ ID NO:22);
5’- csgsugguGfgAfCfUfucucUfCfaauu – 3’ (SEQ ID NO:23)
5’-PasAfsuugAfgAfgAfaguCfcAfccagcsasg – 3’ (SEQ ID NO:24);
5’-csgsuggudGgucdTucucuaaauu – 3’ (SEQ ID NO:35)
5’- asdAsuugagagdAagudCcaccagcsusu – 3’ (SEQ ID NO:36);
5’- gsgsuggaCfuUfCfUfcucaAfUfuuua – 3’ (SEQ ID NO:25)
5’- usAfsaaaUfuGfAfgagaAfgUfccaccsasc – 3’ (SEQ ID NO:26);

5’- gsgsuggaCfuUfCfUfcucaAfUfuuua – 3’ (SEQ ID NO:27)
5’- PusAfsaaaUfuGfAfgagaAfgUfccaccsasc – 3’ (SEQ ID NO:28); and
5’- gsusguGfcAfCfUfucgcuucaca -3’ (SEQ ID NO:41)
5’- usGfsugaAfgCfGfaaguGfcAfcacsusu -3’ (SEQ ID NO:42), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; dA, dC, dG, and dT are deoxyribose A, C, G, and T; s is a phosphorothioate linkage; and P is a 5’-phosphate or 5’phosphate mimic.

In one ~~embodiment~~example, the first and second RNAi agents are
5’-uscsguGfgUfGfGfacuucucuca – 3’ (SEQ ID NO:15)
5’-PusGfsagaGfaAfGfuccaCfcAfcgasusu – 3’ (SEQ ID NO:16);
5’-csgsugguGfgAfCfUfucucUfCfaauu – 3’ (SEQ ID NO:21)
5’-asAfsuugAfgAfgAfaguCfcAfccagcsasg – 3’ (SEQ ID NO:22), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; s is a phosphorothioate linkage; and P is a 5’-phosphate or 5’phosphate mimic.

In another ~~embodiment~~example, the first and second RNAi agents are
5’- gsgsuggaCfuUfCfUfcucaAfUfuuua – 3’ (SEQ ID NO:25)
5’- usAfsaaaUfuGfAfgagaAfgUfccaccsasc – 3’ (SEQ ID NO:26); and
5’- gsusguGfcAfCfUfucgcuucaca -3’ (SEQ ID NO:41)
5’- usGfsugaAfgCfGfaaguGfcAfcacsusu -3’ (SEQ ID NO:42), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; s is a phosphorothioate linkage; and P is a 5’-phosphate or 5’phosphate mimic.

In one ~~aspect~~example, the present ~~invention~~disclosure provides a double stranded RNAi agent comprising the RNAi agents listed in any one of Tables 3, 4, 6, 7, 12, 13, 22, 23, 25, and 26.

The present ~~invention~~disclosure also provides vectors and cells comprising the double stranded RNAi agent of the ~~invention~~disclosure.

In another ~~aspect~~example, the present ~~invention~~disclosure provides pharmaceutical compositions comprising the double stranded RNAi agents of the ~~invention~~disclosure, or the compositions of the ~~invention~~disclosure, or the vectors of the ~~invention~~disclosure.

In one ~~embodiment~~example, the double stranded RNAi agent is administered in an unbuffered solution. In one ~~embodiment~~example, the unbuffered solution is saline or water.

In another ~~embodiment~~example, the double stranded RNAi agent is administered with a buffer solution. In one ~~embodiment~~example, the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof. In another ~~embodiment~~example, the buffer solution is phosphate buffered saline (PBS). In one ~~aspect~~example, the present ~~invention~~disclosure provides methods of inhibiting Hepatitis B virus (HBV) gene expression in a cell. The methods include contacting the cell with the double

stranded RNAi agent of the ~~invention~~disclosure, or the composition of the ~~invention~~disclosure, or the vector of the ~~invention~~disclosure, or the pharmaceutical composition of the ~~invention~~disclosure; and maintaining the cell produced for a time sufficient to obtain degradation of the mRNA transcript of an HBV gene, thereby inhibiting expression of the HBV gene in the cell.

In one ~~embodiment~~example, the HBV gene is selected from the group consisting of C, X, P, S, and a combination thereof.

In one ~~aspect~~example, the present ~~invention~~disclosure provides methods of inhibiting replication of a Hepatitis B virus (HBV) in a cell. The methods include contacting the cell with the double stranded RNAi agent of the ~~invention~~disclosure, or the composition of the ~~invention~~disclosure, or the vector of the ~~invention~~disclosure, or the pharmaceutical composition of the ~~invention~~disclosure; and maintaining the cell produced for a time sufficient to obtain degradation of the mRNA transcript of an HBV gene, thereby inhibiting replication of the HBV in the cell.

In one ~~embodiment~~example, the cell is within a subject. In one ~~embodiment~~example, the subject is a human.

In one ~~embodiment~~example, the subject suffers from an HBV-associated disease.

In one ~~embodiment~~example, HBV gene expression is inhibited by at least about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98% or about 100%.

In one ~~embodiment~~example, replication of HBV in the cell is inhibited by at least about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98% or about 100%.

In one ~~aspect~~example, the present ~~invention~~disclosure provides methods of reducing the level of Hepatitis B virus (HBV) DNA in a subject infected with HBV. The methods include administering to the subject a therapeutically effective amount of the double stranded RNAi agent of the ~~invention~~disclosure, or the composition of the ~~invention~~disclosure, or the vector of the ~~invention~~disclosure, or the pharmaceutical composition of the ~~invention~~disclosure, thereby reducing the level of HBV ccc DNA in the subject.

In another ~~aspect~~example, the present ~~invention~~disclosure provides methods of reducing the level of a Hepatitis B virus (HBV) antigen in a subject infected with HBV. The methods include administering to the subject a therapeutically effective amount of the double stranded RNAi agent of the ~~invention~~disclosure, or the composition of the ~~invention~~disclosure, or the vector of the ~~invention~~disclosure, or the pharmaceutical composition of the ~~invention~~disclosure, thereby reducing the level of the HBV antigen in the subject.

In one ~~embodiment~~example, the HBV antigen is HBsAg. In abother ~~embodiment~~example, the HBV antigen is HBeAg. In another ~~aspect~~example, the present ~~invention~~disclosure provides methods of reducing the viral load of Hepatitis B virus (HBV) in a subject infected with HBV. The methods include administering to the subject a therapeutically effective amount of the double stranded RNAi agent of the

~~invention~~disclosure, or the composition of the ~~invention~~disclosure, or the vector of the ~~invention~~disclosure, or the pharmaceutical composition of the ~~invention~~disclosure, thereby reducing the viral load of HBV in the subject.

In yet another ~~aspect~~example, the present ~~invention~~disclosure provides methods of reducing the level of alanine aminotransferase (ALT) in a subject infected with HBV. The methods include administering to the subject a therapeutically effective amount of the double stranded RNAi agent of the ~~invention~~disclosure, or the composition of the ~~invention~~disclosure, or the vector of the ~~invention~~disclosure, or the pharmaceutical composition of the ~~invention~~disclosure, thereby reducing the level of ALT in the subject.

In another ~~aspect~~example, the present ~~invention~~disclosure provides methods of reducing the level of aspartate aminotransferase (AST) in a subject infected with HBV. The methods include administering to the subject a therapeutically effective amount of the double stranded RNAi agent of the ~~invention~~disclosure, or the composition of the ~~invention~~disclosure, or the vector of the ~~invention~~disclosure, or the pharmaceutical composition of the ~~invention~~disclosure, thereby reducing the level of AST in the subject.

In another ~~aspect~~example, the present ~~invention~~disclosure provides methods of increasing the level of anti-Hepatitis B virus (HBV) antibodies in a subject infected with HBV. The methods include administering to the subject a therapeutically effective amount of the double stranded RNAi agent of the ~~invention~~disclosure, or the composition of the ~~invention~~disclosure, or the vector of the ~~invention~~disclosure, or the pharmaceutical composition of the ~~invention~~disclosure, thereby increasing the level of anti- HBV antibodies in the subject.

In one ~~aspect~~example, the present ~~invention~~disclosure provides methods of treating a subject having a Hepatitis B virus (HBV) infection. The methods include administering to the subject a therapeutically effective amount of the double stranded RNAi agent of the ~~invention~~disclosure, or the composition of the ~~invention~~disclosure, or the vector of the ~~invention~~disclosure, or the pharmaceutical composition of the ~~invention~~disclosure, thereby treating said subject.

In another ~~aspect~~example, the present ~~invention~~disclosure provides methods of treating a subject having a Hepatitis B virus (HBV)-associated disorder. The methods include administering to the subject a therapeutically effective amount of the double stranded RNAi agent of the ~~invention~~disclosure, or the composition of the ~~invention~~disclosure, or the vector of the ~~invention~~disclosure, or the pharmaceutical composition of the ~~invention~~disclosure, thereby treating said subject.

In one ~~embodiment~~example, the HBV-associated disorder is selected from the group consisting of hepatitis D virus infection, delta hepatitis, acute hepatitis B; acute fulminant hepatitis B; chronic hepatitis B; liver fibrosis; end-stage liver disease; hepatocellular carcinoma.

In one ~~embodiment~~example, the HBV-associated disorder is chronic hepatitis and the subject is HBeAg positive. In another ~~embodiment~~example, the HBV-associated disorder is chronic hepatitis and the subject is HBeAg negative.

In one ~~aspect~~example, the present ~~invention~~disclosure provides methods of treating a subject having a Hepatitis B virus (HBV) infection. The methods include administering to the subject a therapeutically effective amount of a double stranded RNAi agent, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,

wherein said sense strand comprises 5'- UCGUGGUGGACUUCUCUCA -3' (SEQ ID NO:5) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), and said antisense strand comprises 5'- UGAGAGAAGUCCACCACGAUU -3' (SEQ ID NO:6) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

In another ~~aspect~~example, the present ~~invention~~disclosure provides methods of treating a subject having a Hepatitis B virus (HBV)-associated disorder. The methods include administering to the subject a therapeutically effective amount of a double stranded RNAi agent, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,

wherein said sense strand comprises 5'- UCGUGGUGGACUUCUCUCA -3' (SEQ ID NO:5) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), and said antisense strand comprises 5'- UGAGAGAAGUCCACCACGAUU -3' (SEQ ID NO:6) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

In one ~~aspect~~example, the present ~~invention~~disclosure provides methods of treating a subject having a Hepatitis B virus (HBV) infection. The methods include administering to the subject a therapeutically effective amount of a double stranded RNAi agent, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,

wherein said sense strand comprises 5'- GUGCACUUCGCUUCACCUCUA -3' (SEQ ID NO:7) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), and

said antisense strand comprises 5'- UAGAGGUGAAGCGAAGUGCACUU -3' (SEQ ID NO:8) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

In another ~~aspect~~example, the present ~~invention~~disclosure provides methods of treating a subject having a Hepatitis B virus (HBV)-associated disorder. The methods include administering to the subject a therapeutically effective amount of a double stranded RNAi agent, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,
wherein said sense strand comprises 5'- GUGCACUUCGCUUCACCUCUA -3' (SEQ ID NO:7) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), and said antisense strand comprises 5'- UAGAGGUGAAGCGAAGUGCACUU -3' (SEQ ID NO:8) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

In one ~~aspect~~example, the present ~~invention~~disclosure provides methods of treating a subject having a Hepatitis B virus (HBV) infection. The methods include administering to the subject a therapeutically effective amount of a double stranded RNAi agent, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,
wherein said sense strand comprises 5'- CGUGGUGGACUUCUCUCAAUU -3' (SEQ ID NO:9) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), and said antisense strand comprises 5'- AAUUGAGAGAAGUCCACCAGCAG -3' (SEQ ID NO:10) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more

GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

In another ~~aspect~~example, the present ~~invention~~disclosure provides methods of treating a subject having a Hepatitis B virus (HBV)-associated disorder. The methods include administering to the subject a therapeutically effective amount of a double stranded RNAi agent, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,
wherein said sense strand comprises 5'- CGUGGUGGACUUCUCUCAAUU -3' (SEQ ID NO:9) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), and said antisense strand comprises 5'- AAUUGAGAGAAGUCCACCAGCAG -3' (SEQ ID NO:10) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

In one ~~aspect~~example, the present ~~invention~~disclosure provides methods of treating a subject having a Hepatitis B virus (HBV) infection. The methods include administering to the subject a therapeutically effective amount of a double stranded RNAi agent, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,
wherein the sense strand comprises 5'- CGUGGUGGUCUUCUCUAAAUU -3' (SEQ ID NO:37), (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), and the antisense strand comprises 5'- AAUUGAGAGAAGUCCACCAGCUU -3' (SEQ ID NO:38) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

In another ~~aspect~~example, the present ~~invention~~disclosure provides methods of treating a subject having a Hepatitis B virus (HBV)-associated disorder. The methods include administering to the subject a therapeutically effective amount of a double stranded RNAi agent, wherein the double stranded RNAi agent comprises a sense strand and an antisense strand forming a

double-stranded region, wherein the sense strand comprises 5'-CGUGGUGGUCUUCUCUAAAUU -3' (SEQ ID NO:37) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), and the antisense strand comprises 5'-AAUUGAGAGAAGUCCACCAGCUU -3' (SEQ ID NO:38) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

In one ~~aspect~~example, the present ~~invention~~disclosure provides methods of treating a subject having a Hepatitis B virus (HBV) infection. The methods include administering to the subject a therapeutically effective amount of a double stranded RNAi agent, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,

wherein said sense strand comprises 5'- GGUGGACUUCUCUCAAUUUUA -3' (SEQ ID NO:11) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), and said antisense strand comprises 5'- UAAAAUUGAGAGAAGUCCACCAC -3' (SEQ ID NO:12) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

In another ~~aspect~~example, the present ~~invention~~disclosure provides methods of treating a subject having a Hepatitis B virus (HBV)-associated disorder. The methods include administering to the subject a therapeutically effective amount of a double stranded RNAi agent, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,

wherein said sense strand comprises 5'- GGUGGACUUCUCUCAAUUUUA -3' (SEQ ID NO:11) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), and said antisense strand comprises 5'- UAAAAUUGAGAGAAGUCCACCAC -3' (SEQ ID NO:12) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence),

wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

In one ~~aspect~~example, the present ~~invention~~disclosure provides methods of treating a subject having a Hepatitis B virus (HBV) infection. The methods include administering to the subject a therapeutically effective amount of a double stranded RNAi agent, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,

wherein said sense strand comprises 5'- GUGUGCACUUCGCUUCACA -3' (SEQ ID NO:39) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), and said antisense strand comprises 5'- UGUGAAGCGAAGUGCACACUU -3' (SEQ ID NO:40) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

In another ~~aspect~~example, the present ~~invention~~disclosure provides methods of treating a subject having a Hepatitis B virus (HBV)-associated disorder. The methods include administering to the subject a therapeutically effective amount of a double stranded RNAi agent, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,

wherein said sense strand comprises 5'- GUGUGCACUUCGCUUCACA -3' (SEQ ID NO:39) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), and said antisense strand comprises 5'- UGUGAAGCGAAGUGCACACUU -3' (SEQ ID NO:40) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

In one ~~embodiment~~example, all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand comprise a modification.

In one ~~embodiment~~example, the at least one of said modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, and a nucleotide comprising a 5'-phosphate mimic.

In one ~~embodiment~~example, the 5'-phosphate mimic is a 5'-vinyl phosphate (5'-VP).

In one ~~embodiment~~example, the sense strand comprises 5'-uscsguGfgUfGfGfacuucucuca – 3' (SEQ ID NO:13) and the antisense strand comprises 5'-usGfsagaGfaAfGfuccaCfcAfcgasusu – 3' (SEQ ID NO:14) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; and s is a phosphorothioate linkage.

In another ~~embodiment~~example, the sense strand comprises 5'-uscsguGfgUfGfGfacuucucuca – 3' (SEQ ID NO:15) and the antisense strand comprises 5'-PusGfsagaGfaAfGfuccaCfcAfcgasusu – 3' (SEQ ID NO:16) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; and s is a phosphorothioate linkage; and P is a 5'-phosphate or 5'phosphate mimic.

In one ~~embodiment~~example, the sense strand comprises 5'-gsusgcacUfuCfGfCfuucaccucua – 3' (SEQ ID NO:17) and the antisense strand comprises 5'-usAfsgagGfugaagcgAfaGfugcacsusu – 3' (SEQ ID NO:18) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; and s is a phosphorothioate linkage.

In another ~~embodiment~~example, the sense strand comprises 5'-gsusgcacUfuCfGfCfuucaccucua – 3' (SEQ ID NO:19) and the antisense strand comprises 5'-PusAfsgagGfugaagcgAfaGfugcacsusu – 3' (SEQ ID NO:20) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; and s is a phosphorothioate linkage; and P is a 5'-phosphate or 5'phosphate mimic.

In one ~~embodiment~~example, the sense strand comprises 5'-csgsugguGfgAfCfUfucucUfCfaauu – 3' (SEQ ID NO:21) and the antisense strand comprises 5'-asAfsuugAfgAfgAfaguCfcAfccagcsasg – 3' (SEQ ID NO:22) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are
2′-fluoro A, G, C or U; and s is a phosphorothioate linkage.

In another ~~embodiment~~example, the sense strand comprises 5'-csgsugguGfgAfCfUfucucUfCfaauu – 3' (SEQ ID NO:23) and the antisense strand comprises 5'-PasAfsuugAfgAfgAfaguCfcAfccagcsasg – 3' (SEQ ID NO:24) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are
2′-fluoro A, G, C or U; and s is a phosphorothioate linkage; and P is a 5'-phosphate or 5'phosphate mimic.

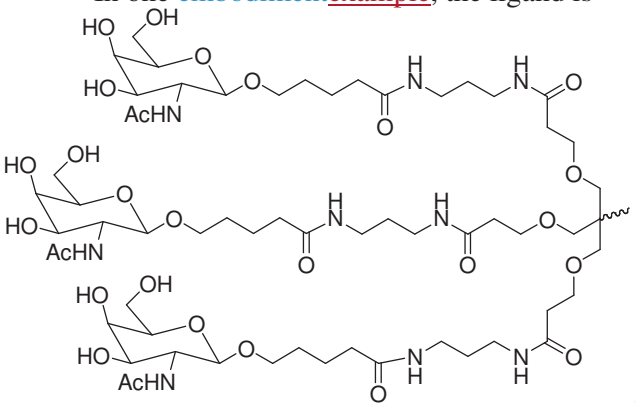
In another ~~embodiment~~example, the sense strand comprises 5'-csgsuggudGgucdTucucuaaauu – 3' (SEQ ID NO:35) and the antisense strand comprises 5'-asdAsuugagagdAagudCcaccagcsusu – 3' (SEQ ID NO:36), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; dA, dC, dG, and dT are deoxyribose A, C, G, and T; and s is a phosphorothioate linkage.

In one ~~embodiment~~example, the sense strand comprises 5'-gsgsuggaCfuUfCfUfcucaAfUfuuua – 3' (SEQ ID NO:25) and the antisense strand comprises 5'- usAfsaaaUfuGfAfgagaAfgUfccaccsasc – 3' (SEQ ID NO:26) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are
2′-fluoro A, G, C or U; and s is a phosphorothioate linkage.

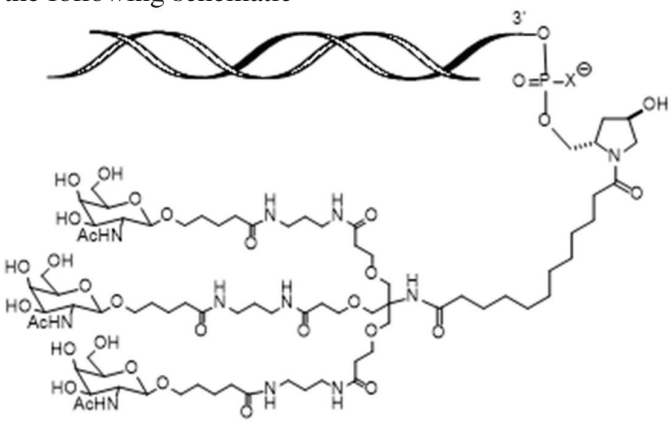
In another ~~embodiment~~example, the sense strand comprises 5'-gsgsuggaCfuUfCfUfcucaAfUfuuua – 3' (SEQ ID NO:27) and the antisense strand comprises 5'- PusAfsaaaUfuGfAfgagaAfgUfccaccsasc – 3' (SEQ ID NO:28) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are
2′-fluoro A, G, C or U; and s is a phosphorothioate linkage; and P is a 5'-phosphate or 5'phosphate mimic.

In another ~~embodiment~~example, the sense strand comprises 5'- gsusguGfcAfCfUfucgcuucaca -3' (SEQ ID NO:41) and the antisense strand comprises 5'- usGfsugaAfgCfGfaaguGfcAfcacsusu -3' (SEQ ID NO:42), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are
2′-fluoro A, G, C or U; and s is a phosphorothioate linkage.

In one ~~embodiment~~example, the ligand is



In one ~~embodiment~~example, the RNAi agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

In one ~~embodiment~~example, the HBV-associated disorder is selected from the group consisting of hepatitis D virus infection, delta hepatitis, acute hepatitis B; acute fulminant hepatitis B; chronic hepatitis B; liver fibrosis; end-stage liver disease; hepatocellular carcinoma.

In one ~~embodiment~~example, the HBV-associated disorder is chronic hepatitis and the subject is HBeAg positive. In another ~~embodiment~~example, the HBV-associated disorder is chronic hepatitis and the subject is HBeAg negative.

In one ~~aspect~~example, the present ~~invention~~disclosure provides methods of treating a subject having a Hepatitis B virus (HBV) infection. The methods include administering to the subject a therapeutically effective amount of a composition for inhibiting expression of hepatitis B virus (HBV) in a cell. The composition includes: (a) a first double-stranded RNAi agent comprising a first sense strand and a first antisense strand forming a double-stranded region, wherein substantially all of the nucleotides of said first sense strand and substantially all of the nucleotides of said first antisense strand are modified nucleotides, wherein said first sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; and

(b) a second double-stranded RNAi agent comprising a second sense strand and a second antisense strand forming a double-stranded region, wherein substantially all of the nucleotides of said second sense strand and substantially all of the nucleotides of said second antisense strand are modified nucleotides, wherein said second sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; wherein the first and second sense strands each independently comprise a sequence selected from the group consisting of

5'- UCGUGGUGGACUUCUCUCA -3' (SEQ IDNO:5),
5'- GUGCACUUCGCUUCACCUCUA -3' (SEQ IDNO:7),
5'- CGUGGUGGACUUCUCUCAAUU -3' (SEQ IDNO:9),
5'- CGUGGUGGUCUUCUCUAAAUU -3' (SEQ IDNO:37),
5'- GGUGGACUUCUCUCAAUUUUA -3' (SEQ IDNO:11), and
5'- GUGUGCACUUCGCUUCACA -3' (SEQ IDNO:39) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to any of the foregoing nucleotide sequences), and wherein the first and second antisense strands each independently comprise a sequence selected from the group consisting of
5'- UGAGAGAAGUCCACCACGAUU -3' (SEQ ID NO:6);
5'- UAGAGGUGAAGCGAAGUGCACUU -3' (SEQ ID NO:8);
5'- AAUUGAGAGAAGUCCACCAGCAG -3' (SEQ ID NO:10);
5'- AAUUGAGAGAAGUCCACCAGCUU -3' (SEQ ID NO:38),
5'- UAAAAUUGAGAGAAGUCCACCAC -3' (SEQ ID NO:12), and
5'- UGUGAAGCGAAGUGCACACUU -3' (SEQ ID NO:40) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to any of the foregoing nucleotide sequences), thereby treating the subject.

In another ~~aspect~~example, the present ~~invention~~disclosure provides methods of treating a subject having a Hepatitis B virus (HBV)-associated disorder. The methods include administering to the subject a therapeutically effective amount of a composition for inhibiting expression of hepatitis B virus (HBV) in a cell. The composition includes: (a) a first double-stranded RNAi agent comprising a first sense strand and a first antisense strand forming a double-stranded region, wherein substantially all of the nucleotides of said first sense strand and substantially all of the nucleotides of said first antisense strand are modified nucleotides, wherein said first sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; and (b) a second double-stranded RNAi agent comprising a second sense strand and a second antisense strand forming a double-stranded region, wherein substantially all of the nucleotides of said second sense strand and substantially all of the nucleotides of said second antisense strand are modified nucleotides, wherein said second sense strand is conjugated to a

ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; wherein the first and second sense strands each independently comprise a sequence selected from the group consisting of

5'- UCGUGGUGGACUUCUCUCA -3' (SEQ IDNO:5),
5'- GUGCACUUCGCUUCACCUCUA -3' (SEQ IDNO:7),
5'- CGUGGUGGACUUCUCUCAAUU -3' (SEQ IDNO:9),
5'- CGUGGUGGUCUUCUCUAAAUU -3' (SEQ IDNO:37),
5'- GGUGGACUUCUCUCAAUUUUA -3' (SEQ IDNO:11), and
5'- GUGUGCACUUCGCUUCACA -3' (SEQ IDNO:39) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to any of the foregoing nucleotide sequences), and wherein the first and second antisense strands each independently comprise a sequence selected from the group consisting of
5'- UGAGAGAAGUCCACCACGAUU -3' (SEQ ID NO:6);
5'- UAGAGGUGAAGCGAAGUGCACUU -3' (SEQ ID NO:8);
5'- AAUUGAGAGAAGUCCACCAGCAG -3' (SEQ ID NO:10);
5'- AAUUGAGAGAAGUCCACCAGCUU -3' (SEQ ID NO:38),
5'- UAAAAUUGAGAGAAGUCCACCAC -3' (SEQ ID NO:12), and
5'- UGUGAAGCGAAGUGCACACUU -3' (SEQ ID NO:40) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to any of the foregoing nucleotide sequences), thereby treating the subject.

In one ~~embodiment~~example, all of the nucleotides of the first and second sense strand and all of the nucleotides of the first and second antisense strand comprise a modification.

In one ~~embodiment~~example, the at least one of said modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, and a nucleotide comprising a 5'-phosphate mimic.

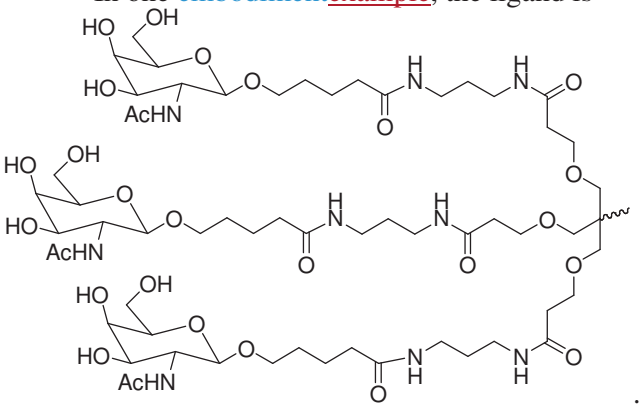
In one ~~embodiment~~example, the first and second RNAi agent are selected from the group consisting of:
5'-uscsguGfgUfGfGfacuucucuca – 3' (SEQ ID NO:13)

5’-usGfsagaGfaAfGfuccaCfcAfcgasusu – 3’ (SEQ ID NO:14);
5’-uscsguGfgUfGfGfacuucucuca – 3’ (SEQ ID NO:15)
5’-PusGfsagaGfaAfGfuccaCfcAfcgasusu – 3’ (SEQ ID NO:16);
5’-gsusgcacUfuCfGfCfuucaccucua – 3’ (SEQ ID NO:17)
5’-usAfsgagGfugaagcgAfaGfugcacsusu – 3’ (SEQ ID NO:18);
5’-gsusgcacUfuCfGfCfuucaccucua – 3’ (SEQ ID NO:19)
5’-PusAfsgagGfugaagcgAfaGfugcacsusu – 3’ (SEQ ID NO:20);
5’-csgsugguGfgAfCfUfucucUfCfaauu – 3’ (SEQ ID NO:21)
5’-asAfsuugAfgAfgAfaguCfcAfccagcsasg – 3’ (SEQ ID NO:22);
5’- csgsugguGfgAfCfUfucucUfCfaauu – 3’ (SEQ ID NO:23)
5’-PasAfsuugAfgAfgAfaguCfcAfccagcsasg – 3’ (SEQ ID NO:24);
5’-csgsuggudGgucdTucucuaaauu – 3’ (SEQ ID NO:35)
5’- asdAsuugagagdAagudCcaccagcsusu – 3’ (SEQ ID NO:36);
5’- gsgsuggaCfuUfCfUfcucaAfUfuuua – 3’ (SEQ ID NO:25)
5’- usAfsaaaUfuGfAfgagaAfgUfccaccsasc – 3’ (SEQ ID NO:26);
5’- gsgsuggaCfuUfCfUfcucaAfUfuuua – 3’ (SEQ ID NO:27)
5’- PusAfsaaaUfuGfAfgagaAfgUfccaccsasc – 3’ (SEQ ID NO:28); and
5’- gsusguGfcAfCfUfucgcuucaca -3’ (SEQ ID NO:41)
5’- usGfsugaAfgCfGfaaguGfcAfcacsusu -3’ (SEQ ID NO:42), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; dA, dC, dG, and dT are deoxyribose A, C, G, and T; s is a phosphorothioate linkage; and P is a 5’-phosphate or 5’phosphate mimic.

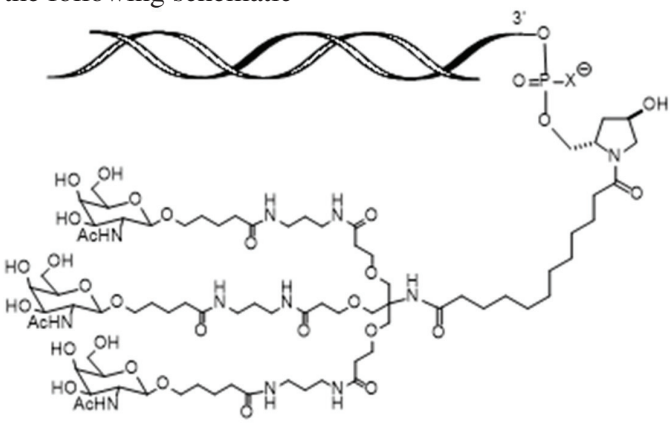
In one ~~embodiment~~example, the first and second RNAi agents are
5’-uscsguGfgUfGfGfacuucucuca – 3’ (SEQ ID NO:15)
5’-PusGfsagaGfaAfGfuccaCfcAfcgasusu – 3’ (SEQ ID NO:16); and
5’-csgsugguGfgAfCfUfucucUfCfaauu – 3’ (SEQ ID NO:21)
5’-asAfsuugAfgAfgAfaguCfcAfccagcsasg – 3’ (SEQ ID NO:22), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; s is a phosphorothioate linkage; and P is a 5’-phosphate or 5’phosphate mimic.

In another ~~embodiment~~example, the first and second RNAi agents are
5’- gsgsuggaCfuUfCfUfcucaAfUfuuua – 3’ (SEQ ID NO:25)
5’- usAfsaaaUfuGfAfgagaAfgUfccaccsasc – 3’ (SEQ ID NO:26); and
5’- gsusguGfcAfCfUfucgcuucaca -3’ (SEQ ID NO:41)
5’- usGfsugaAfgCfGfaaguGfcAfcacsusu -3’ (SEQ ID NO:42), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; s is a phosphorothioate linkage; and P is a 5’-phosphate or 5’phosphate mimic.

In one ~~embodiment~~example, the ligand is



In one ~~embodiment~~example, the RNAi agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

In one ~~embodiment~~example, the subject is a human.

In one ~~embodiment~~example, the HBV-associated disorder is selected from the group consisting of hepatitis D virus infection, delta hepatitis, acute hepatitis B; acute fulminant hepatitis B; chronic hepatitis B; liver fibrosis; end-stage liver disease; hepatocellular carcinoma.

In one ~~embodiment~~example, the HBV-associated disorder is chronic hepatitis and the subject is HBeAg positive. In another ~~embodiment~~example, the HBV-associated disorder is chronic hepatitis and the subject is HBeAg negative.

In one ~~embodiment~~example, the double stranded RNAi agent is administered at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 50 mg/kg.

In one ~~embodiment~~example, the double stranded RNAi agent is administered at a dose of about 10 mg/kg to about 30 mg/kg. In another ~~embodiment~~example, the double stranded RNAi agent is administered at a dose of about 3 mg/kg. In one ~~embodiment~~example, the double stranded RNAi agent is administered at a dose of about 10 mg/kg.

In one ~~embodiment~~example, the double stranded RNAi agent is administered at a dose of about 0.5 mg/kg twice per week.

In one ~~embodiment~~example, the double stranded RNAi agent is administered at a fixed dose of about 50 mg to 200 mg.

In one ~~embodiment~~example, the double stranded RNAi agent is administered subcutaneously. In another ~~embodiment~~example, the double stranded RNAi agent is administered intravenously.

In one ~~embodiment~~example, the RNAi agent is administered in two or more doses.

In one ~~embodiment~~example, the RNAi agent is administered at intervals selected from the group consisting of once every about 12 hours, once every about 24 hours, once every about 48 hours, once every about 72 hours, and once every about 96 hours.

In one ~~embodiment~~example, the RNAi agent is administered twice per week. In another ~~embodiment~~example, the RNAi agent is administered every other week.

In one ~~embodiment~~example, the methods of the ~~invention~~disclosure further include administering to the subject an additional therapeutic agent.

In one ~~embodiment~~example, the additional therapeutic agent is selected from the group consisting of an antiviral agent, a reverse transcriptase inhibitor, an immune stimulator, a therapeutic vaccine, a viral entry inhibitor, an oligonucleotide that inhibits the secretion or release of HbsAg, a capsid inhibitor, a cccDNA inhibitor, and a combination of any of the foregoing.

In another ~~embodiment~~example, the methods of the ~~invention~~disclosure further include administering administering to the subject a reverse transcriptase inhibitor. In yet another ~~embodiment~~example, the methods of the ~~invention~~disclosure further include administering to the subject a reverse transcriptase inhibitor and an immune stimulator.

In one ~~embodiment~~example, the reverse transcriptase inhibitor is slected from the group consisting of Tenofovir disoproxil fumarate (TDF), Tenofovir alafenamide, Lamivudine, Adefovir dipivoxil, Entecavir (ETV), Telbivudine, and AGX-1009.

In some ~~embodiment~~examples, the methods of the ~~invention~~disclosure further comprise treatment of hepatitis D virus (HDV) in the subject. Methods of treatment can include any methods of treatment known in the art. In certain ~~embodiment~~examples, HDV is treated in the subject using one of more of the iRNA agents targeting HBV as described herein.

In some ~~embodiment~~examples, the methods of the ~~invention~~disclosure further include methods to modulate, *e.g.,* decrease, the expression of PD-L1. Compositions and methods to reduce the expression of PD-L1 are provided, for example, in PCT publication no. WO2011/127180, the entire contents of which are hereby incorporated herein by reference.

In one ~~embodiment~~example, the immune stimulator is selected from the group consisting of pegylated interferon alfa 2a (PEG-IFN-α2a), Interferon alfa-2b, a recombinant human interleukin-7, and aToll-like receptor 7 (TLR7) agonist.

In a further ~~aspect~~example, the present ~~invention~~disclosure provides a method of treating a subject having a Hepatitis B virus (HBV)-associated disorder, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,

wherein the double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:29, and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:30,

wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides,

wherein the sense strand is conjugated to a ligand attached at the 3'-terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

In another ~~aspect~~example, the present ~~invention~~disclosure also provides a method of treating a subject having a Hepatitis B virus (HBV) infection, comprising administering to the subject a therapeutically effective amount of a composition for inhibiting expression of hepatitis B virus (HBV) in a cell, said composition comprising

(a) a first double-stranded RNAi agent comprising a first strand and a first antisense strand forming a double-stranded region,

wherein substantially all of the nucleotides of the first sense strand and substantially all of the nucleotides of the first antisense strand are modified nucleotides,

wherein said first sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; and

(b) a second double-stranded RNAi agent comprising a second sense strand and a second antisense strand forming a double-stranded region,

wherein substantially all of the nucleotides of the second sense strand and substantially all of the nucleotides of the second antisense strand are modified nucleotides,

wherein the second sense strand is conjugated to a ligand attached at the 3'-terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker;

wherein the first sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1, and said first antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2,

wherein the sense second strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:29, and the second antisense strand comprises at least 15 contiguous nucleotides differing by no more

than 3 nucleotides from the nucleotide sequence of SEQ ID NO:30, thereby treating the subject.

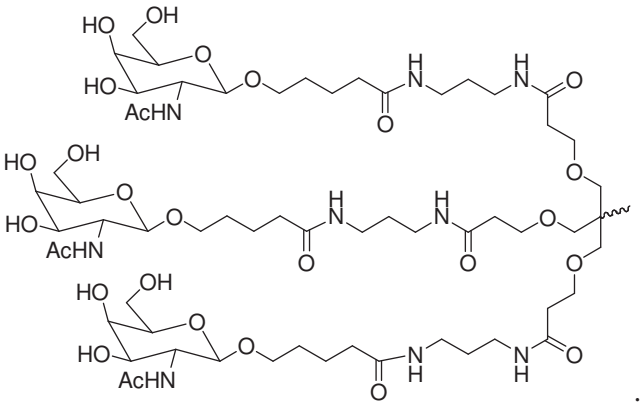
In some ~~embodiment~~examples, the first sense strand comprises a sequence selected from the group consisting of

5'- UCGUGGUGGACUUCUCUCA -3' (SEQ IDNO:5),
5'- GUGCACUUCGCUUCACCUCUA -3' (SEQ IDNO:7),
5'- CGUGGUGGACUUCUCUCAAUU -3' (SEQ IDNO:9),
5'- CGUGGUGGUCUUCUCUAAAUU -3' (SEQ IDNO:37)
5'- GGUGGACUUCUCUCAAUUUUA -3' (SEQ IDNO:11), and
5'- GUGUGCACUUCGCUUCACA -3' (SEQ IDNO:39), (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequences), and the second antisense strand comprises a sequence selected from the group consisting of
5'- UGAGAGAAGUCCACCACGAUU -3' (SEQ ID NO:6);
5'- UAGAGGUGAAGCGAAGUGCACUU -3' (SEQ ID NO:8);
5'- AAUUGAGAGAAGUCCACCAGCAG -3' (SEQ ID NO:10);
5'- AAUUGAGAGAAGUCCACCAGCUU -3' (SEQ ID NO:38);
5'- UAAAAUUGAGAGAAGUCCACCAC -3' (SEQ ID NO:12); and
5'- UGUGAAGCGAAGUGCACACUU -3' (SEQ ID NO:40) (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequences).

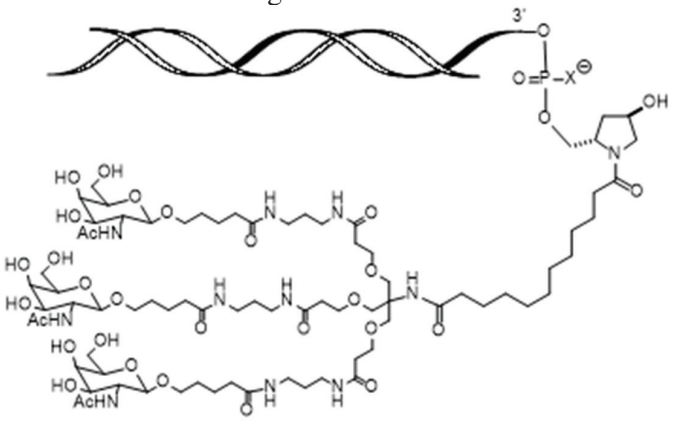
In some ~~aspect~~examples, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

In certain ~~embodiment~~examples, at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, and a nucleotide comprising a 5'-phosphate mimic.

In some ~~embodiment~~examples, the ligand is



In a specific ~~embodiment~~example, the RNAi agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

In certain ~~embodiment~~examples, the double stranded RNAi agents and compositions provided herein are used for treatment of an HDV infection and/or an HDV-associated disorder.

Accordingly, the present ~~invention~~disclosure provides methods of inhibiting replication of a Hepatitis D virus (HDV) in a cell. The methods include (a) contacting the cell with a double stranded RNAi agent, composition, vector, or the pharmaceutical composition provided herein; and (b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of an HBV gene, thereby inhibiting replication of the HDV in the cell.

In certain ~~embodiment~~examples, the cell is within a subject. In certain ~~embodiment~~examples, the subject is a human.

The ~~invention~~disclosure further provides methods of reducing the level of a Hepatitis D virus (HDV) antigen in a subject infected with HDV. The methods include administering to the subject a therapeutically effective amount of a double stranded RNAi agent, composition, vector, or the pharmaceutical composition provided herein, thereby reducing the level of the HDV antigen, *e.g.,* S-HDAg or L-HDAg, in the subject.

The ~~invention~~disclosure also provides methods of reducing the viral load of Hepatitis D virus (HDV) in a subject infected with HDV. The methods include administering to the subject a therapeutically effective amount of a double stranded RNAi agent, composition, vector, or pharmaceutical composition provided herein, thereby reducing the viral load of HDV in the subject.

The ~~invention~~disclosure also provides methods of treating a subject having a Hepatitis D virus (HDV) infection, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent, composition, vector, or pharmaceutical composition provided herein, thereby treating the subject.

In certain ~~embodiment~~examples, the double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region. Sense strand and antisense strands can be selected from the following RNAi agents wherein, the sense strand comprises 5'- UCGUGGUGGACUUCUCUCA -3' (SEQ ID NO:5), and the antisense strand comprises 5'- UGAGAGAAGUCCACCACGAUU -3' (SEQ ID NO:6); the sense strand comprises 5'- GUGCACUUCGCUUCACCUCUA -3' (SEQ ID NO:7), and the antisense strand comprises 5'- UAGAGGUGAAGCGAAGUGCACUU -3' (SEQ ID NO:8); the sense strand comprises 5'- CGUGGUGGACUUCUCUCAAUU -3' (SEQ IDNO:9), and the antisense strand comprises 5'- AAUUGAGAGAAGUCCACCAGCAG -3' (SEQ ID NO:10); the sense strand comprises 5'- CGUGGUGGUCUUCUCUAAAUU -3' (SEQ ID NO:37), and the antisense strand comprises 5'- AAUUGAGAGAAGUCCACCAGCUU -3' (SEQ ID NO:38); the sense strand comprises 5'- GGUGGACUUCUCUCAAUUUUA -3' (SEQ ID NO:11), and the antisense strand comprises 5'- UAAAAUUGAGAGAAGUCCACCAC -3' (SEQ ID NO:12); or the sense strand comprises 5'- GUGUGCACUUCGCUUCACA -3' (SEQ ID NO:39), and the antisense strand comprises 5'- UGUGAAGCGAAGUGCACACUU -3' (SEQ ID NO:40), wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, wherein the sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

In certain ~~embodiment~~examples, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification. In certain ~~embodiment~~examples, at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a

non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, and a nucleotide comprising a 5'-phosphate mimic. In certain ~~embodiment~~examples, the 5'-phosphate mimic is a 5'-vinyl phosphate (5'-VP).

In certain ~~embodiment~~examples, the sense strand comprises 5'-uscsguGfgUfGfGfacuucucuca – 3' (SEQ ID NO:13) and the antisense strand comprises 5'-usGfsagaGfaAfGfuccaCfcAfcgasusu – 3' (SEQ ID NO:14) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; and s is a phosphorothioate linkage.

In certain ~~embodiment~~examples, the sense strand comprises 5'-uscsguGfgUfGfGfacuucucuca – 3' (SEQ ID NO:15) and the antisense strand comprises 5'-PusGfsagaGfaAfGfuccaCfcAfcgasusu – 3' (SEQ ID NO:16) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; and s is a phosphorothioate linkage; and P is a 5'-phosphate or 5'phosphate mimic.

In certain ~~embodiment~~examples, the sense strand comprises 5'-gsusgcacUfuCfGfCfuucaccucua – 3' (SEQ ID NO:17) and the antisense strand comprises 5'-usAfsgagGfugaagcgAfaGfugcacsusu – 3' (SEQ ID NO:18) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; and s is a phosphorothioate linkage.

In certain ~~embodiment~~examples, the sense strand comprises 5'-gsusgcacUfuCfGfCfuucaccucua – 3' (SEQ ID NO:19) and the antisense strand comprises 5'-PusAfsgagGfugaagcgAfaGfugcacsusu – 3' (SEQ ID NO:20) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; and s is a phosphorothioate linkage; and P is a 5'-phosphate or 5'phosphate mimic.

In certain ~~embodiment~~examples, sense strand comprises 5'-csgsugguGfgAfCfUfucucUfCfaauu – 3' (SEQ ID NO:21) and the antisense strand comprises 5'-AfsuugAfgAfgAfaguCfcAfccagcsasg – 3' (SEQ ID NO:22) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are
2′-fluoro A, G, C or U; and s is a phosphorothioate linkage.

In certain ~~embodiment~~examples, the sense strand comprises 5'-csgsugguGfgAfCfUfucucUfCfaauu – 3' (SEQ ID NO:23) and the antisense strand comprises 5'-PasAfsuugAfgAfgAfaguCfcAfccagcsasg – 3' (SEQ ID NO:24) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are

2′-fluoro A, G, C or U; and s is a phosphorothioate linkage; and P is a 5’-phosphate or 5’phosphate mimic.

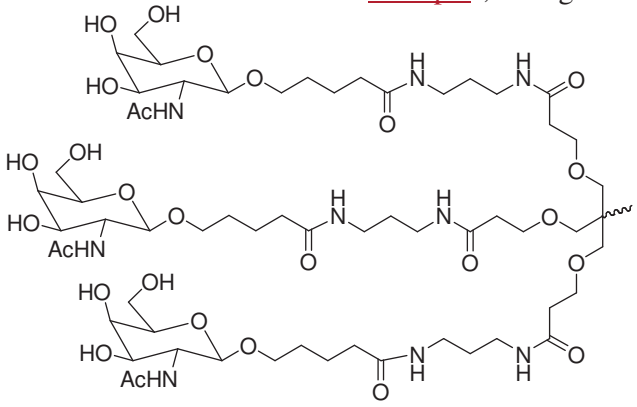
In certain ~~embodiment~~examples, the sense strand comprises 5’-csgsuggudGgucdTucucuaaauu – 3’ (SEQ ID NO:35) and the antisense strand comprises 5’- asdAsuugagagdAagudCcaccagcsusu – 3’ (SEQ ID NO:36), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; dA, dC, dG, and dT are deoxyribose A, C, G, and T; and s is a phosphorothioate linkage.

In certain ~~embodiment~~examples, the sense strand comprises 5’- gsgsuggaCfuUfCfUfcucaAfUfuuua – 3’ (SEQ ID NO:25) and the antisense strand comprises 5’- usAfsaaaUfuGfAfgagaAfgUfccaccsasc – 3’ (SEQ ID NO:26) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; and s is a phosphorothioate linkage.

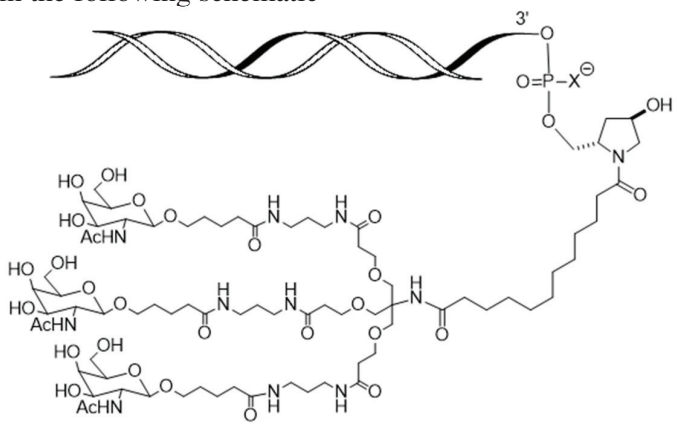
In certain ~~embodiment~~examples, the sense strand comprises 5’- gsgsuggaCfuUfCfUfcucaAfUfuuua – 3’ (SEQ ID NO:27) and the antisense strand comprises 5’- PusAfsaaaUfuGfAfgagaAfgUfccaccsasc – 3’ (SEQ ID NO:28) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; and s is a phosphorothioate linkage; and P is a 5’-phosphate or 5’phosphate mimic.

In certain ~~embodiment~~examples, sense strand comprises 5’- gsusguGfcAfCfUfucgcuucaca -3’ (SEQ ID NO:41) and the antisense strand comprises 5’- usGfsugaAfgCfGfaaguGfcAfcacsusu -3’ (SEQ ID NO:42), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; and s is a phosphorothioate linkage.

In certain ~~embodiment~~examples, the ligand is



In certain ~~embodiment~~examples, the RNAi agent is conjugated to the ligand as shown in the following schematic



, wherein X is O or S.

The ~~invention~~disclosure provides methods of treating a subject having a Hepatitis D virus (HDV) infection. The methods include administering to the subject a therapeutically effective amount of a composition for inhibiting expression of hepatitis B virus (HBV) in a cell, the composition comprising (a) a first double-stranded RNAi agent comprising a first sense strand and a first antisense strand forming a double-stranded region, wherein substantially all of the nucleotides of the first sense strand and substantially all of the nucleotides of the first antisense strand are modified nucleotides, wherein the first sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; and (b) a second double-stranded RNAi agent comprising a second sense strand and a second antisense strand forming a double-stranded region, wherein substantially all of the nucleotides of the second sense strand and substantially all of the nucleotides of the second antisense strand are modified nucleotides, wherein the second sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; wherein the first and second sense strands each independently comprise a sequence selected from the group consisting of

5'- UCGUGGUGGACUUCUCUCA -3' (SEQ ID NO:5),
5'- GUGCACUUCGCUUCACCUCUA -3' (SEQ ID NO:7),
5'- CGUGGUGGACUUCUCUCAAUU -3' (SEQ ID NO:9),
5'- CGUGGUGGUCUUCUCUAAAUU -3' (SEQ ID NO:37),
5'- GGUGGACUUCUCUCAAUUUUA -3' (SEQ ID NO:11), and
5'- GUGUGCACUUCGCUUCACA -3' (SEQ IDNO:39), and wherein the first and second antisense strands each independently comprise a sequence selected from the group consisting of

5'- UGAGAGAAGUCCACCACGAUU -3' (SEQ ID NO:6);
5'- UAGAGGUGAAGCGAAGUGCACUU -3' (SEQ ID NO:8);
5'- AAUUGAGAGAAGUCCACCAGCAG -3' (SEQ ID NO:10);

5’- AAUUGAGAGAAGUCCACCAGCUU -3’ (SEQ ID NO:38),
5’- UAAAAUUGAGAGAAGUCCACCAC -3’ (SEQ ID NO:12), and
5’- UGUGAAGCGAAGUGCACACUU -3’ (SEQ ID NO:40), thereby treating the subject.

In certain ~~embodiment~~examples, all of the nucleotides of the first and second sense strand and all of the nucleotides of the first and second antisense strand comprise a modification. In certain ~~embodiment~~examples, at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3’-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2’-amino-modified nucleotide, a 2’-O-allyl-modified nucleotide, 2’-C-alkyl-modified nucleotide, 2’-hydroxly-modified nucleotide, a 2’-methoxyethyl modified nucleotide, a 2’-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5’-phosphate, and a nucleotide comprising a 5’-phosphate mimic.

In certain ~~embodiment~~examples, the first and second RNAi agent are selected from the group:
5’-uscsguGfgUfGfGfacuucucuca – 3’ (SEQ ID NO:13)
5’-usGfsagaGfaAfGfuccaCfcAfcgasusu – 3’ (SEQ ID NO:14);
5’-uscsguGfgUfGfGfacuucucuca – 3’ (SEQ ID NO:15)
5’-PusGfsagaGfaAfGfuccaCfcAfcgasusu – 3’ (SEQ ID NO:16);
5’-gsusgcacUfuCfGfCfuucaccucua – 3’ (SEQ ID NO:17)
5’-usAfsgagGfugaagcgAfaGfugcacsusu – 3’ (SEQ ID NO:18);
5’-gsusgcacUfuCfGfCfuucaccucua – 3’ (SEQ ID NO:19)
5’-PusAfsgagGfugaagcgAfaGfugcacsusu – 3’ (SEQ ID NO:20);
5’-csgsugguGfgAfCfUfucucUfCfaauu – 3’ (SEQ ID NO:21)
5’-asAfsuugAfgAfgAfaguCfcAfccagcsasg – 3’ (SEQ ID NO:22);
5’- csgsugguGfgAfCfUfucucUfCfaauu – 3’ (SEQ ID NO:23)
5’-PasAfsuugAfgAfgAfaguCfcAfccagcsasg – 3’ (SEQ ID NO:24);
5’-csgsuggudGgucdTucucuaaauu – 3’ (SEQ ID NO:35)
5’- asdAsuugagagdAagudCcaccagcsusu – 3’ (SEQ ID NO:36);
5’- gsgsuggaCfuUfCfUfcucaAfUfuuua – 3’ (SEQ ID NO:25)
5’- usAfsaaaUfuGfAfgagaAfgUfccaccsasc – 3’ (SEQ ID NO:26);
5’- gsgsuggaCfuUfCfUfcucaAfUfuuua – 3’ (SEQ ID NO:27)
5’- PusAfsaaaUfuGfAfgagaAfgUfccaccsasc – 3’ (SEQ ID NO:28); and
5’- gsusguGfcAfCfUfucgcuucaca -3’ (SEQ ID NO:41)

5’- usGfsugaAfgCfGfaaguGfcAfcacsusu -3’ (SEQ ID NO:42), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; dA, dC, dG, and dT are deoxyribose A, C, G, and T; s is a phosphorothioate linkage; and P is a 5’-phosphate or 5’phosphate mimic.

In certain ~~embodiment~~examples, the first and second RNAi agents are

5’-uscsguGfgUfGfGfacuucucuca – 3’ (SEQ ID NO:15)

5’-PusGfsagaGfaAfGfuccaCfcAfcgasusu – 3’ (SEQ ID NO:16); and

5’-csgsugguGfgAfCfUfucucUfCfaauu – 3’ (SEQ ID NO:21)

5’-asAfsuugAfgAfgAfaguCfcAfccagcsasg – 3’ (SEQ ID NO:22), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; s is a phosphorothioate linkage; and P is a 5’-phosphate or 5’phosphate mimic.

In certain ~~embodiment~~examples, the first and second RNAi agents are

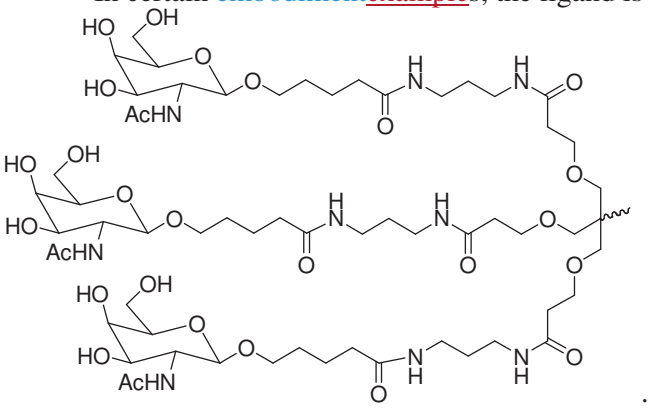
5’- gsgsuggaCfuUfCfUfcucaAfUfuuua – 3’ (SEQ ID NO:25)

5’- usAfsaaaUfuGfAfgagaAfgUfccaccsasc – 3’ (SEQ ID NO:26); and

5’- gsusguGfcAfCfUfucgcuucaca -3’ (SEQ ID NO:41)

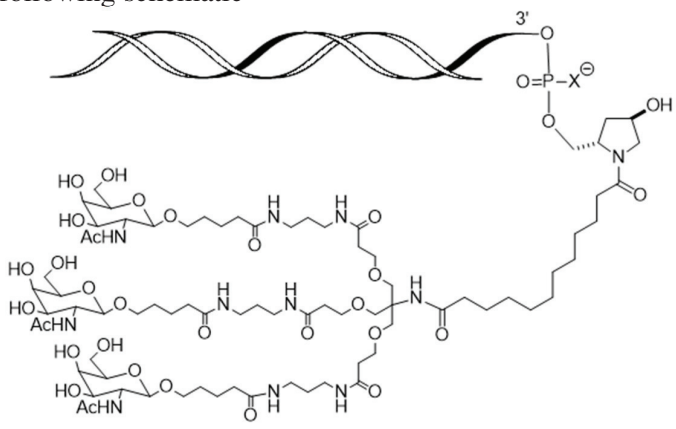
5’- usGfsugaAfgCfGfaaguGfcAfcacsusu -3’ (SEQ ID NO:42), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; s is a phosphorothioate linkage; and P is a 5’-phosphate or 5’phosphate mimic.

In certain ~~embodiment~~examples, the ligand is



.

In certain ~~embodiment~~examples, the RNAi agent is conjugated to the ligand as shown in the following schematic



, wherein X is O or S.

In certain ~~embodiment~~examples, the subject is a human.

In certain ~~embodiment~~examples, the double stranded RNAi agent is administered at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 50 mg/kg. In certain ~~embodiment~~examples, the double stranded RNAi agent is administered at a dose of about 10 mg/kg to about 30 mg/kg. In certain ~~embodiment~~examples, the double stranded RNAi agent is administered at a dose of about 3 mg/kg. In certain ~~embodiment~~examples, the double stranded RNAi agent is administered at a dose of about 10 mg/kg. In certain ~~embodiment~~examples, the double stranded RNAi agent is administered at a dose of about 0.5 mg/kg twice per week. In certain ~~embodiment~~examples, the double stranded RNAi agent is administered at a fixed dose of about 50 mg to 200 mg.

In certain ~~embodiment~~examples, the double stranded RNAi agent is administered subcutaneously.

In certain ~~embodiment~~examples, the double stranded RNAi agent is administered intravenously.

In certain ~~embodiment~~examples, the RNAi agent is administered in two or more doses. In certain ~~embodiment~~examples, the RNAi agent is administered at intervals selected from the group consisting of once every about 12 hours, once every about 24 hours, once every about 48 hours, once every about 72 hours, and once every about 96 hours. In certain ~~embodiment~~examples, the RNAi agent is administered twice per week. In certain ~~embodiment~~examples, the RNAi agent is administered every other week. In certain ~~embodiment~~examples, the RNAi agent is administered once per month. In certain ~~embodiment~~examples, the RNAi agent is administered once every other month. In certain ~~embodiment~~examples, the RNAi agent is administered once every three months.

In certain ~~embodiment~~examples, the RNAi agent is administered to the subject with an additional therapeutic agent. Additional therapeutic agents include, for example, an antiviral agent, a reverse transcriptase inhibitor, an immune stimulator, a therapeutic vaccine, a viral entry inhibitor, an oligonucleotide that inhibits the secretion or release of HbsAg, a capsid inhibitor, a covalently closed circular (ccc) HBV DNA inhibitor, and a combination of any of the foregoing.

In certain ~~embodiment~~examples, the additional agent is a reverse transcriptase inhibitor. In certain ~~embodiment~~examples, the additional agent is a reverse transcriptase inhibitor and an immune stimulator. Exemplary reverse transcriptase inhibitors include Tenofovir disoproxil fumarate (TDF), Tenofovir alafenamide, Lamivudine, Adefovir dipivoxil, Entecavir (ETV), Telbivudine, and AGX-1009. Exemplary immune stimulators include pegylated interferon alfa 2a (PEG-IFN-α2a), Interferon alfa-2b, a recombinant human interleukin-7, and a Toll-like receptor 7 (TLR7) agonist.

The ~~invention~~disclosure further provides methods of treating a subject having a Hepatitis D virus (HDV) infection, comprising administering to the subject a therapeutically effective amount of a composition for inhibiting expression of hepatitis B virus (HBV) in a cell, the composition comprising (a) a first double-stranded RNAi agent comprising a first strand and a first antisense strand forming a double-stranded region, wherein substantially all of the nucleotides of the first sense strand and substantially all of the nucleotides of the first antisense strand are modified nucleotides, wherein the first sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; and (b) a second double-stranded RNAi agent comprising a second sense strand and a second antisense strand forming a double-stranded region, wherein substantially all of the nucleotides of the second sense strand and substantially all of the nucleotides of the second antisense strand are modified nucleotides, wherein the second sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; wherein the first sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1, and the first antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2, wherein the sense second strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:29, and the second antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:30, thereby treating the subject.

In certain ~~embodiment~~examples, the first sense strand comprises a sequence selected from the group consisting of

5'- UCGUGGUGGACUUCUCUCA -3' (SEQ IDNO:5),
5'- GUGCACUUCGCUUCACCUCUA -3' (SEQ ID NO:7),
5'- CGUGGUGGACUUCUCUCAAUU -3' (SEQ ID NO:9),
5'- CGUGGUGGUCUUCUCUAAAUU -3' (SEQ ID NO:37),
5'- GGUGGACUUCUCUCAAUUUUA -3' (SEQ ID NO:11), and
5'- GUGUGCACUUCGCUUCACA -3' (SEQ IDNO:39), and

the second antisense strand comprises a sequence selected from the group consisting of

5’- UGAGAGAAGUCCACCACGAUU -3’ (SEQ ID NO:6);

5’- UAGAGGUGAAGCGAAGUGCACUU -3’ (SEQ ID NO:8);

5’- AAUUGAGAGAAGUCCACCAGCAG -3’ (SEQ ID NO:10);

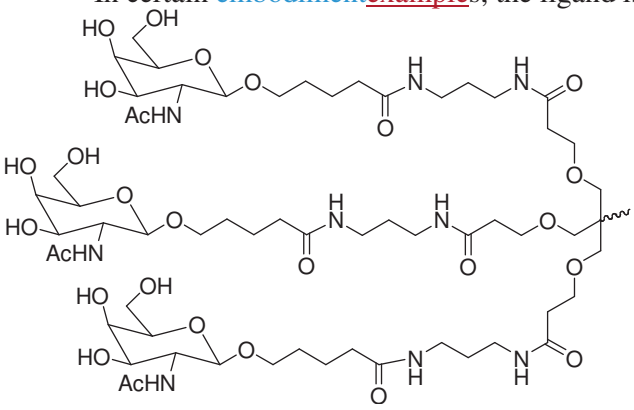
5’- AAUUGAGAGAAGUCCACCAGCUU -3’ (SEQ ID NO:38),

5’- UAAAAUUGAGAGAAGUCCACCAC -3’ (SEQ ID NO:12), and

5’- UGUGAAGCGAAGUGCACACUU -3’ (SEQ ID NO:40).

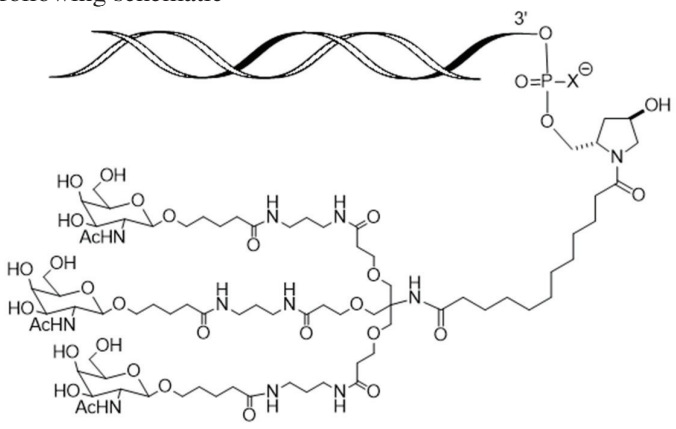
In certain ~~embodiment~~examples, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification. In certain ~~embodiment~~examples, the additional agent is at least one of the modified nucleotides is selected from the group consisting of a dexoy-nucleotide, a 3’-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2’-amino-modified nucleotide, a 2’-O-allyl-modified nucleotide, 2’-C-alkyl-modified nucleotide, 2’-hydroxly-modified nucleotide, a 2’-methoxyethyl modified nucleotide, a 2’-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5’-phosphate, and a nucleotide comprising a 5’-phosphate mimic.

In certain ~~embodiment~~examples, the ligand is



.

In certain ~~embodiment~~examples, the RNAi agent is conjugated to the ligand as shown in the following schematic



, wherein X is O or S.

In one aspect, the present disclosure relates to a double stranded RNAi agent for inhibiting expression of hepatitis B virus (HBV) in a cell, wherein the double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises 5'- GGUGGACUUCUCUCAAUUUUA -3' (SEQ ID NO: 11), and the antisense strand comprises 5'- UAAAAUUGAGAGAAGUCCACCAC -3' (SEQ ID NO: 12), wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides, wherein the sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In another aspect, the present disclosure relates to a composition for inhibiting expression of hepatitis B virus (HBV) in a cell, comprising: (a) a first double-stranded RNAi agent comprising a first sense strand and a first antisense strand forming a first double-stranded region, wherein the first sense strand comprises 5'-GGUGGACUUCUCUCAAUUUUA -3' (SEQ ID NO: 11), and the first antisense strand comprises 5'- UAAAAUUGAGAGAAGUCCACCAC -3' (SEQ ID NO: 12), wherein all of the nucleotides of the first sense strand and all of the nucleotides of the first antisense strand are modified nucleotides, wherein the first sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; and (b) a second double-stranded RNAi agent comprising a second sense strand and a second antisense strand forming a second double-stranded region, wherein the second sense strand comprises 5'-GUGUGCACUUCGCUUCACA -3' (SEQ ID NO: 39), and the second antisense strand comprises 5'-UGUGAAGCGAAGUGCACACUU -3' (SEQ ID NO: 40), wherein all of the nucleotides of the second sense strand and all of the nucleotides of the second antisense strand are modified nucleotides, wherein the second sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In another aspect, the present disclosure relates to a cell containing the double stranded RNAi agent as disclosed herein.

In another aspecit, the present disclosure relates to a pharmaceutical composition comprising: (a) (i) the double stranded RNAi agent as disclosed herein, or (ii) the composition as disclosed herein; and (b) an unbuffered solution or a buffer solution.

In another aspect, the present disclosure relates to the use of the double stranded RNAi agent as disclosed herein, the composition as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for reducing the viral load of Hepatitis B virus (HBV) in a subject infected with HBV.

In another aspect, the present disclosure relates to the use of the double stranded RNAi agent as disclosed herein, the composition as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating Hepatitis B virus (HBV) infection in a subject.

In another aspect, the present disclosure relates to the of the double stranded RNAi agent as disclosed herein, the composition as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating Hepatitis B virus (HBV)-associated disorder in a subject.

The present ~~invention~~disclosure is further illustrated by the following detailed description and drawings.

Brief Description of the Drawings

Figure 1 schematically depicts the structure of the approximately 3.2 kb double-stranded HBV genome. Replication of the HBV genome occurs through an RNA intermediate and produces 4 overlapping viral transcripts (an about 3.5 kb transcript, an about 2.4 kb transcript, an about 2.1 kb transcript, and an about 0.7 kb transcript) encoding seven viral proteins (pre-S1, pre-S2, S, P, X, pre-C and C) translated across three reading frames.

Figure 2 is a graph depicting the log decrease of HBsAg serum levels normalized to pre-dose HBsAg serum levels following administration of a single 3 mg/kg dose of the indicated iRNA agents.

Figure 3 is a graph depicting the log decrease of HBsAg serum levels normalized to pre-dose HBsAg serum levels following administration of a single 3 mg/kg dose of the indicated iRNA agents.

Figure 4 is a graph depicting the percent of pre-dose HBsAg remaining at days 5 and 10 following administration of a single 3 mg/kg dose of the indicated iRNA agents. Figure 4 also depicts the percent of HBsAG remaining at day 10 post-dose relative to the percent of HBsAG remaining at day 10 post-dose in an animal administered 3 mg/kg of a control dsRNA targeting mouse/rat transtherytin (mrTTR).

Figure 5 is a graph depicting the log decrease of HBsAg serum levels normalized to pre-dose HBsAg serum levels following administration of a single 3 mg/kg dose of AD-65403.

Figure 6A is a graph depicting the decrease of HBsAg serum levels normalized to pre-dose HBsAg serum levels on a standard linear scale following administration of a single subcutaneous 0.3 mg/kg, 1 mg/kg, 3 mg/kg, or 9 mg/kg dose of AD-66810.

Table 25. Unmodified HBV X ORF Sense and Antisense Sequences.

DuplexID	Sense Sequence Unmodified (5' to 3')	SEQ ID NO:	Antisense Sequence Umodified (5' to 3')	SEQ ID NO:
AD-66808	GUCUGUGCCUUCUCAUCUA	~~1207~~1253	UAGAUGAGAAGGCACAGACUU	1263
AD-66809	GUCUGUGCCUUCUCAUCUA	~~1208~~1254	UAGAUGAGAAGGCACAGACUU	1264
AD-66810	GUGUGCACUUCGCUUCACA	~~1209~~1255	UGUGAAGCGAAGUGCACACUU	1265
AD-66811	GUGUGCACUUCGCUUCACA	~~1210~~1256	UGUGAAGCGAAGUGCACACUU	1266
AD-66812	UGUGCACUUCGCUUCACCUCU	~~1211~~1257	AGAGGUGAAGCGAAGUGCACAUU	1267
AD-66813	UGUGCACUUCGCUUCACCUCU	~~1212~~1258	AGAGGUGAAGCGAAGUGCACAUU	1268
AD-66814	CACCAGCACCAUGCAACUUUU	~~1213~~1259	AAAAGUUGCAUGGUGCUGGUGUU	1269
AD-66815	CACCAGCACCAUGCAACUUUU	~~1214~~1260	AAAAGUUGCAUGGUGCUGGUGUU	1270
AD-66816	CACCAUGCAACUUUUUCACCU	~~1215~~1261	AGGUGAAAAAGUUGCAUGGUGUU	1271
AD-66817	CACCAUGCAACUUUUUCACCU	~~1216~~1262	AGGUGAAAAAGUUGCAUGGUGUU	1272

We claim:

1. A double stranded RNAi agent for inhibiting expression of hepatitis B virus (HBV) in a cell, wherein ~~said~~ the double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises 5'-GGUGGACUUCUCUCAAUUUUA -3' (SEQ ID NO: 11), and the antisense strand comprises 5'- UAAAAUUGAGAGAAGUCCACCAC -3' (SEQ ID NO: 12), ~~said sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1, and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2,~~

wherein ~~substantially~~ all of the nucleotides of ~~said~~ the sense strand and ~~substantially~~ all of the nucleotides of ~~said~~ the antisense strand are modified nucleotides,

wherein ~~said~~ the sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

~~2. The double stranded RNAi agent of claim 1, wherein one or more of the 3 nucleotide differences in the nucleotide sequence of the antisense strand is a nucleotide mismatch in the antisense strand.~~

~~3. The double stranded RNAi agent of claim 1, wherein one or more of the 3 nucleotide differences in the nucleotide sequence of the antisense strand is a nucleotide mismatch in the sense strand.~~

~~4. The double stranded RNAi agent of claim 1, wherein all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand are modified nucleotides.~~

~~5. The double stranded RNAi agent of claim 1, wherein said sense strand and said antisense strand comprise a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the sequences listed in any one of Tables 3, 4, 6, 7, 12, 13, 22, 23, 25, and 26.~~

~~6~~2. The double stranded RNAi agent of ~~any one of claims 1-5~~ claim 1, wherein at least one of ~~said~~ the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, ~~2'-hydroxly-modified nucleotide~~, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, and a nucleotide comprising a 5'-phosphate mimic.

~~7. The double stranded RNAi agent of any claim 1, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.~~

~~8. The double stranded RNAi agent of claim 1, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.~~

~~9. The double stranded RNAi agent of claim 1, wherein the double-stranded region is 15-30 nucleotide pairs in length.~~

~~10. The double stranded RNAi agent of claim 1, wherein the double-stranded region is 17-23 nucleotide pairs in length.~~

~~11. The double stranded RNAi agent of claim 1, wherein the double-stranded region is 17-25 nucleotide pairs in length.~~

~~12. The double stranded RNAi agent of claim 1, wherein the double-stranded region is 23-27 nucleotide pairs in length.~~

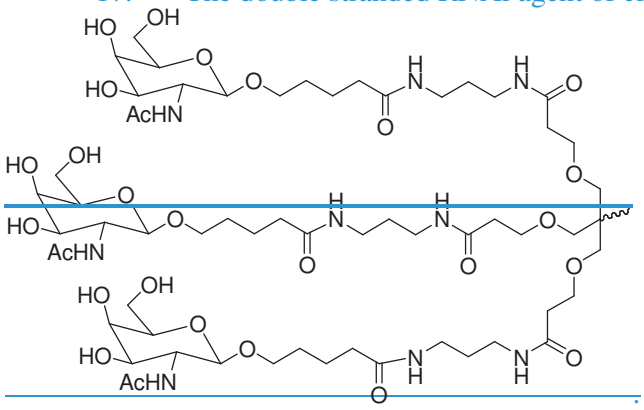
~~13. The double stranded RNAi agent of claim 1, wherein the double-stranded region is 19-21 nucleotide pairs in length.~~

~~14. The double stranded RNAi agent of claim 1, wherein the double-stranded region is 21-23 nucleotide pairs in length.~~

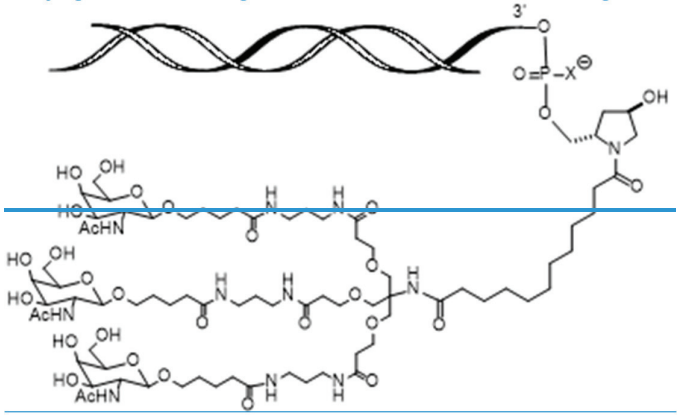
~~15. The double stranded RNAi agent of claim 1, wherein each strand has 15-30 nucleotides.~~

~~16. The double stranded RNAi agent of claim 1, wherein each strand has 19-30 nucleotides.~~

~~17. The double stranded RNAi agent of claim 1, wherein the ligand is~~



~~18. The double stranded RNAi agent of claim 1, wherein the RNAi agent is conjugated to the ligand as shown in the following schematic~~



~~wherein X is O or S.~~

~~19. The double stranded RNAi agent of claim 1, wherein said RNAi agent is selected from the group of RNAi agents listed in any one of Tables 3, 4, 6, 7, 12, 13, 22, 23, 25, and 26.~~

~~20. A double stranded RNAi agent for inhibiting expression of hepatitis B virus (HBV) in a cell, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,~~

~~wherein said sense strand comprises 5' GUGUGCACUUCGCUUCACA 3' (SEQ IDNO:39), and said antisense strand comprises 5' UGUGAAGCGAAGUGCACACUU 3' (SEQ ID NO:40),~~

~~wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,~~

~~wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and~~

~~wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.~~

~~21. A double stranded RNAi agent for inhibiting expression of hepatitis B virus (HBV) in a cell, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,~~

~~wherein said sense strand comprises 5' GGUGGACUUCUCUCAAUUUUA 3' (SEQ IDNO:11), and said antisense strand comprises 5' UAAAAUUGAGAGAAGUCCACCAC -3' (seq id no:12),~~

~~wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,~~

~~wherein said sense strand is conjugated to a ligand attached at the 3' terminus, and~~

~~wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.~~

~~22. A double stranded RNAi agent for inhibiting expression of hepatitis B virus (HBV) in a cell, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,~~

~~wherein said sense strand comprises 5' UCGUGGUGGACUUCUCUCA 3' (SEQ IDNO:5), and said antisense strand comprises 5' UGAGAGAAGUCCACCACGAUU 3' (SEQ ID NO:6),~~

~~wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,~~

~~wherein said sense strand is conjugated to a ligand attached at the 3' terminus, and~~

~~wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.~~

~~23. A double stranded RNAi agent for inhibiting expression of hepatitis B virus (HBV) in a cell, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,~~

~~wherein said sense strand comprises 5' GUGCACUUCGCUUCACCUCUA 3' (SEQ IDNO:7), and said antisense strand comprises 5' UAGAGGUGAAGCGAAGUGCACUU 3' (SEQ ID NO:8),~~

~~wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,~~

~~wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and~~

~~wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.~~

~~24. A double stranded RNAi agent for inhibiting expression of hepatitis B virus (HBV) in a cell, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,~~

~~wherein said sense strand comprises 5' CGUGGUGGACUUCUCUCAAUU 3' (SEQ IDNO:9), and said antisense strand comprises 5' AAUUGAGAGAAGUCCACCAGCAG 3' (SEQ ID NO:10),~~

~~wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,~~

~~wherein said sense strand is conjugated to a ligand attached at the 3' terminus, and~~

~~wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.~~

~~25. A double stranded RNAi agent for inhibiting expression of hepatitis B virus (HBV) in a cell, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,~~

~~wherein said sense strand comprises 5' CGUGGUGGUCUUCUCUAAAUU 3' (SEQ IDNO:37), and said antisense strand comprises 5' AAUUGAGAGAAGUCCACCAGCUU 3' (SEQ ID NO:38),~~

~~wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,~~

~~wherein said sense strand is conjugated to a ligand attached at the 3' terminus, and~~

~~wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.~~

26. The double stranded RNAi agent of any one of claims 20-25, wherein all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand comprise a modification.

27. The double stranded RNAi agent of any one of claims 20-24, wherein at least one of said modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, and a nucleotide comprising a 5'-phosphate mimic.

28. The double stranded RNAi agent of claim 27, wherein the 5'-phosphate mimic is a 5'-vinyl phosphate (5'-VP).

29. The double stranded RNAi agent of claim 22, wherein the sense strand comprises 5'-uscsguGfgUfGfGfacuucucuca-3' (SEQ ID NO:13) and the antisense strand comprises
5'-usGfsagaGfaAfGfuccaCfcAfcgasusu-3' (SEQ ID NO:14), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are
2′-fluoro A, G, C or U; and s is a phosphorothioate linkage.

30. The double stranded RNAi agent of claim 22, wherein the sense strand comprises
5'-uscsguGfgUfGfGfacuucucuca-3' (SEQ ID NO:15) and the antisense strand comprises 5'-PusGfsagaGfaAfGfuccaCfcAfcgasusu-3' (SEQ ID NO:16), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are
2′-fluoro A, G, C or U; and s is a phosphorothioate linkage; and P is a 5'-phosphate or 5'phosphate mimic.

~~31. The double stranded RNAi agent of claim 23, wherein the sense strand comprises~~
~~5’ gsusgcacUfuCfGfCfuucaccucua 3’ (SEQ ID NO:17) and the antisense strand comprises~~
~~5’ usAfsgagGfugaagcgAfaGfugcacsusu 3’ (SEQ ID NO:18), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′ O-methyl (2′ OMe) A, U, C, or G; Af, Cf, Gf or Uf are~~
~~2′ fluoro A, G, C or U; and s is a phosphorothioate linkage.~~

~~32. The double stranded RNAi agent of claim 23, wherein the sense strand comprises~~
~~5’ gsusgcacUfuCfGfCfuucaccucua 3’ (SEQ ID NO:19) and the antisense strand comprises~~
~~5’ PusAfsgagGfugaagcgAfaGfugcacsusu 3’ (SEQ ID NO:20) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′ O-methyl (2′ OMe) A, U, C, or G; Af, Cf, Gf or Uf are~~
~~2′ fluoro A, G, C or U; and s is a phosphorothioate linkage; and P is a 5’ phosphate or 5’phosphate mimic.~~

~~33. The double stranded RNAi agent of claim 24, wherein the sense strand comprises~~
~~5’ csgsugguGfgAfCfUfucucUfCfaauu 3’ (SEQ ID NO:21) and the antisense strand comprises~~
~~5’ asAfsuugAfgAfgAfaguCfcAfccagcsasg 3’ (SEQ ID NO:22), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′ O-methyl (2′ OMe) A, U, C, or G; Af, Cf, Gf or Uf are~~
~~2′ fluoro A, G, C or U; and s is a phosphorothioate linkage.~~

~~34. The double stranded RNAi agent of claim 24, wherein the sense strand comprises~~
~~5’ csgsugguGfgAfCfUfucucUfCfaauu 3’ (SEQ ID NO:23) and the antisense strand comprises~~
~~5’ PasAfsuugAfgAfgAfaguCfcAfccagcsasg 3’ (SEQ ID NO:24) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′ O-methyl (2′ OMe) A, U, C, or G; Af, Cf, Gf or Uf are~~
~~2′ fluoro A, G, C or U; and s is a phosphorothioate linkage; and P is a 5’ phosphate or 5’phosphate mimic.~~

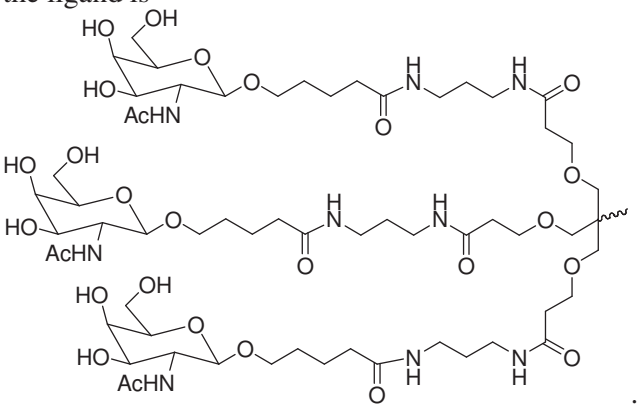
~~35. The double stranded RNAi agent of claim 25, wherein the sense strand comprises~~
~~5’ csgsuggudGgucdTucucuaaaauu 3’ (SEQ ID NO:35) and the antisense strand comprises~~
~~5’ asdAsuugagagdAagudCcaccagcsusu 3’ (SEQ ID NO:36), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′ O methyl (2′ OMe) A, U, C, or G; dA, dC, dG, and dT are deoxyribose A, C, G, and T; and s is a phosphorothioate linkage.~~

~~36~~3. The double stranded RNAi agent of claim 1~~21~~, wherein the sense strand comprises
5’- gsgsuggaCfuUfCfUfcucaAfUfuuua -3’ (SEQ ID NO:25) and the antisense strand comprises
5’- usAfsaaaUfuGfAfgagaAfgUfccaccsasc -3’ (SEQ ID NO:26), wherein
A, C, G, and U are ribose A, C, G and ~~or~~ U, respectively;
a, ~~g, c~~ c, g and u are 2′-O-methyl (2′-OMe) A, ~~U, C, or G~~C, G and U, respectively;
Af, Cf, Gf and ~~or~~ Uf are 2′-fluoro A, ~~G, C~~C, G and~~or~~ U, respectively;
and s is a phosphorothioate -linkage.

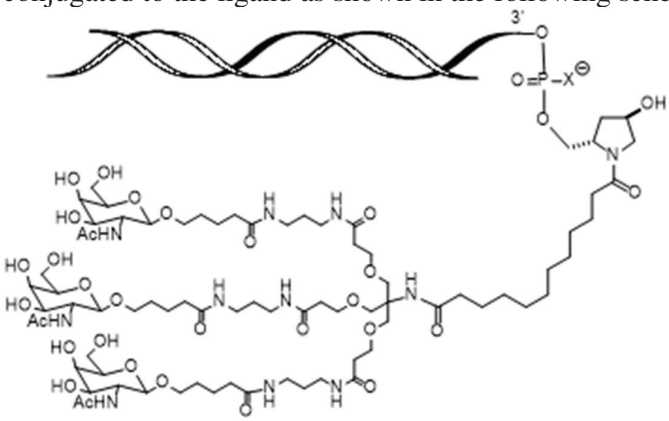
~~37. The double stranded RNAi agent of claim 21, wherein the sense strand comprises~~
~~5’ gsgsuggaCfuUfCfUfcucaAfUfuuua 3’ (SEQ ID NO:27) and the antisense strand comprises~~
~~5’ PusAfsaaaUfuGfAfgagaAfgUfccaccsasc 3’ (SEQ ID NO:28) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′ O methyl (2′ OMe) A, U, C, or G; Af, Cf, Gf or Uf are~~
~~2′ fluoro A, G, C or U; and s is a phosphorothioate linkage; and P is a 5’ phosphate or 5’phosphate mimic.~~

~~38. The double stranded RNAi agent of claim 20, wherein the sense strand comprises~~
~~5’ gsusguGfcAfCfUfucgcuucaca 3’ (SEQ ID NO:41) and the antisense strand comprises~~
~~5’ usGfsugaAfgCfGfaaguGfcAfcacsusu 3’ (SEQ ID NO:42), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′ O methyl (2′ OMe) A, U, C, or G; Af, Cf, Gf or Uf are~~
~~2′ fluoro A, G, C or U; and s is a phosphorothioate linkage.~~

~~39~~4. The double stranded RNAi agent of any one of claims ~~20-38~~1 to 3, wherein the ligand is



~~40~~5. The double stranded RNAi agent of claim ~~39~~4, wherein the RNAi agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

6. The double stranded RNAi agent of claim 1, wherein the sense strand comprises 5'- gsgsuggaCfuUfCfUfcucaAfUfuuuaL96 -3' (SEQ ID NO: 994) and the antisense strand comprises 5'- usAfsaaaUfuGfAfgagaAfgUfccaccsasc -3' (SEQ ID NO: 1023), wherein a, c, g, and u are 2'-O-methyl (2'-OMe) A, 2'-OMe C, 2'-OMe G, and 2'-OMe U, respectively; Af, Cf, Gf, and Uf are 2'-fluoro A, 2'-fluoro C, 2'-fluoro G, and 2'-fluoro U, respectively; s is a phosphorothioate linkage; and L96 is N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol.

~~41. The double-stranded RNAi agent of any one of claims 30, 32, 34, and 37, wherein the P is a 5' phosphate mimic.~~

42. The double-stranded RNAi agent of any one of claims 30, 32, 34, and 37, wherein the 5' phosphate mimic is a 5' vinyl phosphate (5' VP).

43. A composition comprising two or more double stranded RNAi agents for inhibiting expression of hepatitis B virus (HBV) in a cell, wherein each double stranded RNAi agent independently comprises a sense strand and an antisense strand forming a double-stranded region, wherein each of said sense strands independently comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1, and each of said antisense strands independently comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2,

wherein substantially all of the nucleotides of each of said sense strands and substantially all of the nucleotides of each of said antisense strands are independently modified nucleotides,

wherein each of said sense strands are independently conjugated to a ligand attached at the 3' terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

44. The composition of claim 43, wherein one or more of the 3 nucleotide differences in the nucleotide sequence of the antisense strand is a nucleotide mismatch in the antisense strand.

45. The composition of claim 43, wherein one or more of the 3 nucleotide differences in the nucleotide sequence of the antisense strand is a nucleotide mismatch in the sense strand.

46. The composition of claim 43, wherein all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand are modified nucleotides.

47. The composition of claim 43, wherein said sense strand and said antisense strand comprise a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the sequences listed in any one of Tables 3, 4, 6, 7, 12, 13, 22, 23, 25, and 26.

~~48. The composition of any one of claims 43-47, wherein at least one of said modified nucleotides is selected from the group consisting of a a deoxy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, and a nucleotide comprising a 5'-phosphate mimic.~~

~~49~~7. A composition for inhibiting expression of hepatitis B virus (HBV) in a cell, ~~said composition~~ comprising:

(a) a first double-stranded RNAi agent comprising a first sense strand and a first antisense strand forming a first double-stranded region,

wherein the first sense strand comprises 5'- GGUGGACUUCUCUCAAUUUUA -3' (SEQ ID NO: 11), and the first antisense strand comprises 5'-UAAAAUUGAGAGAAGUCCACCAC -3' (SEQ ID NO: 12),

wherein ~~substantially~~ all of the nucleotides of the ~~said~~ first sense strand and ~~substantially~~ all of the nucleotides of ~~said~~ the first antisense strand are modified nucleotides,

wherein ~~said~~ the first sense strand is conjugated to a ligand attached at the 3'-terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; and

(b) a second double-stranded RNAi agent comprising a second sense strand and a second antisense strand forming a second double-stranded region,

wherein the second sense strand comprises 5'- GUGUGCACUUCGCUUCACA -3' (SEQ ID NO: 39), and the second antisense strand comprises 5'-UGUGAAGCGAAGUGCACACUU -3' (SEQ ID NO: 40),

wherein ~~substantially~~ all of the nucleotides of ~~said~~ the second sense strand and ~~substantially~~ all of the nucleotides of ~~said~~ the second antisense strand are modified nucleotides,

wherein ~~said~~ the second sense strand is conjugated to a ligand attached at the 3'-terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker. ;

wherein the first and second sense strands each independently comprise a sequence selected from the group consisting of

5’- UCGUGGUGGACUUCUCUCA -3’ (SEQ IDNO:5),

5’- GUGCACUUCGCUUCACCUCUA -3’ (SEQ IDNO:7),

5’- CGUGGUGGACUUCUCUCAAUU -3’ (SEQ IDNO:9),

5’- CGUGGUGGUCUUCUCUAAAUU -3’ (SEQ IDNO:37),

5’- GGUGGACUUCUCUCAAUUUUA -3’ (SEQ IDNO:11), and

5’- GUGUGCACUUCGCUUCACA -3’ (SEQ IDNO:39),

and

wherein the first and second antisense strands each independently comprise a sequence selected from the group consisting of

5’- UGAGAGAAGUCCACCACGAUU -3’ (SEQ ID NO:6),

5’- UAGAGGUGAAGCGAAGUGCACUU -3’ (SEQ ID NO:8),

5’- AAUUGAGAGAAGUCCACCAGCAG -3’ (SEQ ID NO:10),

5’- AAUUGAGAGAAGUCCACCAGCUU -3’ (SEQ ID NO:38),

5’- UAAAAUUGAGAGAAGUCCACCAC -3’ (SEQ ID NO:12) and

5’- UGUGAAGCGAAGUGCACACUU -3’ (seq id no:40).

50. The composition of claim 49, wherein all of the nucleotides of said first and second sense strand and/or all of the nucleotides of said first and second antisense strand comprise a modification.

518. The composition of claim 497, wherein at least one of said the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3’-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2’-amino-modified nucleotide, a 2’-O-allyl-modified nucleotide, 2’-C-alkyl-modified nucleotide, 2’ hydroxly modified nucleotide, a 2’-methoxyethyl modified nucleotide, a 2’-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5’-phosphate, orand a nucleotide comprising a 5’-phosphate mimic.

~~52. The composition of claim 49, wherein the first and second RNAi agent are selected from the group consisting of:~~

~~5' usesguGfgUfGfGfacuucucuca 3' (SEQ ID NO:13)~~

~~5' usGfsagaGfaAfGfuccaCfcAfcgasusu 3' (SEQ ID NO:14);~~

~~5' usesguGfgUfGfGfacuucucuca 3' (SEQ ID NO:15)~~

~~5' PusGfsagaGfaAfGfuccaCfcAfcgasusu 3' (SEQ ID NO:16);~~

~~5' gsusgcacUfuCfGfCfuucaccucua 3' (SEQ ID NO:17)~~

~~5' usAfsgagGfugaagcgAfaGfugcacsusu 3' (SEQ ID NO:18);~~

~~5' gsusgcacUfuCfGfCfuucaccucua – 3' (SEQ ID NO:19)~~

~~5' PusAfsgagGfugaagcgAfaGfugcacsusu 3' (SEQ ID NO:20);~~

~~5' csgsugguGfgAfCfUfucucUfCfaauu 3' (SEQ ID NO:21)~~

~~5' asAfsuugAfgAfgAfaguCfcAfccagcsasg 3' (SEQ ID NO:22);~~

~~5' csgsugguGfgAfCfUfucucUfCfaauu 3' (SEQ ID NO:23)~~

~~5' PasAfsuugAfgAfgAfaguCfcAfccagcsasg 3' (SEQ ID NO:24);~~

~~5' csgsuggudGgucdTucucuaaaauu 3' (SEQ ID NO:35)~~

~~5' asdAsuugagagdAagudCcaccagcsusu 3' (SEQ ID NO:36);~~

~~5' gsgsuggaCfuUfCfUfcucaAfUfuuua 3' (SEQ ID NO:25)~~

~~5' usAfsaaaUfuGfAfgagaAfgUfccaccsasc – 3' (SEQ ID NO:26);~~

~~5' gsgsuggaCfuUfCfUfcucaAfUfuuua 3' (SEQ ID NO:27)~~

~~5' PusAfsaaaUfuGfAfgagaAfgUfccaccsasc 3' (SEQ ID NO:28); and~~

~~5' gsusguGfcAfCfUfucgcuucaca 3' (SEQ ID NO:41)~~

~~5' usGfsugaAfgCfGfaaguGfcAfcacsusu 3' (SEQ ID NO:42),~~

~~wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′ O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′ fluoro A, G, C or U; dA, dC, dG, and dT are deoxyribose A, C, G, and T; s is a phosphorothioate linkage; and P is a 5' phosphate or 5'phosphate mimic.~~

~~53. The composition of claim 49, wherein the first and second RNAi agents are~~

~~5' usesguGfgUfGfGfacuucucuca 3' (SEQ ID NO:15)~~

~~5' PusGfsagaGfaAfGfuccaCfcAfcgasusu 3' (SEQ ID NO:16); and~~

~~5' csgsugguGfgAfCfUfucucUfCfaauu 3' (SEQ ID NO:21)~~

~~5' asAfsuugAfgAfgAfaguCfcAfccagcsasg 3' (SEQ ID NO:22),~~

~~wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′ O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; s is a phosphorothioate linkage; and P is a 5' phosphate or 5'phosphate mimic.~~

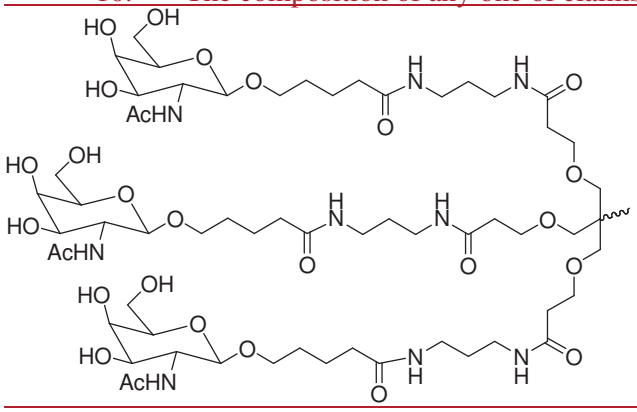
~~54~~9. The composition of claim ~~49~~7, wherein

(a) ~~the first and second RNAi agents are~~ the first sense strand comprises 5’-gsgsuggaCfuUfCfUfcucaAfUfuuua – 3’ (SEQ ID NO:25) and the first antisense strand comprises 5’- usAfsaaaUfuGfAfgagaAfgUfccaccsasc – 3’ (SEQ ID NO:26); and

(b) the second sense strand comprises 5’- gsusguGfcAfCfUfucgcuucaca -3’ (SEQ ID NO:41) and the second antisense strand comprises 5’- usGfsugaAfgCfGfaaguGfcAfcacsusu -3’ (SEQ ID NO:42);~~,~~

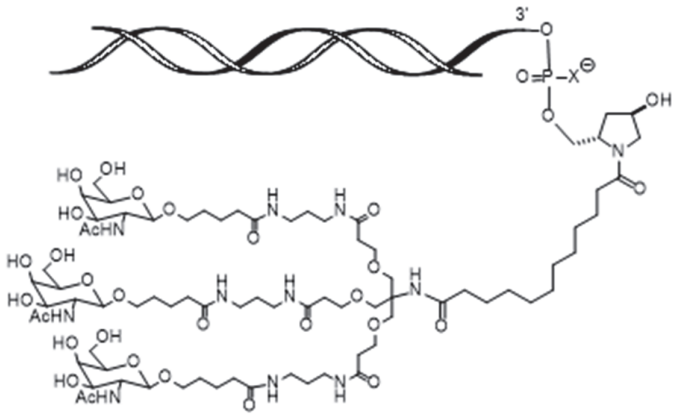
wherein ~~A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′ O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′ fluoro A, G, C or U;~~ a, c, g, and u are 2'-O-methyl (2'-OMe) A, 2'-OMe C, 2'-OMe G, and 2'-OMe U, respectively; Af, Cf, Gf, and Uf are 2'-fluoro A, 2'-fluoro C, 2'-fluoro G, and 2'-fluoro U, respectively; and s is a phosphorothioate linkage~~; and P is a 5’ phosphate or 5’phosphate mimic~~.

10. The composition of any one of claims 7 to 9, wherein the ligand is



.

11. The composition of claim 10, wherein the RNAi agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

12. The composition of claim 7, wherein

(a) the first sense strand comprises 5'- gsgsuggaCfuUfCfUfcucaAfUfuuuaL96 -3' (SEQ ID NO: 994) and the first antisense strand comprises 5'- usAfsaaaUfuGfAfgagaAfgUfccaccsasc -3' (SEQ ID NO: 1023); and

(b) the second sense strand comprises 5'- gsusguGfcAfCfUfucgcuucacaL96 -3' (SEQ ID NO: 1275) and the second antisense strand comprises 5'- usGfsugaAfgCfGfaaguGfcAfcacsusu -3' (SEQ ID NO: 1285);

wherein a, c, g, and u are 2'-O-methyl (2'-OMe) A, 2'-OMe C, 2'-OMe G, and 2'-OMe U, respectively; Af, Cf, Gf, and Uf are 2'-fluoro A, 2'-fluoro C, 2'-fluoro G, and 2'-fluoro U, respectively; s is a phosphorothioate linkage; and L96 is N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol.

~~55. A double stranded RNAi agent comprising the RNAi agents listed in any one of Tables 3, 4, 6, 7, 12, 13, 22, 23, 25, and 26.~~

~~56. A vector containing the double stranded RNAi agent of any one of claims 1 and 20-25.~~

~~57~~13. A cell containing the double stranded RNAi agent of any one of claims 1 to 6. ~~and 20-25.~~

~~58~~14. A pharmaceutical composition comprising:

(a) (i) the double stranded RNAi agent of any one of claims 1 to 6~~and 20-25~~, or

(ii) the composition of any one of claims 7 to 12; and ~~43 and 49, or the vector of claim 56.~~

~~59.~~ (b) ~~The pharmaceutical composition of claim 58, wherein double stranded RNAi agent is administered in~~ an unbuffered solution~~.~~

~~60. The pharmaceutical composition of claim 59, wherein said unbuffered solution is saline or water.~~

61. The pharmaceutical composition of claim 58, wherein said double stranded RNAi agent is administered with or a buffer solution.

62. The pharmaceutical composition of claim 61, wherein said buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

63. The pharmaceutical composition of claim 62, wherein said buffer solution is phosphate buffered saline (PBS).

64. A method of inhibiting Hepatitis B virus (HBV) gene expression in a cell, the method comprising:

(a) contacting the cell with the double stranded RNAi agent of any one of claims 1 and 20-25, or the composition of any one of claims 43 and 49, or the vector of claim 56, or the pharmaceutical composition of any one of claims 58-63; and

(b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of an HBV gene, thereby inhibiting expression of the HBV gene in the cell.

65. The method of claim 64, wherein the HBV gene is selected from the group consisting of C, X, P, S, and a combination thereof.

66. A method of inhibiting replication of a Hepatitis B virus (HBV) in a cell, the method comprising:

(a) contacting the cell with the double stranded RNAi agent of any one of claims 1 and 20-25, or the composition of any one of claims 43 and 49, or the vector of claim 56, or the pharmaceutical composition of any one of claims 58-63; and

(b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of an HBV gene, thereby inhibiting replication of the HBV in the cell.

67. The method of claim 64 or 66, wherein said cell is within a subject.

68. The method of claim 67, wherein the subject is a human.

69. The method of claim 68, wherein the subject suffers from an HBV-associated disease.

~~70. The method of claim 64, wherein the HBV gene expression is inhibited by at least about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98% or about 100%.~~

~~71. The method of claim 66, wherein replication of HBV in the cell is inhibited by at least about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98% or about 100%.~~

~~72. A method of reducing the level of Hepatitis B virus (HBV) covalently closed circular (ccc) DNA in a subject infected with HBV, comprising administering to the subject a therapeutically effective amount of the double stranded RNAi agent of any one of claims 1 and 20-25, or the composition of any one of claims 43 and 49, or the vector of claim 56, or the pharmaceutical composition of any one of claims 58-63, thereby reducing the level of covalently closed circular HBV DNA in the subject.~~

~~73. A method of reducing the level of a Hepatitis B virus (HBV) antigen in a subject infected with HBV, comprising administering to the subject a therapeutically effective amount of the double stranded RNAi agent of any one of claims 1 and 20-25, or the composition of any one of claims 43 and 49, or the vector of claim 56, or the pharmaceutical composition of any one of claims 58-63, thereby reducing the level of the HBV antigen in the subject.~~

~~74. The method of claim 73, wherein the HBV antigen is HBsAg.~~

~~75. The method of claim 73, wherein the HBV antigen is HBeAg.~~

~~76~~15. ~~A method of~~ The use of the double stranded RNAi agent of any one of claims 1 to 6, the composition of any one of claims 7 to 12, or the pharmaceutical composition of claim 14 in the manufacture of a medicament for reducing the viral load of Hepatitis B virus (HBV) in a subject infected with HBV.~~, comprising administering to the subject a therapeutically effective amount of the double stranded RNAi agent of any one of claims 1 and 20-25, or the composition of any one of claims 43 and 49, or the vector of claim 56, or the pharmaceutical composition of any one of claims 58-63, thereby reducing the viral load of HBV in the subject.~~

~~77. A method of reducing the level of alanine aminotransferase (ALT) in a subject infected with HBV, comprising administering to the subject a therapeutically effective amount of the double stranded RNAi agent of any one of claims 1 and 20-25, or the~~

~~composition of any one of claims 43 and 49, or the vector of claim 56, or the pharmaceutical composition of any one of claims 58-63, thereby reducing the level of ALT in the subject.~~

~~78. A method of reducing the level of aspartate aminotransferase (AST) in a subject infected with HBV, comprising administering to the subject a therapeutically effective amount of the double stranded RNAi agent of any one of claims 1 and 20-25, or the composition of any one of claims 43 and 49, or the vector of claim 56, or the pharmaceutical composition of any one of claims 58-63, thereby reducing the level of AST in the subject.~~

~~79. A method of increasing the level of anti-Hepatitis B virus (HBV) antibodies in a subject infected with HBV, comprising administering to the subject a therapeutically effective amount of the double stranded RNAi agent of any one of claims 1 and 20-25, or the composition of any one of claims 43 and 49, or the vector of claim 56, or the pharmaceutical composition of any one of claims 58-63, thereby increasing the level of anti-HBV antibodies in the subject.~~

~~80~~16. ~~A method of~~ The use of the double stranded RNAi agent of any one of claims 1 to 6, the composition of any one of claims 7 to 12, or the pharmaceutical composition of claim 14 in the manufacture of a medicament for treating ~~a subject having a~~ Hepatitis B virus (HBV) infection in a subject. ~~, comprising administering to the subject a therapeutically effective amount of the double stranded RNAi agent of any one of claims 1 and 20-25, or the composition of any one of claims 43 and 49, or the vector of claim 56, or the pharmaceutical composition of any one of claims 58-63, thereby treating said subject.~~

~~81~~17. ~~A method of~~ The use of the double stranded RNAi agent of any one of claims 1 to 6, the composition of any one of claims 7 to 12, or the pharmaceutical composition of claim 14 in the manufacture of a medicament for treating ~~a subject having a~~ Hepatitis B virus (HBV)-associated disorder in a subject. ~~, comprising administering to the subject a therapeutically effective amount of the double stranded RNAi agent of any one of claims 1 and 20-25, or the composition of any one of claims 43 and 49, or the vector of claim 56, or the pharmaceutical composition of any one of claims 58-63, thereby treating said subject.~~

~~82~~18. The ~~method~~ use of claim ~~71~~17, wherein the HBV-associated disorder is~~:~~ ~~selected from the group consisting of~~ hepatitis D virus (HDV) infection, delta hepatitis, acute

hepatitis B; acute fulminant hepatitis B; chronic hepatitis B; liver fibrosis; end-stage liver disease; or hepatocellular carcinoma.

19. The use of claim 17, wherein the HBV-associated disorder is hepatitis D virus (HDV) infection.

~~83. The method of claim 71, wherein the HBV-associated disorder is chronic hepatitis and the subject is HBeAg positive.~~

~~84. The method of claim 71, wherein the HBV-associated disorder is chronic hepatitis and the subject is HBeAg negative.~~

~~85. A method of treating a subject having a Hepatitis B virus (HBV) infection, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,~~

~~wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,~~

~~wherein said sense strand comprises 5'- UCGUGGUGGACUUCUCUCA -3' (SEQ IDNO:5), and said antisense strand comprises 5'- UGAGAGAAGUCCACCACGAUU -3' (SEQ ID NO:6),~~

~~wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,~~

~~wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and~~

~~wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.~~

~~86. A method of treating a subject having a Hepatitis B virus (HBV)-associated disorder, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,~~

~~wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,~~

~~wherein said sense strand comprises 5'- UCGUGGUGGACUUCUCUCA -3' (SEQ IDNO:5), and said antisense strand comprises 5'- UGAGAGAAGUCCACCACGAUU -3' (SEQ ID NO:6),~~

~~wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,~~

~~wherein said sense strand is conjugated to a ligand attached at the 3' terminus, and~~

~~wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.~~

~~87. A method of treating a subject having a Hepatitis B virus (HBV) infection, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,~~

~~wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,~~

~~wherein said sense strand comprises 5' GUGCACUUCGCUUCACCUCUA 3' (SEQ IDNO:7), and said antisense strand comprises 5' UAGAGGUGAAGCGAAGUGCACUU 3' (SEQ ID NO:8),~~

~~wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,~~

~~wherein said sense strand is conjugated to a ligand attached at the 3' terminus, and~~

~~wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.~~

~~88. A method of treating a subject having a Hepatitis B virus (HBV) associated disorder, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,~~

~~wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,~~

~~wherein said sense strand comprises 5' GUGCACUUCGCUUCACCUCUA 3' (SEQ IDNO:7), and said antisense strand comprises 5' UAGAGGUGAAGCGAAGUGCACUU 3' (SEQ ID NO:8),~~

~~wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,~~

~~wherein said sense strand is conjugated to a ligand attached at the 3' terminus, and~~

~~wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.~~

~~89. A method of treating a subject having a Hepatitis B virus (HBV) infection, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,~~

~~wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,~~

wherein said sense strand comprises 5’- CGUGGUGGACUUCUCUCAAUU -3’ (SEQ IDNO:9), and said antisense strand comprises 5’- AAUUGAGAGAAGUCCACCAGCAG -3’ (SEQ ID NO:10),

wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,

wherein said sense strand is conjugated to a ligand attached at the 3’ terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

90. A method of treating a subject having a Hepatitis B virus (HBV) associated disorder, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,

wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein said sense strand comprises 5’- CGUGGUGGACUUCUCUCAAUU -3’ (SEQ IDNO:9), and said antisense strand comprises 5’- AAUUGAGAGAAGUCCACCAGCAG -3’ (SEQ ID NO:10),

wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,

wherein said sense strand is conjugated to a ligand attached at the 3’ terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

91. A method of treating a subject having a Hepatitis B virus (HBV) infection, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,

wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein said sense strand comprises 5’- CGUGGUGGUCUUCUCUAAAUU -3’ (SEQ IDNO:37), and said antisense strand comprises 5’- AAUUGAGAGAAGUCCACCAGCUU -3’ (SEQ ID NO:38),

wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,

wherein said sense strand is conjugated to a ligand attached at the 3’ terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

92. A method of treating a subject having a Hepatitis B virus (HBV)-associated disorder, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,

wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,

wherein said sense strand comprises 5'- CGUGGUGGUCUUCUCUAAAUU -3' (SEQ IDNO:37), and said antisense strand comprises 5'- AAUUGAGAGAAGUCCACCAGCUU -3' (SEQ ID NO:38),

wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,

wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

93. A method of treating a subject having a Hepatitis B virus (HBV) infection, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,

wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,

wherein said sense strand comprises 5'- GGUGGACUUCUCUCAAUUUUA -3' (SEQ IDNO:11), and said antisense strand comprises 5'- UAAAAUUGAGAGAAGUCCACCAC -3' (SEQ ID NO:12),

wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,

wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

94. A method of treating a subject having a Hepatitis B virus (HBV)-associated disorder, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,

wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,

wherein said sense strand comprises 5'- GGUGGACUUCUCUCAAUUUUA -3' (SEQ IDNO:11), and said antisense strand comprises 5'- UAAAAUUGAGAGAAGUCCACCAC -3' (SEQ ID NO:12),

wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,

wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

95. A method of treating a subject having a Hepatitis B virus (HBV) infection, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,

wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,

wherein said sense strand comprises 5' GUGUGCACUUCGCUUCACA 3' (SEQ IDNO:39), and said antisense strand comprises 5' UGUGAAGCGAAGUGCACACUU 3' (SEQ ID NO:40),

wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,

wherein said sense strand is conjugated to a ligand attached at the 3' terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

96. A method of treating a subject having a Hepatitis B virus (HBV) associated disorder, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,

wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,

wherein said sense strand comprises 5' GUGUGCACUUCGCUUCACA 3' (SEQ IDNO:39), and said antisense strand comprises 5' UGUGAAGCGAAGUGCACACUU 3' (SEQ ID NO:40),

wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,

wherein said sense strand is conjugated to a ligand attached at the 3' terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

97. The method of any one of claims 85-96, wherein all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand comprise a modification.

98. The method of any one of claims 85-96, wherein at least one of said modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3' terminal deoxy-thymine (dT) nucleotide, a 2' O-methyl modified nucleotide, a 2' fluoro modified nucleotide,

a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, and a nucleotide comprising a 5'-phosphate mimic.

99. Themethod of claim 98, wherein the 5'-phosphate mimic is a 5'-vinyl phosphate (5'-VP).

100. The method of claim 85 or 86, wherein the sense strand comprises 5'-uscsguGfgUfGfGfacuucucuca-3' (SEQ ID NO:13) and the antisense strand comprises 5'-usGfsagaGfaAfGfuccaCfcAfcgasusu-3' (SEQ ID NO:14), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are
2′-fluoro A, G, C or U; and s is a phosphorothioate linkage.

101. The method of claim 85 or 86, wherein the sense strand comprises 5'-uscsguGfgUfGfGfacuucucuca-3' (SEQ ID NO:15) and the antisense strand comprises 5'-PusGfsagaGfaAfGfuccaCfcAfcgasusu-3' (SEQ ID NO:16), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are
2′-fluoro A, G, C or U; and s is a phosphorothioate linkage; and P is a 5'-phosphate or 5'phosphate mimic.

102. The method of claim 87 or 88, wherein the sense strand comprises 5'-gsusgcacUfuCfGfCfuucaccucua-3' (SEQ ID NO:17) and the antisense strand comprises 5'-usAfsgagGfugaagcgAfaGfugcacsusu-3' (SEQ ID NO:18), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are
2′-fluoro A, G, C or U; and s is a phosphorothioate linkage.

~~103. The method of claim 87 or 88, wherein the sense strand comprises 5' gsusgcacUfuCfGfCfuucaccucua 3' (SEQ ID NO:19) and the antisense strand comprises 5' PusAfsgagGfugaagcgAfaGfugcacsusu 3' (SEQ ID NO:20) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2' O-methyl (2' OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2' fluoro A, G, C or U; and s is a phosphorothioate linkage; and P is a 5' phosphate or 5'phosphate mimic.~~

~~104. The method of claim 89 or 90, wherein the sense strand comprises 5' csgsugguGfgAfCfUfucucUfCfaauu 3' (SEQ ID NO:21) and the antisense strand comprises 5' asAfsuugAfgAfgAfaguCfcAfccagcsasg 3' (SEQ ID NO:22) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2' O-methyl (2' OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2' fluoro A, G, C or U; and s is a phosphorothioate linkage.~~

~~105. The method of claim 89 or 90, wherein the sense strand comprises 5' csgsugguGfgAfCfUfucucUfCfaauu 3' (SEQ ID NO:23) and the antisense strand comprises 5' PasAfsuugAfgAfgAfaguCfcAfccagcsasg 3' (SEQ ID NO:24) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2' O-methyl (2' OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2' fluoro A, G, C or U; and s is a phosphorothioate linkage; and P is a 5' phosphate or 5'phosphate mimic.~~

~~106. The method of claim 91 or 92, wherein the sense strand comprises 5' csgsuggudGgucdTucucuaaaauu 3' (SEQ ID NO:35) and the antisense strand comprises 5' asdAsuugagagdAagudCcaccagcsusu 3' (SEQ ID NO:36), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2' O-methyl (2' OMe) A, U, C, or G; dA, dC, dG, and dT are deoxyribose A, C, G, and T; and s is a phosphorothioate linkage.~~

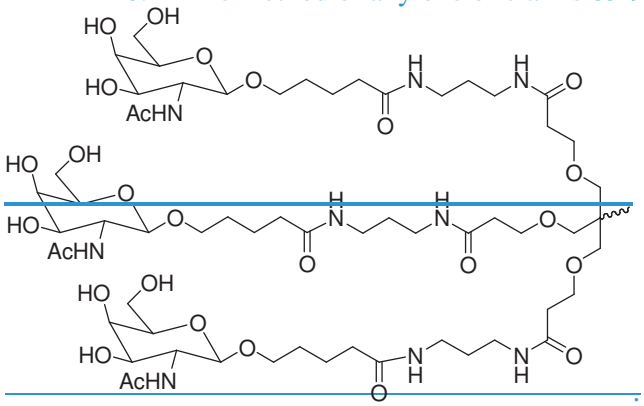
~~107. The method of claim 93 or 94, wherein the sense strand comprises 5' gsgsuggaCfuUfCfUfcucaAfUfuuua 3' (SEQ ID NO:25) and the antisense strand comprises 5' usAfsaaaUfuGfAfgagaAfgUfccaccsasc 3' (SEQ ID NO:26) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2' O-methyl (2' OMe) A, U, C, or G; Af, Cf, Gf or Uf are~~

2′-fluoro A, G, C or U; and s is a phosphorothioate linkage.

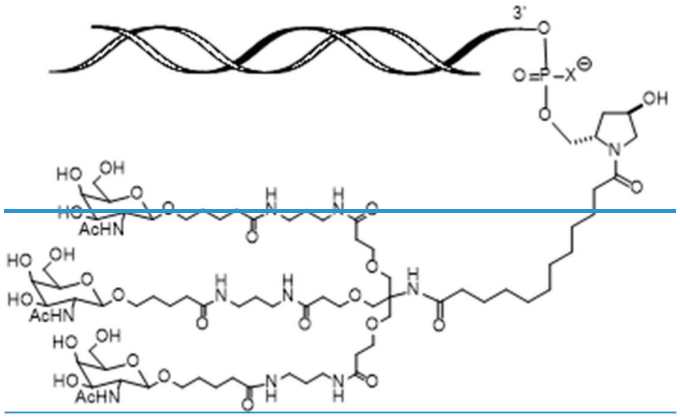
108. The method of claim 93 or 94, wherein the sense strand comprises 5’ gsgsuggaCfuUfCfUfcucaAfUfuuua 3’ (SEQ ID NO:27) and the antisense strand comprises
5’ PusAfsaaaUfuGfAfgagaAfgUfccaccsasc 3’ (SEQ ID NO:28) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are
2′-fluoro A, G, C or U; and s is a phosphorothioate linkage; and P is a 5’-phosphate or 5’phosphate mimic.

109. The method of claim 95 or 96, wherein the sense strand comprises 5’ gsusguGfcAfCfUfucgcuucaca 3’ (SEQ ID NO:41) and the antisense strand comprises 5’ usGfsugaAfgCfGfaaguGfcAfcacsusu 3’ (SEQ ID NO:42), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are
2′-fluoro A, G, C or U; and s is a phosphorothioate linkage.

110. The method of any one of claims 85-96, wherein the ligand is



111. The method of claim 110, wherein the RNAi agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

112. The method of any one of claims 86, 88, 90, 92, 94, and 96, wherein the HBV-associated disorder is selected from the group consisting of hepatitis D virus infection, delta hepatitis, acute hepatitis B; acute fulminant hepatitis B; chronic hepatitis B; liver fibrosis; end-stage liver disease; hepatocellular carcinoma.

113. The method of any one of claims 86, 88, 90, 92, 94, and 96, wherein the HBV-associated disorder is chronic hepatitis and the subject is HBeAg positive.

114. The method of any one of claims 86, 88, 90, 92, 94, and 96, wherein the HBV-associated disorder is chronic hepatitis and the subject is HBeAg negative.

115. A method of treating a subject having a Hepatitis B virus (HBV) infection, comprising administering to the subject a therapeutically effective amount of a composition for inhibiting expression of hepatitis B virus (HBV) in a cell, said composition comprising

(a) a first double-stranded RNAi agent comprising a first sense strand and a first antisense strand forming a double-stranded region,

wherein substantially all of the nucleotides of said first sense strand and substantially all of the nucleotides of said first antisense strand are modified nucleotides,

wherein said first sense strand is conjugated to a ligand attached at the 3' terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; and

(b) a second double-stranded RNAi agent comprising a second sense strand and a second antisense strand forming a double-stranded region,

wherein substantially all of the nucleotides of said second sense strand and substantially all of the nucleotides of said second antisense strand are modified nucleotides,

wherein said second sense strand is conjugated to a ligand attached at the 3'-terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker;

wherein the first and second sense strands each independently comprise a sequence selected from the group consisting of

5' UCGUGGUGGACUUCUCUCA 3' (SEQ ID NO:5),

5' GUGCACUUCGCUUCACCUCUA 3' (SEQ ID NO:7),

5'- CGUGGUGGACUUCUCUCAAUU -3' (SEQ ID NO:9),

5' CGUGGUGGUCUUCUCUAAAUU 3' (SEQ ID NO:37),

5' GGUGGACUUCUCUCAAUUUUA 3' (SEQ ID NO:11), and

5' GUGUGCACUUCGCUUCACA 3' (SEQ IDNO:39),

and wherein the first and second antisense strands each independently comprise a sequence selected from the group consisting of

5' UGAGAGAAGUCCACCACGAUU 3' (SEQ ID NO:6);

5' UAGAGGUGAAGCGAAGUGCACUU 3' (SEQ ID NO:8);

5' AAUUGAGAGAAGUCCACCAGCAG 3' (SEQ ID NO:10);

5'- AAUUGAGAGAAGUCCACCAGCUU -3' (SEQ ID NO:38),

5' UAAAAUUGAGAGAAGUCCACCAC 3' (SEQ ID NO:12), and

5' UGUGAAGCGAAGUGCACACUU 3' (SEQ ID NO:40), thereby treating the subject.

116. A method of treating a subject having a Hepatitis B virus (HBV) associated disorder, comprising administering to the subject a therapeutically effective amount of a composition for inhibiting expression of hepatitis B virus (HBV) in a cell, said composition comprising

(a) a first double-stranded RNAi agent comprising a first sense strand and a first antisense strand forming a double-stranded region,

wherein substantially all of the nucleotides of said first sense strand and substantially all of the nucleotides of said first antisense strand are modified nucleotides,

wherein said first sense strand is conjugated to a ligand attached at the 3' terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; and

(b) a second double-stranded RNAi agent comprising a second sense strand and a second antisense strand forming a double-stranded region,

wherein substantially all of the nucleotides of said second sense strand and substantially all of the nucleotides of said second antisense strand are modified nucleotides,

wherein said second sense strand is conjugated to a ligand attached at the 3'-terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker;

wherein the first and second sense strands each independently comprise a sequence selected from the group consisting of

5’- UCGUGGUGGACUUCUCUCA -3’ (SEQ ID NO:5),

5’- GUGCACUUCGCUUCACCUCUA -3’ (SEQ ID NO:7),

5’- CGUGGUGGACUUCUCUCAAUU -3’ (SEQ ID NO:9),

5’- CGUGGUGGUCUUCUCUAAAUU -3’ (SEQ ID NO:37),

5’- GGUGGACUUCUCUCAAUUUUA -3’ (SEQ IDNO:11), and

5’- GUGUGCACUUCGCUUCACA -3’ (SEQ IDNO:39), and

wherein the first and second antisense strands each independently comprise a sequence selected from the group consisting of

5’- UGAGAGAAGUCCACCACGAUU -3’ (SEQ ID NO:6);

5’- UAGAGGUGAAGCGAAGUGCACUU -3’ (SEQ ID NO:8);

5’- AAUUGAGAGAAGUCCACCAGCAG -3’ (SEQ ID NO:10);

5’- AAUUGAGAGAAGUCCACCAGCUU -3’ (SEQ ID NO:38),

5’- UAAAAUUGAGAGAAGUCCACCAC -3’ (SEQ ID NO:12), and

5’- UGUGAAGCGAAGUGCACACUU -3’ (SEQ ID NO:40), thereby treating the subject.

117. The method of any one of claims 115 and 116, wherein all of the nucleotides of said first and second sense strand and all of the nucleotides of said first and second antisense strand comprise a modification.

118. The method of any one of claims 115 and 116, wherein at least one of said modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3’-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2’-amino-modified nucleotide, a 2’-O-allyl-modified nucleotide, 2’-C-alkyl-modified nucleotide, 2’-hydroxly-modified nucleotide, a 2’-methoxyethyl modified nucleotide, a 2’-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5’-phosphate, and a nucleotide comprising a 5’-phosphate mimic.

~~119. The method of claim 115 or 116, wherein the first and second RNAi agent are selected from the group consisting of:~~

~~5’ usesguGfgUfGfGfacuucucuca 3’ (SEQ ID NO:13)~~

~~5’ usGfsagaGfaAfGfuccaCfcAfcgasusu 3’ (SEQ ID NO:14);~~

~~5’ usesguGfgUfGfGfacuucucuca 3’ (SEQ ID NO:15)~~

~~5’ PusGfsagaGfaAfGfuccaCfcAfcgasusu 3’ (SEQ ID NO:16);~~

~~5’ gsusgcacUfuCfGfCfuucaccucua 3’ (SEQ ID NO:17)~~

~~5’ usAfsgagGfugaagcgAfaGfugcacsusu 3’ (SEQ ID NO:18);~~

~~5’ gsusgcacUfuCfGfCfuucaccucua – 3’ (SEQ ID NO:19)~~

~~5’ PusAfsgagGfugaagcgAfaGfugcacsusu 3’ (SEQ ID NO:20);~~

~~5’ csgsugguGfgAfCfUfucucUfCfaauu 3’ (SEQ ID NO:21)~~

~~5’ asAfsuugAfgAfgAfaguCfcAfccagcsasg 3’ (SEQ ID NO:22);~~

~~5’ csgsugguGfgAfCfUfucucUfCfaauu 3’ (SEQ ID NO:23)~~

~~5’ PasAfsuugAfgAfgAfaguCfcAfccagcsasg 3’ (SEQ ID NO:24);~~

~~5’ csgsuggudGgucdTucucuaaaauu 3’ (SEQ ID NO:35)~~

~~5’ asdAsuugagagdAagudCcaccagcsusu 3’ (SEQ ID NO:36);~~

~~5’ gsgsuggaCfuUfCfUfcucaAfUfuuua 3’ (SEQ ID NO:25)~~

~~5’- usAfsaaaUfuGfAfgagaAfgUfccaccsasc – 3’ (SEQ ID NO:26);~~

~~5’ gsgsuggaCfuUfCfUfcucaAfUfuuua 3’ (SEQ ID NO:27)~~

~~5’ PusAfsaaaUfuGfAfgagaAfgUfccaccsasc 3’ (SEQ ID NO:28); and~~

~~5’ gsusguGfcAfCfUfucgcuucaca 3’ (SEQ ID NO:41)~~

~~5’ usGfsugaAfgCfGfaaguGfcAfcacsusu 3’ (SEQ ID NO:42),~~

~~wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′ O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′ fluoro A, G, C or U; dA, dC, dG, and dT are deoxyribose A, C, G, and T; s is a phosphorothioate linkage; and P is a 5’ phosphate or 5’phosphate mimic.~~

~~120. The method of claim 115 or 116, wherein the first and second RNAi agents are~~

~~5’ usesguGfgUfGfGfacuucucuca 3’ (SEQ ID NO:15)~~

~~5’ PusGfsagaGfaAfGfuccaCfcAfcgasusu 3’ (SEQ ID NO:16); and~~

~~5’ csgsugguGfgAfCfUfucucUfCfaauu 3’ (SEQ ID NO:21)~~

~~5’ asAfsuugAfgAfgAfaguCfcAfccagcsasg 3’ (SEQ ID NO:22),~~

~~wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′ fluoro A, G, C or U; s is a phosphorothioate linkage; and P is a 5’ phosphate or 5’phosphate mimic.~~

~~121. The method of claim 115 or 116, wherein the first and second RNAi agents are~~

~~5' gsgsuggaCfuUfCfUfcucaAfUfuuua 3' (SEQ ID NO:25)~~

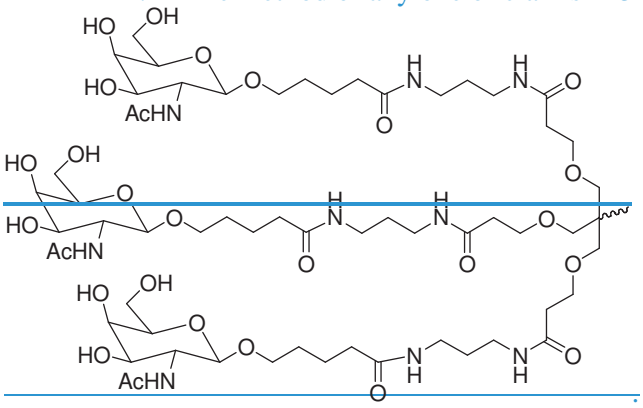
~~5' usAfsaaaUfuGfAfgagaAfgUfccacesasc 3' (SEQ ID NO:26); and~~

~~5' gsusguGfcAfCfUfucgcuucaca 3' (SEQ ID NO:41)~~

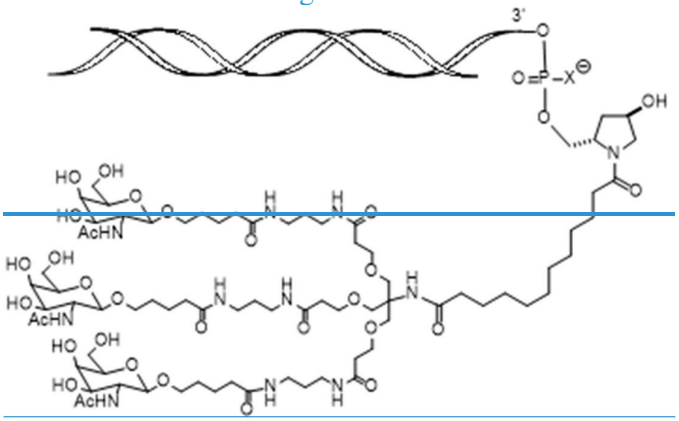
~~5' usGfsugaAfgCfGfaaguGfcAfcacsusu 3' (SEQ ID NO:42),~~

~~wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′ O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′ fluoro A, G, C or U; s is a phosphorothioate linkage; and P is a 5' phosphate or 5'phosphate mimic.~~

~~122. The method of any one of claims 115 and 116, wherein the ligand is~~



~~123. The method of claim 122, wherein the RNAi agent is conjugated to the ligand as shown in the following schematic~~



~~wherein X is O or S.~~

~~124. The method of any one of claims 115 and 116, wherein the subject is a human.~~

~~125. The method of claim 116, wherein the HBV-associated disorder is selected from the group consisting of hepatitis D virus infection, delta hepatitis, acute hepatitis B; acute fulminant hepatitis B; chronic hepatitis B; liver fibrosis; end-stage liver disease; and hepatocellular carcinoma.~~

~~126. The method of claim 116, wherein the HBV-associated disorder is chronic hepatitis and the subject is HBeAg-positive.~~

~~127. The method of claim 116, wherein the HBV-associated disorder is chronic hepatitis and the subject is HBeAg-negative.~~

~~128~~20. The ~~method~~ use of any one of claims ~~85-127~~15 to 19, wherein the double stranded RNAi agent is to be administered to the subject at a weight-based dose of ~~about~~ 0.01 mg/kg to ~~about~~ 10 mg/kg or ~~about~~ 0.5 mg/kg to ~~about~~ 50 mg/kg; ~~.~~

~~129. The method of claim 128, wherein the double stranded RNAi agent is administered at a dose of about~~ a weight-based dose of 10 mg/kg to ~~about~~ 30 mg/kg;~~.~~

~~130. The method of claim 128, wherein the double stranded RNAi agent is administered at a dose of about~~ a weight-based dose of 3 mg/kg;~~.~~

~~131. The method of claim 128, wherein the double stranded RNAi agent is administered at a dose of about~~ a weight-based dose of 10 mg/kg;~~.~~

~~132. The method of claim 128, wherein the double stranded RNAi agent is administered at a dose of about 0.5 mg/kg twice per week.~~

~~133. The method of any one of claims 82-120, wherein the double stranded RNAi agent is administered at~~ or a fixed dose of about 50 mg to 200 mg.

~~134~~21. The ~~method~~ use of any one of claims ~~85-127~~15 to 20, wherein the double stranded RNAi agent is to be administered subcutaneously ~~.~~

~~135. The method of any one of claims 85-127, wherein the double stranded RNAi agent is administered~~ or intravenously.

~~136. The method of any one of claims 85-127, wherein said RNAi agent is administered in two or more doses.~~

~~137. The method of any one of claims 85-127, wherein said RNAi agent is administered at intervals selected from the group consisting of once every about 12 hours, once every about 24 hours, once every about 48 hours, once every about 72 hours, and once every about 96 hours.~~

~~138. The method of any one of claims 85-127, wherein said RNAi agent is administered twice per week.~~

~~139. The method of any one of claims 85-127, wherein said RNAi agent is administered every other week.~~

~~140~~22. The ~~method~~ use of any one of claims ~~85-127~~15 to 21, ~~further comprising administering to the subject~~ wherein the double stranded RNAi agent is to be administered with an additional therapeutic agent.

~~141~~23. The ~~method~~ use of claim ~~140~~22, wherein the additional therapeutic agent is ~~selected from the group consisting of~~ an antiviral agent, a reverse transcriptase inhibitor, an immune stimulator, a therapeutic vaccine, a viral entry inhibitor, an oligonucleotide that inhibits the secretion or release of HbsAg, a capsid inhibitor, a covalently closed circular (ccc) HBV DNA inhibitor, ~~and~~or a combination of any of the foregoing.

~~142. The method of any one of claims 85-127, further comprising administering to the subject a reverse transcriptase inhibitor.~~

~~143. The method of any one of claims 85-127, further comprising administering to the subject a reverse transcriptase inhibitor and an immune stimulator.~~

~~144. The method of claim 142 or 143, wherein the a reverse transcriptase inhibitor is slected from the group consisting of Tenofovir disoproxil fumarate (TDF), Tenofovir alafenamide, Lamivudine, Adefovir dipivoxil, Entecavir (ETV), Telbivudine, and AGX-1009.~~

~~145. The method of claim 143, wherein the immune stimulator is selected from the group consisting of pegylated interferon alfa 2a (PEG-IFN -2a), Interferon alfa-2b, a recombinant human interleukin-7, and a Toll-like receptor 7 (TLR7) agonist.~~

146. A method of treating a subject having a Hepatitis B virus (HBV) associated disorder, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,

wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,

wherein said sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:29, and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:30,

wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,

wherein said sense strand is conjugated to a ligand attached at the 3' terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

147. A method of treating a subject having a Hepatitis B virus (HBV) infection, comprising administering to the subject a therapeutically effective amount of a composition for inhibiting expression of hepatitis B virus (HBV) in a cell, said composition comprising

(a) a first double-stranded RNAi agent comprising a first strand and a first antisense strand forming a double-stranded region,

wherein substantially all of the nucleotides of said first sense strand and substantially all of the nucleotides of said first antisense strand are modified nucleotides,

wherein said first sense strand is conjugated to a ligand attached at the 3' terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; and

(b) a second double-stranded RNAi agent comprising a second sense strand and a second antisense strand forming a double-stranded region,

wherein substantially all of the nucleotides of said second sense strand and substantially all of the nucleotides of said second antisense strand are modified nucleotides,

wherein said second sense strand is conjugated to a ligand attached at the 3' terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker;

wherein said first sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1, and said first antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2,

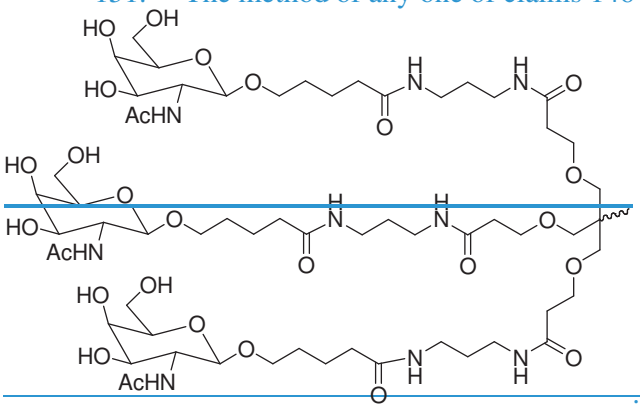
wherein said sense second strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:29, and said second antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:30, thereby treating the subject.

148. The method of claim 146, wherein the first sense strand comprises a sequence selected from the group consisting of
5'- UCGUGGUGGACUUCUCUCA -3' (SEQ IDNO:5),
5'- GUGCACUUCGCUUCACCUCUA -3' (SEQ ID NO:7),
5'- CGUGGUGGACUUCUCUCAAUU -3' (SEQ ID NO:9),
5'- CGUGGUGGUCUUCUCUAAAUU -3' (SEQ ID NO:37),
5'- GGUGGACUUCUCUCAAUUUUA -3' (SEQ ID NO:11), and
5'- GUGUGCACUUCGCUUCACA -3' (SEQ IDNO:39), and
wherein the second antisense strand comprises a sequence selected from the group consisting of
5'- UGAGAGAAGUCCACCACGAUU -3' (SEQ ID NO:6);
5'- UAGAGGUGAAGCGAAGUGCACUU -3' (SEQ ID NO:8);
5'- AAUUGAGAGAAGUCCACCAGCAG -3' (SEQ ID NO:10);
5'- AAUUGAGAGAAGUCCACCAGCUU -3' (SEQ ID NO:38),
5'- UAAAAUUGAGAGAAGUCCACCAC -3' (SEQ ID NO:12), and
5'- UGUGAAGCGAAGUGCACACUU -3' (SEQ ID NO:40).

149. The method of any one of claims 146-148, wherein all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand comprise a modification.

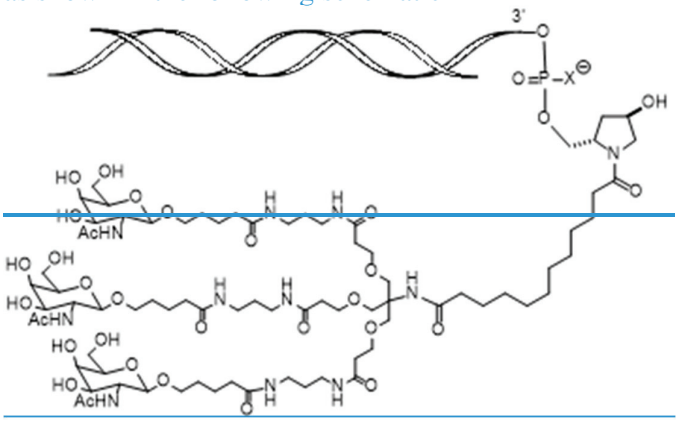
150. The method of any one of claims 146-149, wherein at least one of said modified nucleotides is selected from the group consisting of a dexoy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, and a nucleotide comprising a 5'-phosphate mimic.

151. The method of any one of claims 146-149, wherein the ligand is



.

152. The method of claim 151, wherein the RNAi agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

153. A method of inhibiting replication of a Hepatitis D virus (HDV) in a cell, the method comprising:

(a) contacting the cell with the double stranded RNAi agent of any one of claims 1 and 20-25, or the composition of any one of claims 43 and 49, or the vector of claim 56, or the pharmaceutical composition of any one of claims 58-63; and

(b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of an HBV gene, thereby inhibiting replication of the HDV in the cell.

154. The method of claim 153, wherein said cell is within a subject.

155. The method of claim 154, wherein the subject is a human.

156. A method of reducing the level of a Hepatitis D virus (HDV) antigen in a subject infected with HDV, comprising administering to the subject a therapeutically effective amount of the double stranded RNAi agent of any one of claims 1 and 20-25, or the composition of any one of claims 43 and 49, or the vector of claim 56, or the pharmaceutical composition of any one of claims 58-63, thereby reducing the level of the HDV antigen in the subject.

157. The method of claim 156, wherein the HDV antigen is S-HDAg.

158. The method of claim 156, wherein the HDV antigen is L-HDAg.

159. A method of reducing the viral load of Hepatitis D virus (HDV) in a subject infected with HBV, comprising administering to the subject a therapeutically effective amount of the double stranded RNAi agent of any one of claims 1 and 20-25, or the composition of any one of claims 43 and 49, or the vector of claim 56, or the pharmaceutical composition of any one of claims 58-63, thereby reducing the viral load of HDV in the subject.

160. A method of treating a subject having a Hepatitis D virus (HDV) infection, comprising administering to the subject a therapeutically effective amount of the double stranded RNAi agent of any one of claims 1 and 20-25, or the composition of any one of claims 43 and 49, or the vector of claim 56, or the pharmaceutical composition of any one of claims 58-63, thereby treating said subject.

161. A method of treating a subject having a Hepatitis D virus (HDV) infection, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,

wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,

wherein said sense strand comprises 5'-UCGUGGUGGACUUCUCUCA-3' (SEQ IDNO:5), and said antisense strand comprises 5'-UGAGAGAAGUCCACCACGAUU-3' (SEQ ID NO:6),

wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,

wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

~~162. A method of treating a subject having a Hepatitis D virus- (HDV-) associated disorder, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,~~

~~wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,~~

~~wherein said sense strand comprises 5' UCGUGGUGGACUUCUCUCA 3' (SEQ IDNO:5), and said antisense strand comprises 5' UGAGAGAAGUCCACCACGAUU 3' (SEQ ID NO:6),~~

~~wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,~~

~~wherein said sense strand is conjugated to a ligand attached at the 3' terminus, and~~

~~wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.~~

~~163. A method of treating a subject having a Hepatitis D virus (HDV) infection, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,~~

~~wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,~~

~~wherein said sense strand comprises 5' GUGCACUUCGCUUCACCUCUA 3' (SEQ IDNO:7), and said antisense strand comprises 5' UAGAGGUGAAGCGAAGUGCACUU 3' (SEQ ID NO:8),~~

~~wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,~~

~~wherein said sense strand is conjugated to a ligand attached at the 3' terminus, and~~

~~wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.~~

~~164. A method of treating a subject having a Hepatitis D virus (HDV) associated disorder, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,~~

~~wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,~~

~~wherein said sense strand comprises 5' GUGCACUUCGCUUCACCUCUA 3' (SEQ IDNO:7), and said antisense strand comprises 5' UAGAGGUGAAGCGAAGUGCACUU 3' (SEQ ID NO:8),~~

~~wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,~~

wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

165. A method of treating a subject having a Hepatitis D virus (HDV) infection, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,

wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,

wherein said sense strand comprises 5' CGUGGUGGACUUCUCUCAAUU 3' (SEQ IDNO:9), and said antisense strand comprises 5' AAUUGAGAGAAGUCCACCAGCAG 3' (SEQ ID NO:10),

wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,

wherein said sense strand is conjugated to a ligand attached at the 3' terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

166. A method of treating a subject having a Hepatitis D virus (HDV) associated disorder, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,

wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,

wherein said sense strand comprises 5' CGUGGUGGACUUCUCUCAAUU 3' (SEQ IDNO:9), and said antisense strand comprises 5' AAUUGAGAGAAGUCCACCAGCAG 3' (SEQ ID NO:10),

wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,

wherein said sense strand is conjugated to a ligand attached at the 3' terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

167. A method of treating a subject having a Hepatitis D virus (HDV) infection, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,

wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,

wherein said sense strand comprises 5’- CGUGGUGGUCUUCUCUAAAUU -3’ (SEQ IDNO:37), and said antisense strand comprises 5’- AAUUGAGAGAAGUCCACCAGCUU -3’ (SEQ ID NO:38),

wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,

wherein said sense strand is conjugated to a ligand attached at the 3’ terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

168. A method of treating a subject having a Hepatitis D virus (HDV) associated disorder, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,

wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein said sense strand comprises 5’ CGUGGUGGUCUUCUCUAAAUU 3’ (SEQ IDNO:37), and said antisense strand comprises 5’- AAUUGAGAGAAGUCCACCAGCUU -3’ (SEQ ID NO:38),

wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,

wherein said sense strand is conjugated to a ligand attached at the 3’ terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

169. A method of treating a subject having a Hepatitis D virus (HDV) infection, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,

wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein said sense strand comprises 5’ GGUGGACUUCUCUCAAUUUUA 3’ (SEQ IDNO:11), and said antisense strand comprises 5’- UAAAAUUGAGAGAAGUCCACCAC -3’ (SEQ ID NO:12),

wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,

wherein said sense strand is conjugated to a ligand attached at the 3’-terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

~~170. A method of treating a subject having a Hepatitis D virus- (HDV-) associated disorder, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,~~

~~wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,~~

~~wherein said sense strand comprises 5' GGUGGACUUCUCUCAAUUUUA 3' (SEQ IDNO:11), and said antisense strand comprises 5' UAAAAUUGAGAGAAGUCCACCAC 3' (SEQ ID NO:12),~~

~~wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,~~

~~wherein said sense strand is conjugated to a ligand attached at the 3' terminus, and~~

~~wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.~~

~~171. A method of treating a subject having a Hepatitis D virus (HDV) infection, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,~~

~~wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,~~

~~wherein said sense strand comprises 5' GUGUGCACUUCGCUUCACA 3' (SEQ IDNO:39), and said antisense strand comprises 5' UGUGAAGCGAAGUGCACACUU 3' (SEQ ID NO:40),~~

~~wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,~~

~~wherein said sense strand is conjugated to a ligand attached at the 3' terminus, and~~

~~wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.~~

~~172. A method of treating a subject having a Hepatitis D virus (HDV-) associated disorder, comprising administering to the subject a therapeutically effective amount of a double stranded RNAi agent,~~

~~wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,~~

~~wherein said sense strand comprises 5'- GUGUGCACUUCGCUUCACA -3' (SEQ IDNO:39), and said antisense strand comprises 5' UGUGAAGCGAAGUGCACACUU 3' (SEQ ID NO:40),~~

~~wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,~~

wherein said sense strand is conjugated to a ligand attached at the 3'-terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

173. The method of any one of claims 161-172, wherein all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand comprise a modification.

174. The method of any one of claims 161-172, wherein at least one of said modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, and a nucleotide comprising a 5'-phosphate mimic.

175. Themethod of claim 174, wherein the 5'-phosphate mimic is a 5'-vinyl phosphate (5'-VP).

176. The method of claim 161 or 162, wherein the sense strand comprises 5'-uscsguGfgUfGfGfacuucucuca-3' (SEQ ID NO:13) and the antisense strand comprises 5'-usGfsagaGfaAfGfuccaCfcAfcgasusu-3' (SEQ ID NO:14), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; and s is a phosphorothioate linkage.

177. The method of claim 161 or 162, wherein the sense strand comprises 5'-uscsguGfgUfGfGfacuucucuca-3' (SEQ ID NO:15) and the antisense strand comprises 5'-PusGfsagaGfaAfGfuccaCfcAfcgasusu-3' (SEQ ID NO:16), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′-O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; and s is a phosphorothioate linkage; and P is a 5'-phosphate or 5'phosphate mimic.

178. The method of claim 163 or 164, wherein the sense strand comprises 5’ gsusgcacUfuCfGfCfuucaccucua 3’ (SEQ ID NO:17) and the antisense strand comprises 5’ usAfsgagGfugaagcgAfaGfugcacsusu 3’ (SEQ ID NO:18) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′ O-methyl (2′ OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′ fluoro A, G, C or U; and s is a phosphorothioate linkage.

179. The method of claim 163 or 164, wherein the sense strand comprises 5’ gsusgcacUfuCfGfCfuucaccucua 3’ (SEQ ID NO:19) and the antisense strand comprises 5’ PusAfsgagGfugaagcgAfaGfugcacsusu – 3’ (SEQ ID NO:20) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′ O-methyl (2′ OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′ fluoro A, G, C or U; and s is a phosphorothioate linkage; and P is a 5’ phosphate or 5’phosphate mimic.

180. The method of claim 165 or 166, wherein the sense strand comprises 5’ csgsugguGfgAfCfUfucucUfCfaauu 3’ (SEQ ID NO:21) and the antisense strand comprises 5’ asAfsuugAfgAfgAfaguCfcAfccagcsasg 3’ (SEQ ID NO:22) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′ O-methyl (2′ OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′-fluoro A, G, C or U; and s is a phosphorothioate linkage.

181. The method of claim 165 or 166, wherein the sense strand comprises 5’ csgsugguGfgAfCfUfucucUfCfaauu 3’ (SEQ ID NO:23) and the antisense strand comprises 5’ PasAfsuugAfgAfgAfaguCfcAfccagcsasg 3’ (SEQ ID NO:24) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′ O-methyl (2′ OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′ fluoro A, G, C or U; and s is a phosphorothioate linkage; and P is a 5’ phosphate or 5’phosphate mimic.

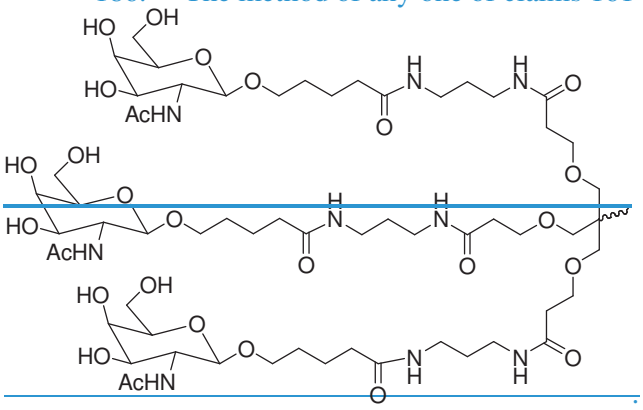
182. The method of claim 167 or 168, wherein the sense strand comprises 5’ csgsuggudGgucdTucucuaaaau 3’ (SEQ ID NO:35) and the antisense strand comprises 5’ asdAsuugagagdAagudCcaccagcsusu 3’ (SEQ ID NO:36), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′ O-methyl (2′ OMe) A, U, C, or G; dA, dC, dG, and dT are deoxyribose A, C, G, and T; and s is a phosphorothioate linkage.

183. The method of claim 169 or 170, wherein the sense strand comprises 5’ gsgsuggaCfuUfCfUfcucaAfUfuuua – 3’ (SEQ ID NO:25) and the antisense strand comprises 5’ usAfsaaaUfuGfAfgagaAfgUfccaccsasc 3’ (SEQ ID NO:26) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′ O-methyl (2′ OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′ fluoro A, G, C or U; and s is a phosphorothioate linkage.

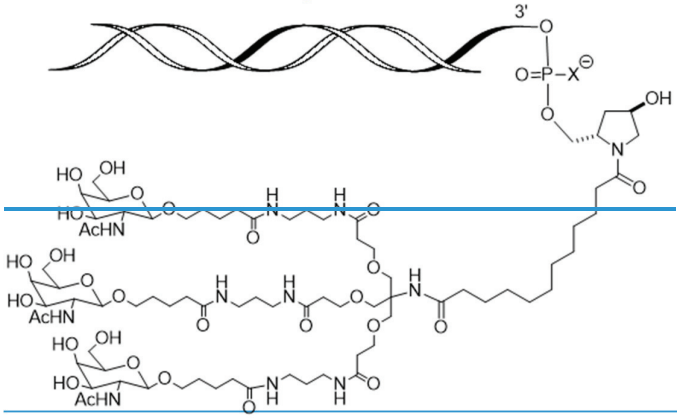
184. The method of claim 169 or 170, wherein the sense strand comprises 5’ gsgsuggaCfuUfCfUfcucaAfUfuuua 3’ (SEQ ID NO:27) and the antisense strand comprises 5’ PusAfsaaaUfuGfAfgagaAfgUfccaccsasc 3’ (SEQ ID NO:28) , wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′ O-methyl (2′ OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′ fluoro A, G, C or U; and s is a phosphorothioate linkage; and P is a 5’ phosphate or 5’phosphate mimic.

185. The method of claim 171 or 172, wherein the sense strand comprises 5’ gsusguGfcAfCfUfucgcuucaca 3’ (SEQ ID NO:41) and the antisense strand comprises 5’ usGfsugaAfgCfGfaaguGfcAfcacsusu 3’ (SEQ ID NO:42), wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′ O-methyl (2′ OMe) A, U, C, or G; Af, Cf, Gf or Uf are
2′ fluoro A, G, C or U; and s is a phosphorothioate linkage.

186. The method of any one of claims 161-172, wherein the ligand is



187. The method of claim 186, wherein the RNAi agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

188. A method of treating a subject having a Hepatitis D virus (HDV) infection, comprising administering to the subject a therapeutically effective amount of a composition for inhibiting expression of hepatitis B virus (HBV) in a cell, said composition comprising

(a) a first double-stranded RNAi agent comprising a first sense strand and a first antisense strand forming a double-stranded region,

wherein substantially all of the nucleotides of said first sense strand and substantially all of the nucleotides of said first antisense strand are modified nucleotides,

wherein said first sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; and

(b) a second double-stranded RNAi agent comprising a second sense strand and a second antisense strand forming a double-stranded region,

wherein substantially all of the nucleotides of said second sense strand and substantially all of the nucleotides of said second antisense strand are modified nucleotides,

wherein said second sense strand is conjugated to a ligand attached at the 3'-terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker;

wherein the first and second sense strands each independently comprise a sequence selected from the group consisting of

5'-UCGUGGUGGACUUCUCUCA-3' (SEQ ID NO:5),

5'-GUGCACUUCGCUUCACCUCUA-3' (SEQ ID NO:7),

5'-CGUGGUGGACUUCUCUCAAUU-3' (SEQ ID NO:9),

5'-CGUGGUGGUCUUCUCUAAAUU-3' (SEQ ID NO:37),

5'-GGUGGACUUCUCUCAAUUUUA-3' (SEQ ID NO:11), and

5'-GUGUGCACUUCGCUUCACA-3' (SEQ IDNO:39),

and wherein the first and second antisense strands each independently comprise a sequence selected from the group consisting of

5'-UGAGAGAAGUCCACCACGAUU-3' (SEQ ID NO:6);

5'-UAGAGGUGAAGCGAAGUGCACUU-3' (SEQ ID NO:8);

5'-AAUUGAGAGAAGUCCACCAGCAG-3' (SEQ ID NO:10);

5'-AAUUGAGAGAAGUCCACCAGCUU-3' (SEQ ID NO:38),

5'-UAAAAUUGAGAGAAGUCCACCAC-3' (SEQ ID NO:12), and

5'-UGUGAAGCGAAGUGCACACUU-3' (SEQ ID NO:40), thereby treating the subject.

189. The method of claim 188, wherein all of the nucleotides of said first and second sense strand and all of the nucleotides of said first and second antisense strand comprise a modification.

190. The method of claim 188, wherein at least one of said modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3' terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, and a nucleotide comprising a 5'-phosphate mimic.

191. The method of claim 188, wherein the first and second RNAi agent are selected from the group consisting of:
5'-usesguGfgUfGfGfacuucucuca-3' (SEQ ID NO:13)
5'-usGfsagaGfaAfGfuccaCfcAfcgasusu-3' (SEQ ID NO:14);
5'-usesguGfgUfGfGfacuucucuca-3' (SEQ ID NO:15)
5'-PusGfsagaGfaAfGfuccaCfcAfcgasusu-3' (SEQ ID NO:16);
5'-gsusgcacUfuCfGfCfuucaccucua-3' (SEQ ID NO:17)
5'-usAfsgagGfugaagcgAfaGfugcacsusu-3' (SEQ ID NO:18);
5'-gsusgcacUfuCfGfCfuucaccucua-3' (SEQ ID NO:19)
5'-PusAfsgagGfugaagcgAfaGfugcacsusu-3' (SEQ ID NO:20);
5'-csgsugguGfgAfCfUfucucUfCfaauu-3' (SEQ ID NO:21)
5'-asAfsuugAfgAfgAfaguCfcAfccagcsasg-3' (SEQ ID NO:22);
5'-csgsugguGfgAfCfUfucucUfCfaauu-3' (SEQ ID NO:23)
5'-PasAfsuugAfgAfgAfaguCfcAfccagcsasg-3' (SEQ ID NO:24);
5'-csgsuggudGgucdTucucuaaaauu-3' (SEQ ID NO:35)
5'-asdAsuugagagdAagudCcaccagcsusu-3' (SEQ ID NO:36);
5'-gsgsuggaCfuUfCfUfcucaAfUfuuua-3' (SEQ ID NO:25)
5'-usAfsaaaUfuGfAfgagaAfgUfccacesasc-3' (SEQ ID NO:26);
5'-gsgsuggaCfuUfCfUfcucaAfUfuuua-3' (SEQ ID NO:27)
5'-PusAfsaaaUfuGfAfgagaAfgUfccacesasc-3' (SEQ ID NO:28); and
5'-gsusguGfcAfCfUfucgcuucaca-3' (SEQ ID NO:41)

5’- usGfsugaAfgCfGfaaguGfcAfcacsusu -3’ (SEQ ID NO:42),

wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′ O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′ fluoro A, G, C or U; dA, dC, dG, and dT are deoxyribose A, C, G, and T; s is a phosphorothioate linkage; and P is a 5’ phosphate or 5’phosphate mimic.

192. The method of claim 188, wherein the first and second RNAi agents are

5’ usesguGfgUfGfGfacuucucuca 3’ (SEQ ID NO:15)

5’ PusGfsagaGfaAfGfuccaCfcAfcgasusu – 3’ (SEQ ID NO:16); and

5’ csgsugguGfgAfCfUfucucUfCfaauu 3’ (SEQ ID NO:21)

5’ asAfsuugAfgAfgAfaguCfcAfccagcsasg 3’ (SEQ ID NO:22),

wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′ O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′ fluoro A, G, C or U; s is a phosphorothioate linkage; and P is a 5’ phosphate or 5’phosphate mimic.

193. The method of claim 188, wherein the first and second RNAi agents are

5’ gsgsuggaCfuUfCfUfcucaAfUfuuua 3’ (SEQ ID NO:25)

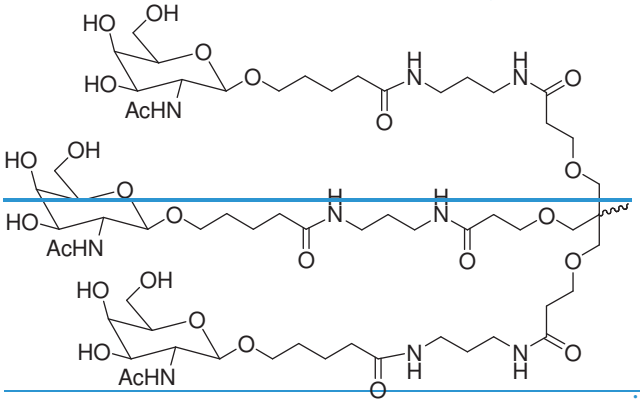
5’- usAfsaaaUfuGfAfgagaAfgUfccaccsasc – 3’ (SEQ ID NO:26); and

5’ gsusguGfcAfCfUfucgcuucaca 3’ (SEQ ID NO:41)

5’ usGfsugaAfgCfGfaaguGfcAfcacsusu 3’ (SEQ ID NO:42),

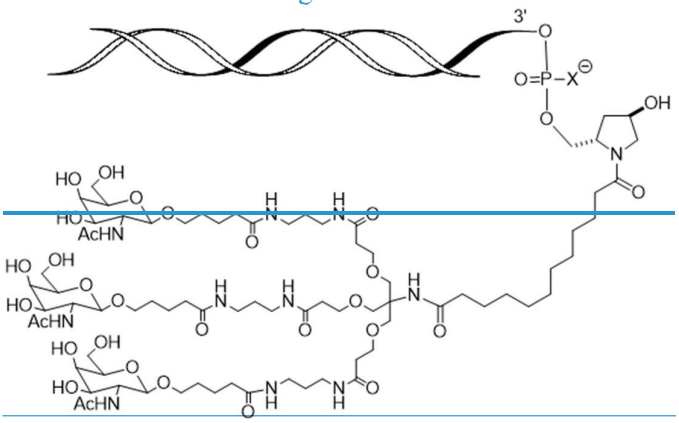
wherein A, C, G, and U are ribose A, C, G or U; a, g, c and u are 2′ O-methyl (2′-OMe) A, U, C, or G; Af, Cf, Gf or Uf are 2′ fluoro A, G, C or U; s is a phosphorothioate linkage; and P is a 5’ phosphate or 5’phosphate mimic.

194. The method of claim 188, wherein the ligand is



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~~195. The method of claim 194, wherein the RNAi agent is conjugated to the ligand as shown in the following schematic~~



~~wherein X is O or S.~~

~~196. The method of claim 188, wherein the subject is a human.~~

~~197. The method of any one of claims 161-196, wherein the double stranded RNAi agent is administered at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 50 mg/kg.~~

~~198. The method of claim 197, wherein the double stranded RNAi agent is administered at a dose of about 10 mg/kg to about 30 mg/kg.~~

~~199. The method of claim 197, wherein the double stranded RNAi agent is administered at a dose of about 3 mg/kg.~~

~~200. The method of claim 197, wherein the double stranded RNAi agent is administered at a dose of about 10 mg/kg.~~

~~201. The method of claim 199, wherein the double stranded RNAi agent is administered at a dose of about 0.5 mg/kg twice per week.~~

~~202. The method of any one of claims 161-196, wherein the double stranded RNAi agent is administered at a fixed dose of about 50 mg to 200 mg.~~

~~203. The method of any one of claims 161-196, wherein the double stranded RNAi agent is administered subcutaneously.~~

~~204. The method of any one of claims 161-196, wherein the double stranded RNAi agent is administered intravenously.~~

~~205. The method of any one of claims 161-196, wherein said RNAi agent is administered in two or more doses.~~

~~206. The method of any one of claims 161-196, wherein said RNAi agent is administered at intervals selected from the group consisting of once every about 12 hours, once every about 24 hours, once every about 48 hours, once every about 72 hours, and once every about 96 hours.~~

~~207. The method of any one of claims 161-196, wherein said RNAi agent is administered twice per week.~~

~~208. The method of any one of claims 161-196, wherein said RNAi agent is administered every other week.~~

~~209. The method of any one of claims 161-196, further comprising administering to the subject an additional therapeutic agent.~~

~~210. The method of claim 209, wherein the additional therapeutic agent is selected from the group consisting of an antiviral agent, a reverse transcriptase inhibitor, an immune stimulator, a therapeutic vaccine, a viral entry inhibitor, an oligonucleotide that inhibits the secretion or release of HbsAg, a capsid inhibitor, a covalently closed circular (ccc) HBV DNA inhibitor, and a combination of any of the foregoing.~~

~~211. The method of any one of claims 161-196, further comprising administering to the subject a reverse transcriptase inhibitor.~~

~~212. The method of any one of claims 161-196, further comprising administering to the subject a reverse transcriptase inhibitor and an immune stimulator.~~

~~213. The method of claim 211 or 212, wherein the a reverse transcriptase inhibitor is slected from the group consisting of Tenofovir disoproxil fumarate (TDF), Tenofovir alafenamide, Lamivudine, Adefovir dipivoxil, Entecavir (ETV), Telbivudine, and AGX-1009.~~

~~214. The method of claim 213, wherein the immune stimulator is selected from the group consisting of pegylated interferon alfa 2a (PEG-IFN 2a), Interferon alfa-2b, a recombinant human interleukin-7, and a Toll-like receptor 7 (TLR7) agonist.~~

~~215. A method of treating a subject having a Hepatitis D virus (HDV) infection, comprising administering to the subject a therapeutically effective amount of a composition for inhibiting expression of hepatitis D virus (HDV) in a cell, said composition comprising~~

~~(a) a first double-stranded RNAi agent comprising a first strand and a first antisense strand forming a double-stranded region,~~

~~wherein substantially all of the nucleotides of said first sense strand and substantially all of the nucleotides of said first antisense strand are modified nucleotides,~~

~~wherein said first sense strand is conjugated to a ligand attached at the 3' terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; and~~

~~(b) a second double-stranded RNAi agent comprising a second sense strand and a second antisense strand forming a double-stranded region,~~

~~wherein substantially all of the nucleotides of said second sense strand and substantially all of the nucleotides of said second antisense strand are modified nucleotides,~~

~~wherein said second sense strand is conjugated to a ligand attached at the 3' terminus, and~~

~~wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker;~~

~~wherein said first sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1, and said first antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2,~~

~~wherein said sense second strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:29, and said second antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:30, thereby treating the subject.~~

~~216. The method of claim 215, wherein the first sense strand comprises a sequence selected from the group consisting of~~

~~5' UCGUGGUGGACUUCUCUCA 3' (SEQ IDNO:5),~~

~~5' GUGCACUUCGCUUCACCUCUA 3' (SEQ ID NO:7),~~

~~5' CGUGGUGGACUUCUCUCAAUU 3' (SEQ ID NO:9),~~

~~5' CGUGGUGGUCUUCUCUAAAUU 3' (SEQ ID NO:37),~~

~~5' GGUGGACUUCUCUCAAUUUUA 3' (SEQ ID NO:11), and~~

~~5' GUGUGCACUUCGCUUCACA 3' (SEQ IDNO:39), and~~

~~wherein the second antisense strand comprises a sequence selected from the group consisting of~~

~~5' UGAGAGAAGUCCACCACGAUU 3' (SEQ ID NO:6);~~

~~5' UAGAGGUGAAGCGAAGUGCACUU 3' (SEQ ID NO:8);~~

~~5' AAUUGAGAGAAGUCCACCAGCAG 3' (SEQ ID NO:10);~~

~~5' AAUUGAGAGAAGUCCACCAGCUU 3' (SEQ ID NO:38),~~

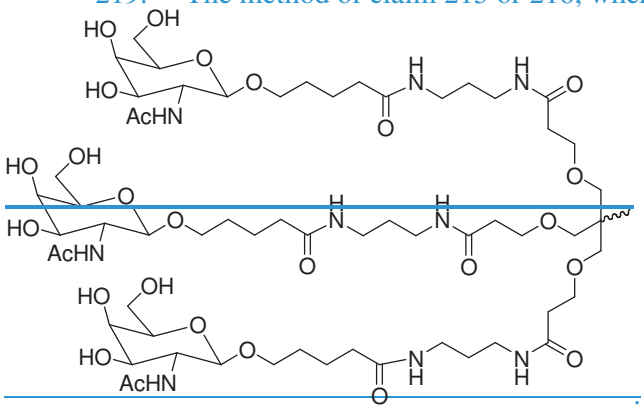
~~5' UAAAAUUGAGAGAAGUCCACCAC 3' (SEQ ID NO:12), and~~

~~5' UGUGAAGCGAAGUGCACACUU 3' (SEQ ID NO:40).~~

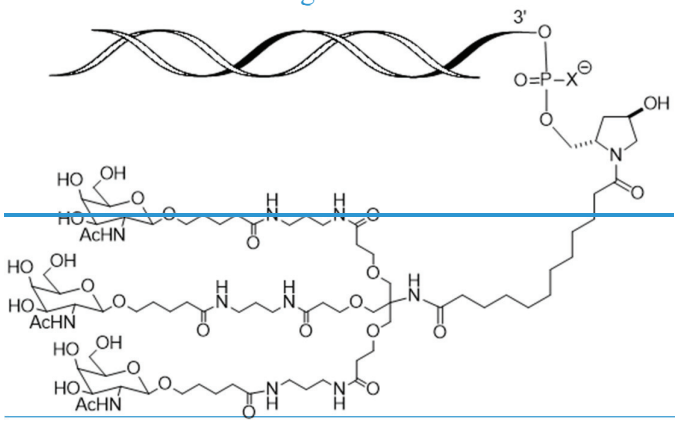
~~217. The method of claim 215 or 216, wherein all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand comprise a modification.~~

~~218. The method of claim 215 or 216, wherein at least one of said modified nucleotides is selected from the group consisting of a dexoy-nucleotide, a 3' terminal deoxy-thymine (dT) nucleotide, a 2' O-methyl modified nucleotide, a 2' fluoro modified nucleotide, a 2' deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2' hydroxly-modified nucleotide, a 2' methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5' phosphate, and a nucleotide comprising a 5' phosphate mimic.~~

~~219. The method of claim 215 or 216, wherein the ligand is~~



~~220. The method of claim 219, wherein the RNAi agent is conjugated to the ligand as shown in the following schematic~~



~~wherein X is O or S.~~