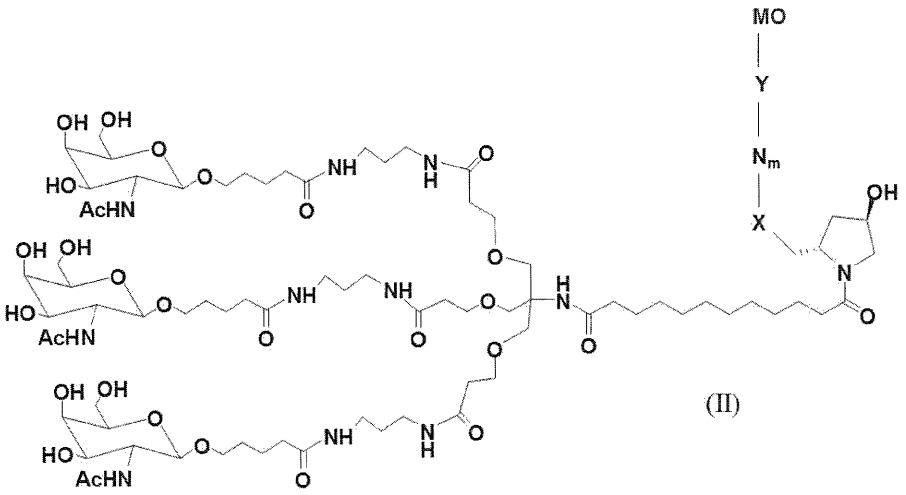
emergence of resistance mutations in HCV requires treatment with additional agents. Developing therapies include NS3/4A protease inhibitors, NS5A protein inhibitors, nucleoside/tide NS5B polymerase inhibitors and non-nucleoside NS5B inhibitors. However, there remains a need for additional therapies to treat infected individuals who do not respond to current treatments, who relapse following successful treatment, or who have a low tolerability for one or more currently used drugs. Resistance to antiviral therapy is a major problem associated with a high mutation rate of HCV and is seen even with combinations of drugs working through multiple mechanisms. Accordingly, therapeutics that target conserved, mutation-resistant viral host factors, such as miR-122, represent an opportunity to effect higher and more durable cure rates.

SUMMARY

In one aspect, the present invention refers to a compound comprising a modified oligonucleotide having the structure $A_E^{Me}C_EA_E^{Me}C_E^{Me}C_EA_ETGU_SC_SAC_SAC_STC_SC_S$ (SEQ ID NO: 4), wherein the superscript "Me" indicates 5-methylcytosine, wherein nucleosides not followed by a subscript are β-D-deoxyribonucleosides, nucleosides followed by a subscript "E" are 2'-MOE nucleosides, nucleosides followed by a subscript "S" are S-cEt nucleosides, and each internucleoside linkage is a phosphorothioate internucleoside linkage. In one example, there is disclosed a compound comprising a modified oligonucleotide consisting of 16 to 22 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is complementary to miR-122 (SEQ ID NO: 1) and wherein the modified oligonucleotide comprises at least 16 contiguous nucleosides of the following nucleoside pattern I in the 5' to 3' orientation: (R)X-NQ-NQ-NB-NB-NQ-NB-NQ-NB-NQ-NB-NB-(NZ)Y, wherein each R is, independently, a non-bicyclic nucleoside or a bicyclic nucleoside; X is from 4 to 10; each NB is, independently, a bicyclic nucleoside; each NQ is, independently, a non-bicyclic nucleoside; Y is 0 or 1; and NZ is a modified nucleoside or an unmodified nucleoside. In another aspect, the present invention refers to a compound of the structure:



(II)

wherein X is a phosphodiester linkage; m is 1; N of N_m is a β-D-deoxyriboadenosine; Y is a phosphodiester linkage; and MO is a modified oligonucleotide having the structure

$A_E{}^{Me}C_EA_E{}^{Me}C_E{}^{Me}C_EA_ET_ETGU_SC_SAC_SAC_STC_SC_S$ (SEQ ID NO: 4), wherein the superscript "Me" indicates 5-methylcytosine, wherein nucleosides not followed by a subscript are β-D-deoxyribonucleosides, nucleosides followed by a subscript "E" are 2'-MOE nucleosides, nucleosides followed by a subscript "S" are S-cEt nucleosides, and each internucleoside linkage is a phosphorothioate internucleoside linkage; and wherein Y is linked to the 3' terminus of the modified oligonucleotide.In another aspect, the present invention refers to a pharmaceutical composition comprising the compound as described herein and a pharmaceutically acceptable carrier. In a further aspect, the present invention refers to use of a compound as disclosed herein, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a hepatitis C virus (HCV)-infected human subject. In one example, there is disclosed the use of a compound as disclosed herein, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating an HCV-infected human subject.

Provided herein are compounds comprising a modified oligonucleotide consisting of 16 to 22 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is complementary to miR-122 (SEQ ID NO: 1) and wherein the modified oligonucleotide comprises at least 16 contiguous nucleosides of the following nucleoside pattern I in the 5' to 3' orientation:

$(R)_X$-N^Q-N^Q-N^B-N^B-N^Q-N^B-N^Q-N^B-N^Q-N^B-N^B-$(N^Z)_Y$

wherein each R is, independently, a non-bicyclic nucleoside or a bicyclic nucleoside;

X is from 4 to 10;

each N^B is, independently, a bicyclic nucleoside;

each N^Q is, independently, a non-bicyclic nucleoside;

Y is 0 or 1; and

N^Z is a modified nucleoside or an unmodified nucleoside.

In certain examples, a compound provided herein comprises a modified oligonucleotide comprising at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, or 22 contiguous nucleosides of nucleoside pattern I.

In certain examples, each bicyclic nucleoside is independently selected from an LNA nucleoside, a cEt nucleoside, and an ENA nucleoside. In certain examples, at least two bicyclic nucleosides are different from one another. In certain examples, all bicyclic nucleosides have the same sugar moiety as one another. In certain examples, each bicyclic nucleoside is a cEt nucleoside. In certain examples, a cEt nucleoside is an S-cEt nucleoside. In certain examples, a cEt nucleoside is an R-cEt nucleoside. In certain examples, each bicyclic nucleoside is an LNA nucleoside.

CLAIMS

1. A compound comprising a modified oligonucleotide having the structure:

   $A_E^{Me}C_EA_E^{Me}C_E^{Me}C_EA_ET_ETGU_SC_SAC_SAC_STC_SC_S$ (SEQ ID NO: 4),

   wherein the superscript "Me" indicates 5-methylcytosine, wherein nucleosides not followed by a subscript are β-D-deoxyribonucleosides, nucleosides followed by a subscript "E" are 2'-MOE nucleosides, nucleosides followed by a subscript "S" are S-cEt nucleosides, and each internucleoside linkage is a phosphorothioate internucleoside linkage.

2. The compound of claim 1, wherein the compound comprises a conjugate moiety linked to the 5' terminus or the 3' terminus of the modified oligonucleotide.

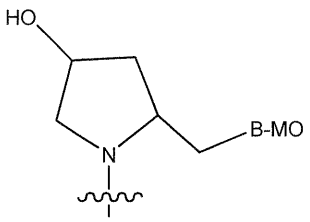
3. The compound of claim 2, wherein the conjugate moiety comprises at least one ligand selected from a carbohydrate, cholesterol, a lipid, a phospholipid, an antibody, a lipoprotein, a hormone, a peptide, a vitamin, a steroid, and a cationic lipid.

4. The compound of claim 2 or claim 3, wherein the compound has the structure:

   L_n-linker-X_1-N_m-X_2-MO

wherein each L is, independently, a ligand and n is from 1 to 10; each N is, independently, a modified or unmodified nucleoside and m is from 1 to 5; X_1 and X_2 are each, independently, a phosphodiester linkage or a phosphorothioate linkage; and MO is the modified oligonucleotide.

5. The compound of claim 4, wherein the compound has the structure:



wherein:

B is selected from –O-, -S-, -N(R^N)-, –Z-P(Z')(Z")O-, –Z-P(Z')(Z")O-N_m-X-, and –Z-P(Z')(Z")O-N_m-Y-;

MO is the modified oligonucleotide;

R^N is selected from H, methyl, ethyl, propyl, isopropyl, butyl, and benzyl;

Z, Z', and Z" are each independently selected from O and S;

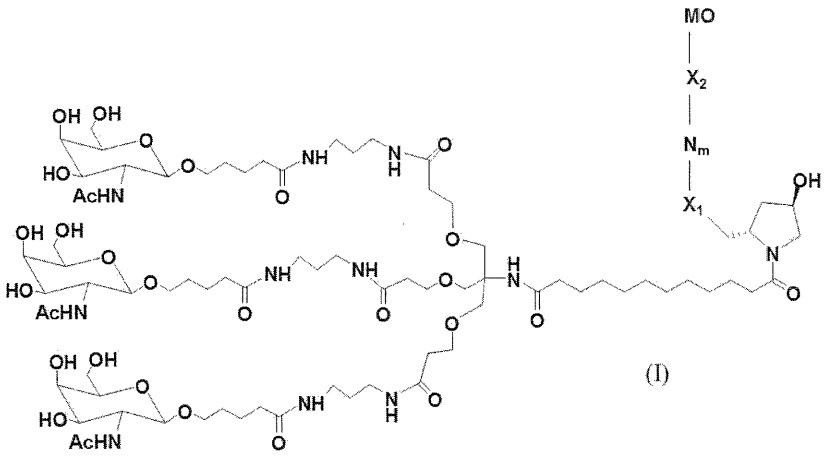
each N is, independently, a modified or unmodified nucleoside;
m is from 1 to 5;
X is selected from a phosphodiester linkage and a phosphorothioate linkage;
Y is a phosphodiester linkage; and
the wavy line indicates the connection to the rest of the linker and ligand(s).

6. The compound of any of claim 4 or claim 5, wherein n is 3.

7. The compound of any one of claims 4 to 6, wherein at least one ligand is a carbohydrate, and wherein the carbohydrate is optionally selected from N-acetylgalactosamine, galactose, galactosamine, N-formylgalactosamine, N-propionyl-galactosamine, N-n-butanoylgalactosamine, and N-iso-butanoyl-galactosamine.

8. The compound of any one of claims 4 to 7, wherein each ligand is N-acetylgalactosamine.

9. The compound of any one of claims 4 to 8, wherein the compound has the structure:



wherein each N of N_m is, independently, a modified or unmodified nucleoside and m is from 1 to 5; X_1 and X_2 are each, independently, a phosphodiester linkage or a phosphorothioate linkage; and MO is the modified oligonucleotide.

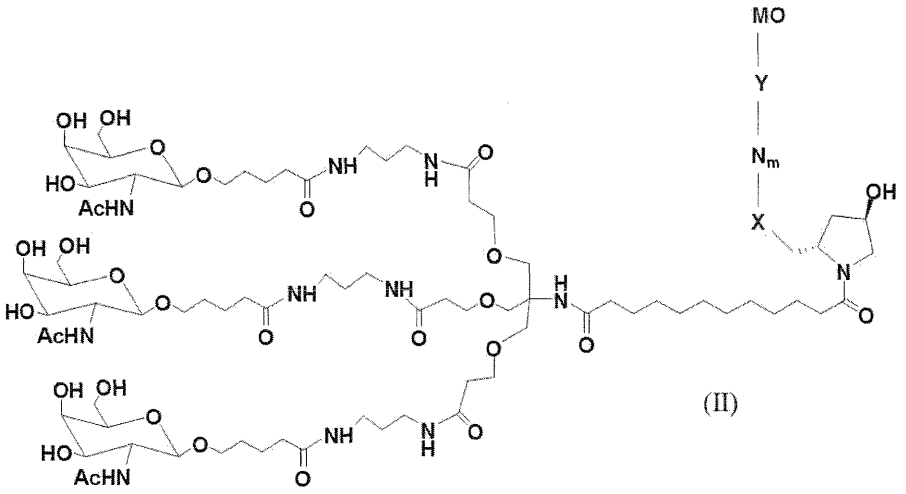
10. The compound of claim 9, wherein each of X_1 and X_2 is a phosphodiester linkage.

11. The compound of any one of claims 4 to 10, wherein m is 1.

12. The compound of any one of claims 4 to 11, wherein each N comprises an unmodified sugar moiety, wherein each unmodified sugar moiety is, independently, a β-D-ribose or a β-D-deoxyribose.

13. The compound of any one of claims 4 to 12, wherein at least one N comprises a purine nucleobase, wherein each purine nucleobase is independently selected from adenine, guanine, hypoxanthine, xanthine, and 7-methylguanine.

14. A compound of the structure:



wherein X is a phosphodiester linkage; m is 1; N of N_m is a β-D-deoxyriboadenosine; Y is a phosphodiester linkage; and MO is a modified oligonucleotide having the structure $A_E{}^{Me}C_EA_E{}^{Me}C_E{}^{Me}C_EA_ET_ETGU_SC_SAC_SAC_STC_SC_S$ (SEQ ID NO: 4), wherein the superscript "Me" indicates 5-methylcytosine, wherein nucleosides not followed by a subscript are β-D-deoxyribonucleosides, nucleosides followed by a subscript "E" are 2'-MOE nucleosides, nucleosides followed by a subscript "S" are S-cEt nucleosides, and each internucleoside linkage is a phosphorothioate internucleoside linkage; and wherein Y is linked to the 3' terminus of the modified oligonucleotide.

15. A pharmaceutical composition comprising the compound of claim 14 and a pharmaceutically acceptable carrier.

16. The pharmaceutical composition of claim 14, which is a sterile aqueous solution.

17. Use of a compound of claim 14, or the pharmaceutical composition of claim 15 or claim 16, in the manufacture of a medicament for treating a hepatitis C virus (HCV)-infected human subject .

18. The use of claim 17 wherein the medicament reduces the symptoms of HCV infection, prevents a rebound in serum HCV RNA, and/or delays a rebound in serum HCV RNA.

19. The use of claim 17 or claim 18, wherein the medicament reduces HCV RNA level.

20. The use of any one of claims 17 to 19, wherein the use achieves a sustained virological response.

21. The use of any one of claims 17 to 20, wherein the subject is infected with one or more HCV genotypes selected from genotype 1, genotype 2, genotype 3, genotype 4, genotype 5, and genotype 6.

22. The use of claim 21, wherein the HCV genotype is selected from genotype 1a, genotype 1b, genotype 2a, genotype 2b, genotype 2c, genotype 2d, genotype 3a, genotype 3b, genotype 3c, genotype 3d, genotype 3e, genotype 3f, genotype 4a, genotype 4b, genotype 4c, genotype 4d, genotype 4e, genotype 4f, genotype 4g, genotype 4h, genotype 4i, genotype 4j, genotype 5a, and genotype 6a.

23. The use of any one of claims 17 to 22, wherein the medicament is to be administered with at least one additional therapeutic agent.

24. The use of claim 23, wherein the at least one therapeutic agent is selected from a protease inhibitor, a polymerase inhibitor, a cofactor inhibitor, an RNA polymerase inhibitor, a structural protein inhibitor, a non-structural protein inhibitor, a cyclophilin inhibitor, an entry inhibitor, a TLR7 agonist, and an interferon.

25. The use of claim 23, wherein the at least one therapeutic agent is selected from a protease inhibitor, an NS5A inhibitor, an NS3/4A inhibitor, a nucleoside NS5B inhibitor, a nucleotide NS5B inhibitor, a non-nucleoside NS5B inhibitor, a cyclophilin inhibitor and an interferon.

26. The use of claim 23, wherein the at least one therapeutic agent is selected from interferon alfa-2a, interferon alpha-2b, interferon alfacon-1, peginterferon alpha-2b, peginterferon alpha-2a, interferon-alpha-2b extended release, interferon lambda, sofosbuvir, ledipasvir, ribavirin, telapravir, boceprevir, vaniprevir, asunaprevir, ritonavir, setrobuvir, daclastavir, simeprevir, alisporivir, mericitabine, tegobuvir, danoprevir, sovaprevir, and neceprevir.

27. The use of claim 26, wherein the at least one therapeutic agent is sofosbuvir.

28. The use of claim 26, wherein the at least one therapeutic agent is sofosbuvir and ledipasvir.

29. The use of claim 26, wherein the at least one therapeutic agent is daclatasvir.

30. The use of claim 26, wherein the at least one therapeutic agent is simeprevir.

31. The use of any one of claims 17 to 30, wherein the subject is a direct-acting anti-viral non-responder.

32. The use of any one of claims 17 to 31, wherein the subject has an HCV-associated disease, wherein the HCV-associated disease is optionally selected from cirrhosis, liver fibrosis, steatohepatitis, steatosis, and hepatocellular carcinoma.

33. The use of any one of claims 17 to 32, wherein the compound or pharmaceutical composition is to be administered once per week, once per two weeks, once per three weeks, once per month, once per two months, or once per three months.

34. The use of any one of claims 17 to 33, wherein the dose of the compound or conjugate is less than or equal to 10 mg/kg, less than or equal to 7.5 mg/kg, less than or equal to 5 mg/kg per week, less than or equal to 4.5 mg/kg, less than or equal to 4.0 mg/kg, less than or equal to 3.5 mg/kg, less than or equal to 3.0 mg/kg, less than or equal to 2.5 mg/kg, less than or equal to 2.0 mg/kg, less than or equal to 1.5 mg/kg, or less than or equal to 1.0 mg/kg.