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(54) Title: COMPOSITIONS AND METHODS FOR INHIBITING HMGB1 EXPRESSION

(57) Abstract: This disclosure relates to oligonucleotides, compositions and methods useful for reducing HMGB1 expression, particu-
larly in hepatocytes. Disclosed oligonucleotides for the reduction of HMGB1 expression may be either double-stranded or single-strand-
ed and may be modified for improved characteristics such as stronger resistance to nucleases and lower immunogenicity. Disclosed
oligonucleotides for the reduction of HMGB1 expression may also be designed to include targeting ligands to target a particular cell or
organ, such as the hepatocytes of the liver, and may be used to treat liver fibrosis and related conditions.

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COMPOSITIONS AND METHODS FOR INHIBITING HMGB1 EXPRESSION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. § 119(e) of U.S. provisional application no. 62/786,287, filed December 28, 2018, U.S. provisional application no. 62/787,038, filed December 31, 2018, and U.S. provisional application no. 62/788,111, filed January 3, 2019, the entire contents of each of which is incorporated herein by reference.

REFERENCE TO SEQUENCE LISTING, TABLE OR COMPUTER PROGRAM

[0002] The official copy of the Sequence Listing is submitted concurrently with the specification as an ASCII formatted text file via EFS-Web, with a file name of “400930-014WO_ST25.txt,” a creation date of December 12, 2019, and a size of 306 kilobytes. The Sequence Listing filed via EFS-Web is part of the specification and is hereby incorporated in its entirety by reference herein.

FIELD OF THE INVENTION

[0003] The present application relates to oligonucleotides and uses thereof, particularly uses relating to the treatment of conditions involving fibrosis.

BACKGROUND OF THE INVENTION

[0004] Tissue fibrosis is a condition characterized by an abnormal accumulation of extracellular matrix and inflammatory factors that result in scarring and promote chronic organ injury. In liver, fibrosis is a multi-cellular response to hepatic injury that can lead to cirrhosis and hepatocellular cancer. The response is often triggered by liver injury associated with conditions such as alcohol abuse, viral hepatitis, metabolic diseases, and liver diseases, such as a cholestatic liver disease, nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). Studies have implicated the high mobility group box 1 (HMGB1) protein as having a pro-fibrotic role in liver fibrosis (see, e.g., Li L-C, et al., J. Cell. Mol. Med., 2014, 18(12):2331-39). HMGB1 is a nuclear protein released from injured cells that functions as a proinflammatory mediator and has been shown to recruit hepatic stellate cells and liver endothelial cells to sites of liver injury (Seo et al., Am J Physiol Gastrointest Liver Physiol., 2013, 305:G838–G848). Hepatic stellate cells are believed to play a central role in the progression of liver fibrosis through their transformation into proliferative myofibroblastic cells that promote fibrogenic activity in the liver (see, Kao YH, et al., Transplant Proc., 2008, 40:2704–5).

BRIEF SUMMARY OF THE INVENTION

[0005] Aspects of the disclosure relate to compositions and methods for treating fibrosis (e.g., liver fibrosis) in a subject using oligonucleotides that selectively inhibit HMGB1 expression. In some embodiments, potent RNAi oligonucleotides have been developed for selectively inhibiting HMGB1

expression. Accordingly, in some embodiments, RNAi oligonucleotides provided herein are useful for reducing HMGB1 expression, particularly in hepatocytes, and thereby decreasing or preventing fibrosis. In some embodiments, RNAi oligonucleotides incorporating nicked tetraloop structures are conjugated with GalNAc moieties to facilitate delivery to liver hepatocytes to inhibit HMGB1 expression for the treatment of liver fibrosis (see, e.g., Examples 3 and 4, evaluating GalNAc-conjugated HMGB1 oligonucleotides in primary monkey or human hepatocytes). In some embodiments, methods are provided herein involving the use of RNAi oligonucleotides for treating subjects having or suspected of having liver conditions such as, for example, cholestatic liver disease, nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). In further embodiments, the disclosure is based on an identification of key targeting sequences of HMGB1 mRNA that are particularly amenable to bringing about mRNA knockdown using RNAi oligonucleotide-based approaches. Furthermore, RNAi oligonucleotides having particular modification patterns are developed herein (as outline in Table 2) and that are particularly useful for reducing HMGB1 mRNA expression level in vivo are provided herein.

[0006] Some aspects of the present disclosure provide oligonucleotides for reducing expression of HMGB1, the oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand of 15 to 30 nucleotides in length, wherein the sense strand forms a duplex region with the antisense strand, wherein the sense strand comprises a sequence as set forth in any one of SEQ ID NOs: 1-13 and wherein the antisense strand comprises a complementary sequence selected from SEQ ID NOs: 14-26.

[0007] In some embodiments, the sense strand sequence comprises or consists of a sequence as set forth in any one of SEQ ID NOs: 27-39. In some embodiments, the antisense strand sequence consists of a sequence as set forth in any one of SEQ ID NOs: 14-26.

[0008] In some embodiments, the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 27 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 14.

[0009] In some embodiments, the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 28 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 15.

[0010] In some embodiments, the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 29 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 16.

[0011] In some embodiments, the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 30 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 17.

[0012] In some embodiments, the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 31 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 18.

[0013] In some embodiments, the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 32 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 19.

[0014] In some embodiments, the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 33 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 20.

[0015] In some embodiments, the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 34 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 21.

[0016] In some embodiments, the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 35 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 22.

[0017] In some embodiments, the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 36 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 23.

[0018] In some embodiments, the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 37 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 24.

[0019] In some embodiments, the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 38 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 25.

[0020] In some embodiments, the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 39 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 26.

[0021] In some embodiments, the oligonucleotide comprises at least one modified nucleotide.

[0022] In some embodiments, all of the nucleotides of the oligonucleotide described herein are modified. In some embodiments, the modified nucleotide comprises a 2'-modification. In some embodiments, the 2'-modification is a 2'-fluoro or 2'-O-methyl.

[0023] In some embodiments, one or more of positions 1, 2, 4, 6, 7, 12, 14, 16, 18-27, and 31-36 of the sense strand, and/or one or more of positions 1, 4, 6, 8, 9, 11, 13, 15, 18, and 20-22 of the antisense strand are modified with a 2'-O-methyl. In some embodiments, all of positions 1, 2, 4, 6, 7, 12, 14, 16, 18-27, and 31-36 of the sense strand, and all of positions 1, 4, 6, 8, 9, 11, 13, 15, 18, and 20-22 of the antisense strand are modified with a 2'-O-methyl. In some embodiments, one or more of positions 3, 5, 8-11, 13, 15, and 17 of the sense strand, and/or one or more of positions 2, 3, 5, 7, 10, 12, 14, 16, 17, and 19 of the antisense strand are modified with a 2'-fluoro. In some embodiments, all of positions 3, 5, 8-11, 13, 15, and 17 of the sense strand, and all of positions 2, 3, 5, 7, 10, 12, 14, 16, 17, and 19 of the antisense strand are modified with a 2'-fluoro.

[0024] In some embodiments, one or more of positions 1-7, 12-27, and 31-36 of the sense strand, and/or one or more of positions 1, 4, 6, 8, 9, 11-13, and 15-22 of the antisense strand are modified with a 2'-O-methyl. In some embodiments, all of positions 1-7, 12-27, and 31-36 of the sense strand, and all of positions 1, 4, 6, 8, 9, 11-13, and 15-22 of the antisense strand are modified with a 2'-O-

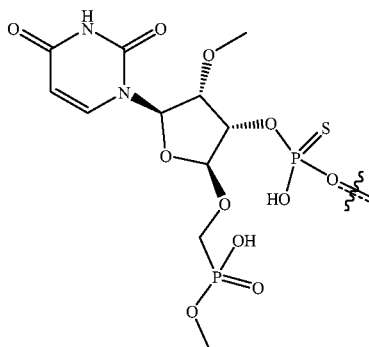
methyl. In some embodiments, one or more of positions 8-11 of the sense strand, and/or one or more of positions 2, 3, 5, 7, 10, and 14 of the antisense strand are modified with a 2'-fluoro. In some embodiments, all of positions 8-11 of the sense strand, and all of positions 2, 3, 5, 7, 10, and 14 of the antisense strand are modified with a 2'-fluoro.

[0025] In some embodiments, one or more of positions 1, 2, 4-7, 9, 11, 14-16, 18-27, and 31-36 of the sense strand, and/or one or more of positions 1, 6, 8, 9, 11, 13, 15, 18, and 20-22 of the antisense strand are modified with a 2'-O-methyl. In some embodiments, all of positions 1, 2, 4-7, 9, 11, 14-16, 18-27, and 31-36 of the sense strand, and all of positions 1, 6, 8, 9, 11, 13, 15, 18, and 20-22 of the antisense strand are modified with a 2'-O-methyl. In some embodiments, one or more of positions 3, 8, 10, 12, 13, and 17 of the sense strand, and/or one or more of positions 2-5, 7, 10, 12, 14, 16, 17, and 19 of the antisense strand are modified with a 2'-fluoro. In some embodiments, all of positions 3, 8, 10, 12, 13, and 17 of the sense strand, and all of positions 2-5, 7, 10, 12, 14, 16, 17, and 19 of the antisense strand are modified with a 2'-fluoro.

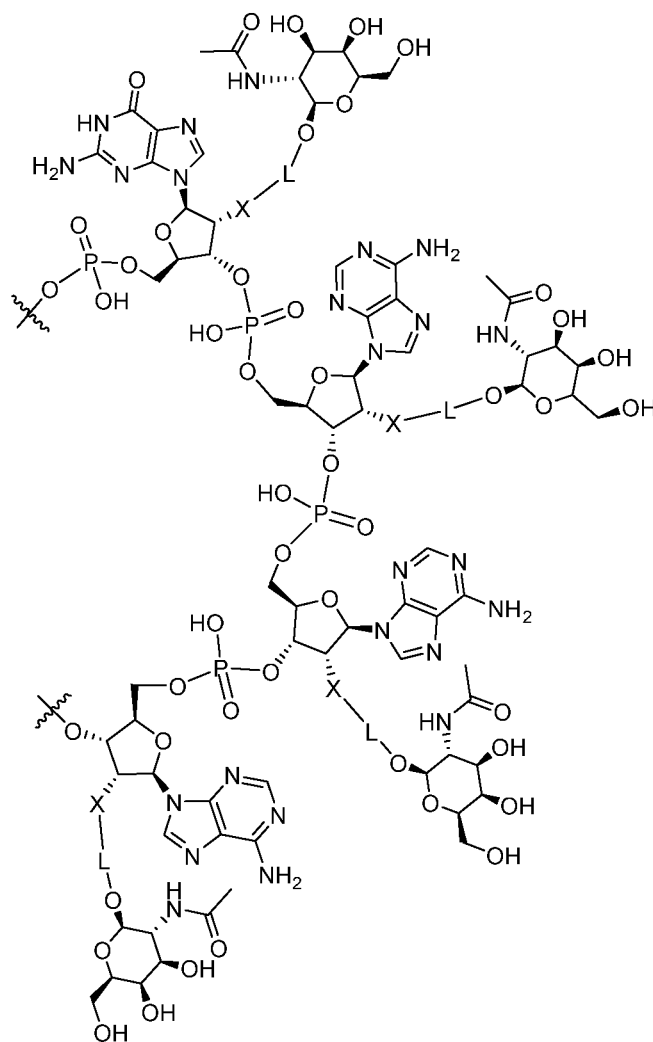
[0026] In some embodiments, the oligonucleotide comprises at least one modified internucleotide linkage. In some embodiments, the at least one modified internucleotide linkage is a phosphorothioate linkage.

[0027] In some embodiments, the oligonucleotide has a phosphorothioate linkage between one or more of: positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 3 and 4 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand. In some embodiments, the oligonucleotide has a phosphorothioate linkage between each of: positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand.

[0028] In some embodiments, the uridine at the first position of the antisense strand comprises a phosphate analog. In some embodiments, the oligonucleotide comprises the following structure at position 1 of the antisense strand:



[0029] In some embodiments, one or more of the nucleotides of the –AAA– sequence at positions 28-30 on the sense strand is conjugated to a monovalent GalNAc moiety. In some embodiments, each of the nucleotides of the –AAA– sequence at positions 28-30 on the sense strand is conjugated to a monovalent GalNAc moiety. In some embodiments, the –AAA– motif at positions 28-30 on the sense strand comprises the structure:

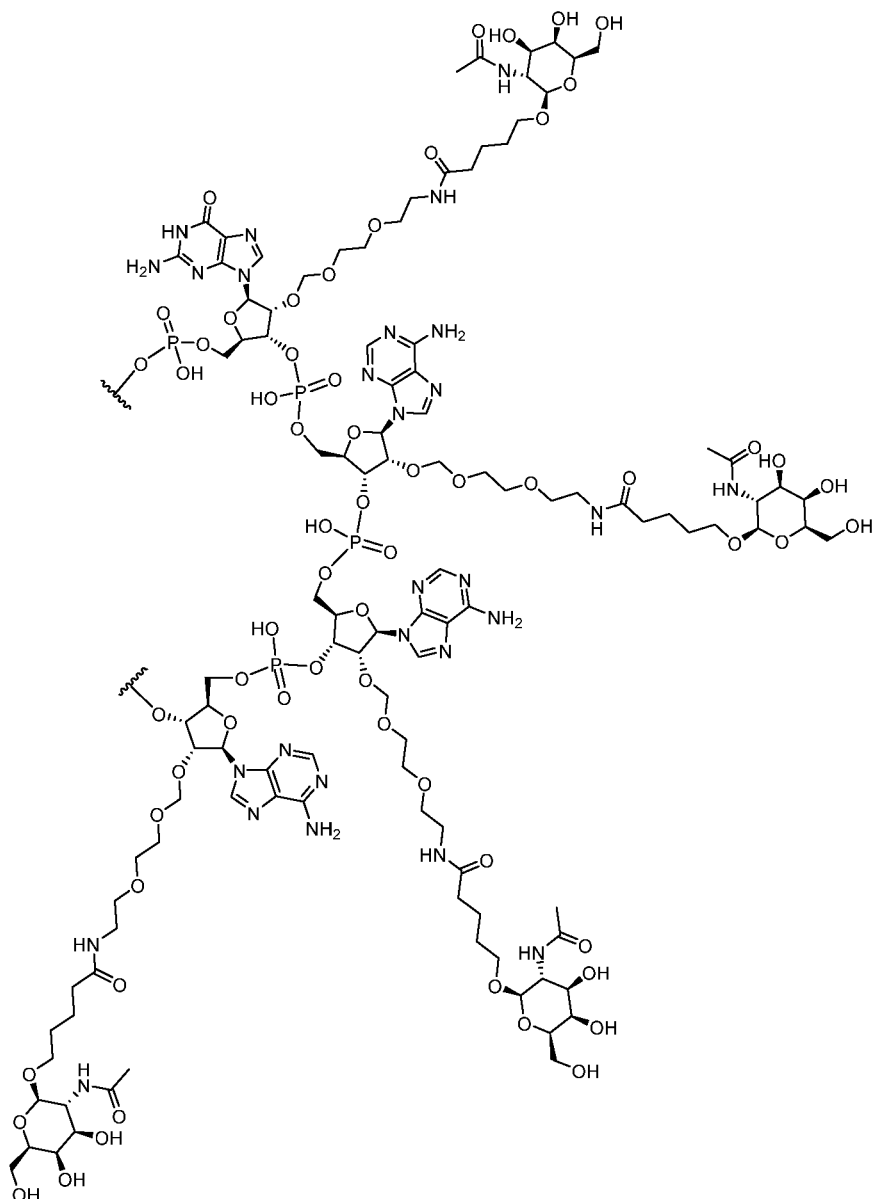


wherein:

L represents a bond, click chemistry handle, or a linker of 1 to 20, inclusive, consecutive, covalently bonded atoms in length, selected from the group consisting of substituted and unsubstituted alkylene, substituted and unsubstituted alkenylene, substituted and unsubstituted alkynylene, substituted and unsubstituted heteroalkylene, substituted and unsubstituted heteroalkenylene, substituted and unsubstituted heteroalkynylene, and combinations thereof; and X is O, S, or N.

[0030] In some embodiments, L is an acetal linker. In some embodiments, X is O.

[0031] In some embodiments, the –AAA– sequence at positions 28-30 on the sense strand comprises the structure:



[0032] Other aspects of the present disclosure provide oligonucleotides for reducing expression of HMGB1, the oligonucleotide comprising an antisense strand of 15 to 30 nucleotides in length, wherein the antisense strand has a region of complementarity to HMGB1 that is complementary to at least 15 contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 1-13.

[0033] In some embodiments, the antisense strand is 19 to 27 nucleotides in length. In some embodiments, the antisense strand is 22 nucleotides in length. In some embodiments, the oligonucleotide further comprises a sense strand of 15 to 50 nucleotides in length, wherein the sense

strand forms a duplex region with the antisense strand. In some embodiments, the sense strand is 19 to 50 nucleotides in length. In some embodiments, the duplex region is 20 nucleotides in length.

[0034] In some embodiments, the oligonucleotide for reducing expression of HMGB1 comprising a sense strand and an antisense strand, wherein:

(a) the sense strand comprises a sequence as set forth in SEQ ID NO: 788 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 814;

(b) the sense strand comprises a sequence as set forth in SEQ ID NO: 789 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 815;

(c) the sense strand comprises a sequence as set forth in SEQ ID NO: 790 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 816;

(d) the sense strand comprises a sequence as set forth in SEQ ID NO: 791 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 817;

(e) the sense strand comprises a sequence as set forth in SEQ ID NO: 792 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 818;

(f) the sense strand comprises a sequence as set forth in SEQ ID NO: 793 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 819;

(g) the sense strand comprises a sequence as set forth in SEQ ID NO: 794 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 820;

(h) the sense strand comprises a sequence as set forth in SEQ ID NO: 795 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 821;

(i) the sense strand comprises a sequence as set forth in SEQ ID NO: 796 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 822;

(j) the sense strand comprises a sequence as set forth in SEQ ID NO: 797 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 823;

(k) the sense strand comprises a sequence as set forth in SEQ ID NO: 798 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 824;

(l) the sense strand comprises a sequence as set forth in SEQ ID NO: 799 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 825;

(m) the sense strand comprises a sequence as set forth in SEQ ID NO: 800 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 826;

(n) the sense strand comprises a sequence as set forth in SEQ ID NO: 801 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 827;

(o) the sense strand comprises a sequence as set forth in SEQ ID NO: 802 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 828;

(p) the sense strand comprises a sequence as set forth in SEQ ID NO: 803 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 829;

(q) the sense strand comprises a sequence as set forth in SEQ ID NO: 804 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 830;

(r) the sense strand comprises a sequence as set forth in SEQ ID NO: 805 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 831;

(s) the sense strand comprises a sequence as set forth in SEQ ID NO: 806 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 832;

(t) the sense strand comprises a sequence as set forth in SEQ ID NO: 807 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 833;

(u) the sense strand comprises a sequence as set forth in SEQ ID NO: 808 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 834;

(v) the sense strand comprises a sequence as set forth in SEQ ID NO: 809 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 835;

(w) the sense strand comprises a sequence as set forth in SEQ ID NO: 810 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 836;

(x) the sense strand comprises a sequence as set forth in SEQ ID NO: 811 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 837;

(y) the sense strand comprises a sequence as set forth in SEQ ID NO: 812 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 838; or

(z) the sense strand comprises a sequence as set forth in SEQ ID NO: 813 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 839.

[0035] Further provided herein are compositions comprising any of the oligonucleotides described herein and an excipient.

[0036] Further provided herein are methods of delivering an oligonucleotide to a subject, the method comprising administering the composition comprising any of the oligonucleotides described herein to the subject.

[0037] In some embodiments, the subject has or is at risk of having liver fibrosis. In some embodiments, the subject has cholestatic or autoimmune liver disease. In some embodiments, expression of HMGB1 protein is reduced by administering to the subject the oligonucleotide.

[0038] Further provided herein are methods of treating a subject having or at risk of having liver fibrosis, the method comprising administering to the subject any of the oligonucleotides described herein. In some embodiments, the subject has cholestatic or autoimmune liver disease. In some embodiments, the subject has nonalcoholic steatohepatitis (NASH). In some embodiments, the oligonucleotide is administered prior to exposure of the subject to a hepatotoxic agent. In some embodiments, the oligonucleotide is administered subsequent to exposure of the subject to a hepatotoxic agent. In some embodiments, the oligonucleotide is administered simultaneously with the

subject's exposure to a hepatotoxic agent. In some embodiments, the administration results in a reduction in liver HMGB1 levels. In some embodiments, the administration results in a reduction in serum HMGB1 levels.

[0039] Further provided herein are the use of any of the oligonucleotides described herein for treating a subject having or at risk of having liver fibrosis. In some embodiments, the subject has cholestatic or autoimmune liver disease. In some embodiments, the subject has nonalcoholic steatohepatitis (NASH).

BRIEF DESCRIPTION OF THE DRAWINGS

[0040] The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate certain embodiments, and together with the written description, serve to provide non-limiting examples of certain aspects of the compositions and methods disclosed herein.

[0041] FIG. 1A and FIG. 1B: In vivo activity evaluation of 3 GalNAc-conjugated HMGB1 oligonucleotides (FIG. 1A) with 3 different modification patterns (FIG. 1B). NM_002128.5 location numbers were used on x-axis.

[0042] FIG. 2: In vivo activity evaluation of 3 GalNAc-conjugated HMGB1 oligonucleotides at three different concentrations. NM_002128.5 location numbers were used on x-axis.

[0043] FIG. 3: In vivo activity evaluation of three GalNAc-conjugated HMGB1 oligonucleotides at 4-different time points. NM_002128.5 location numbers were used on x-axis.

[0044] FIGs. 4A-4F: Screening of 288 triple commons HMGB1 RNAi oligonucleotides in Huh-7(Human liver) cells. The nucleotide position in NM_002128.5 that corresponds to the 3' end of the sense strand of each siRNA is indicated on the x axis. The percent mRNA remaining is shown for each of the 5' assay (red) and the 3' assay (blue).

[0045] FIG.5: In vivo activity evaluation of 22 HMGB1 RNAi oligonucleotides identified in the screen of FIGs. 4A-4F. The 22 HMGB1 oligonucleotides are GalNAc-conjugated with 2 different modification patterns (M2 and M3, see FIG. 1B for modification patterns). NM_002128.5 location numbers were used on x-axis.

[0046] FIG. 6: In vivo activity evaluation of lead GalNAc-conjugated HMGB1 oligonucleotides 21 days after administration. NM_002128.5 location numbers were used on x-axis

[0047] FIG. 7: GalNAc-conjugated HMGB1 oligonucleotides that were tested in primary monkey/human hepatocytes. Arrow indicates that the oligonucleotide is also selected to be tested in non-human primate screen.

[0048] FIGs. 8A-8D: Activity of the 6 GalNAc-conjugates HMGB1 oligonucleotides in primary monkey (cynomolgous) and human hepatocytes shown by IC50 curve. (FIG. 8A) Cyno hepatocyte

#1. (FIG. 8B) Cyno hepatocyte #2. (FIG. 8C) Human hepatocyte #1. (FIG. 8D) Positive control GalNAc-conjugated LDHA oligonucleotide.

[0049] FIGs. 9A-9B: In vivo activity evaluation of GalNAc-conjugated HMGB1 oligonucleotides in non-human primates. (FIG. 9A) 4 mg/kg, one dose. (FIG. 9B) 2 mg/kg dosing, 4 repeat doses.

[0050] FIGs. 10A-10F: Screening of 6 HMGB1 RNAi oligonucleotides at 3 different concentrations (0.03 nM, 0.1 nM and 1 nM) in mouse, monkey, and human cell lines. (FIG. 10A) Mouse cell line, 5' assay. (FIG. 10B) Mouse cell line, 3' assay. (FIG. 10C) Monkey cell line, 5' assay. (FIG. 10D) Monkey cell line, 3' assay. (FIG. 10E) Human cell line, 5' assay. (FIG. 10F) Human cell line, 3' assay.

[0051] FIGs. 11A-11C: Activity of 4 GalNAc-conjugate HMGB1 oligonucleotides in Huh-7 cells by IC50 curve. IC50 curves of HMGB1 (FIG. 11A), HMGB2 (FIG. 11B) and HMGB3 (FIG. 11C), normalized to mock.

DETAILED DESCRIPTION OF THE INVENTION

[0052] According to some aspects, the disclosure provides oligonucleotides targeting HMGB1 mRNA that are effective for reducing HMGB1 expression in cells, particularly liver cells (e.g., hepatocytes) for the treatment of liver fibrosis. Accordingly, in related aspects, the disclosure provides methods of treating fibrosis that involve selectively reducing HMGB1 gene expression in liver. In certain embodiments, HMGB1 targeting oligonucleotides provided herein are designed for delivery to selected cells of target tissues (e.g., liver hepatocytes) to treat fibrosis in those tissues. RNAi oligonucleotides having particular modification patterns are disclosed herein (as outlined in Table 2) that are particularly useful for knocking down HMGB1 mRNA in vivo.

[0053] Further aspects of the disclosure, including a description of defined terms, are provided below.

I. Definitions

[0054] Approximately: As used herein, the term “approximately” or “about,” as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In certain embodiments, the term “approximately” or “about” refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[0055] Administering: As used herein, the terms “administering” or “administration” means to provide a substance (e.g., an oligonucleotide) to a subject in a manner that is pharmacologically useful (e.g., to treat a condition in the subject).

[0056] Asialoglycoprotein receptor (ASGPR): As used herein, the term “Asialoglycoprotein receptor” or “ASGPR” refers to a bipartite C-type lectin formed by a major 48 kDa (ASGPR-1) and minor 40 kDa subunit (ASGPR-2). ASGPR is primarily expressed on the sinusoidal surface of hepatocyte cells, and has a major role in binding, internalization, and subsequent clearance of circulating glycoproteins that contain terminal galactose or N-acetylgalactosamine residues (asialoglycoproteins).

[0057] Attenuates: As used herein, the term “attenuates” means reduces or effectively halts. As a non-limiting example, one or more of the treatments provided herein may reduce or effectively halt the onset or progression of liver fibrosis or liver inflammation in a subject. This attenuation may be exemplified by, for example, a decrease in one or more aspects (e.g., symptoms, tissue characteristics, and cellular, inflammatory or immunological activity, etc.) of liver fibrosis or liver inflammation, no detectable progression (worsening) of one or more aspects of liver fibrosis or liver inflammation, or no detectable aspects of liver fibrosis or liver inflammation in a subject when they might otherwise be expected.

[0058] Complementary: As used herein, the term “complementary” refers to a structural relationship between two nucleotides (e.g., on two opposing nucleic acids or on opposing regions of a single nucleic acid strand) that permits the two nucleotides to form base pairs with one another. For example, a purine nucleotide of one nucleic acid that is complementary to a pyrimidine nucleotide of an opposing nucleic acid may base pair together by forming hydrogen bonds with one another. In some embodiments, complementary nucleotides can base pair in the Watson-Crick manner or in any other manner that allows for the formation of stable duplexes. In some embodiments, two nucleic acids may have regions of multiple nucleotides that are complementary with each other so as to form regions of complementarity, as described herein.

[0059] Deoxyribonucleotide: As used herein, the term “deoxyribonucleotide” refers to a nucleotide having a hydrogen in place of a hydroxyl at the 2' position of its pentose sugar as compared with a ribonucleotide. A modified deoxyribonucleotide is a deoxyribonucleotide having one or more modifications or substitutions of atoms other than at the 2' position, including modifications or substitutions in or of the sugar, phosphate group or base.

[0060] Double-stranded oligonucleotide: As used herein, the term “double-stranded oligonucleotide” refers to an oligonucleotide that is substantially in a duplex form. In some embodiments, the complementary base-pairing of duplex region(s) of a double-stranded oligonucleotide is formed between of antiparallel sequences of nucleotides of covalently separate nucleic acid strands. In some embodiments, complementary base-pairing of duplex region(s) of a double-stranded oligonucleotide is formed between antiparallel sequences of nucleotides of nucleic acid strands that are covalently linked. In some embodiments, complementary base-pairing of duplex

region(s) of a double-stranded oligonucleotide is formed from single nucleic acid strand that is folded (e.g., via a hairpin) to provide complementary antiparallel sequences of nucleotides that base pair together. In some embodiments, a double-stranded oligonucleotide comprises two covalently separate nucleic acid strands that are fully duplexed with one another. However, in some embodiments, a double-stranded oligonucleotide comprises two covalently separate nucleic acid strands that are partially duplexed, e.g., having overhangs at one or both ends. In some embodiments, a double-stranded oligonucleotide comprises antiparallel sequence of nucleotides that are partially complementary, and thus, may have one or more mismatches, which may include internal mismatches or end mismatches.

[0061] Duplex: As used herein, the term “duplex,” in reference to nucleic acids (e.g., oligonucleotides), refers to a structure formed through complementary base pairing of two antiparallel sequences of nucleotides.

[0062] Excipient: As used herein, the term “excipient” refers to a non-therapeutic agent that may be included in a composition, for example, to provide or contribute to a desired consistency or stabilizing effect.

[0063] Hepatocyte: As used herein, the term “hepatocyte” or “hepatocytes” refers to cells of the parenchymal tissues of the liver. These cells make up approximately 70-85% of the liver’s mass and manufacture serum albumin, fibrinogen, and the prothrombin group of clotting factors (except for Factors 3 and 4). Markers for hepatocyte lineage cells may include, but are not limited to: transthyretin (Ttr), glutamine synthetase (Glul), hepatocyte nuclear factor 1a (Hnf1a), and hepatocyte nuclear factor 4a (Hnf4a). Markers for mature hepatocytes may include, but are not limited to: cytochrome P450 (Cyp3a11), fumarylacetoacetate hydrolase (Fah), glucose 6-phosphate (G6p), albumin (Alb), and OC2-2F8 (see, e.g., Huch et al., *Nature*, 2013, 494(7436):247-250, the contents of which relating to hepatocyte markers is incorporated herein by reference.

[0064] Hepatotoxic agent: As used herein, a “hepatotoxic agent” is a chemical compound, virus, or other substance that is itself toxic to the liver or can be processed to form a metabolite that is toxic to the liver. Hepatotoxic agents may include, but are not limited to, carbon tetrachloride (CCl₄), acetaminophen (paracetamol), vinyl chloride, arsenic, chloroform, and nonsteroidal anti-inflammatory drugs (such as aspirin and phenylbutazone).

[0065] Liver inflammation: As used herein, the term “liver inflammation” or “hepatitis” refers to a physical condition in which the liver becomes swollen, dysfunctional, and/or painful, especially as a result of injury or infection, as may be caused by exposure to a hepatotoxic agent. Symptoms may include jaundice (yellowing of the skin or eyes), fatigue, weakness, nausea, vomiting, appetite reduction, and weight loss. Liver inflammation, if left untreated, may progress to fibrosis, cirrhosis, liver failure, or liver cancer.

[0066] Liver fibrosis: As used herein, the term “liver fibrosis” or “fibrosis of the liver” refers to an excessive accumulation in the liver of extracellular matrix proteins, which could include collagens (I, III, and IV), fibronectin, undulin, elastin, laminin, hyaluronan, and proteoglycans resulting from inflammation and liver cell death. Liver fibrosis, if left untreated, may progress to cirrhosis, liver failure, or liver cancer.

[0067] Loop: As used herein the term, “loop” refers to a unpaired region of a nucleic acid (e.g., oligonucleotide) that is flanked by two antiparallel regions of the nucleic acid that are sufficiently complementary to one another, such that under appropriate hybridization conditions (e.g., in a phosphate buffer, in a cell), the two antiparallel regions, which flank the unpaired region, hybridize to form a duplex (referred to as a “stem”).

[0068] Modified Internucleotide Linkage: As used herein, the term “modified internucleotide linkage” refers to an internucleotide linkage having one or more chemical modifications compared with a reference internucleotide linkage comprising a phosphodiester bond. In some embodiments, a modified nucleotide is a non-naturally occurring linkage. Typically, a modified internucleotide linkage confers one or more desirable properties to a nucleic acid in which the modified internucleotide linkage is present. For example, a modified nucleotide may improve thermal stability, resistance to degradation, nuclease resistance, solubility, bioavailability, bioactivity, reduced immunogenicity, etc.

[0069] Modified Nucleotide: As used herein, the term “modified nucleotide” refers to a nucleotide having one or more chemical modifications compared with a corresponding reference nucleotide selected from: adenine ribonucleotide, guanine ribonucleotide, cytosine ribonucleotide, uracil ribonucleotide, adenine deoxyribonucleotide, guanine deoxyribonucleotide, cytosine deoxyribonucleotide and thymidine deoxyribonucleotide. In some embodiments, a modified nucleotide is a non-naturally occurring nucleotide. In some embodiments, a modified nucleotide has one or more chemical modification in its sugar, nucleobase, and/or phosphate group. In some embodiments, a modified nucleotide has one or more chemical moieties conjugated to a corresponding reference nucleotide. Typically, a modified nucleotide confers one or more desirable properties to a nucleic acid in which the modified nucleotide is present. For example, a modified nucleotide may improve thermal stability, resistance to degradation, nuclease resistance, solubility, bioavailability, bioactivity, reduced immunogenicity, etc.

[0070] Nicked Tetraloop Structure: A “nicked tetraloop structure” is a structure of a RNAi oligonucleotide characterized by the presence of separate sense (passenger) and antisense (guide) strands, in which the sense strand has a region of complementarity with the antisense strand, and in which at least one of the strands, generally the sense strand, has a tetraloop configured to stabilize an adjacent stem region formed within the at least one strand.

[0071] Oligonucleotide: As used herein, the term “oligonucleotide” refers to a short nucleic acid, e.g., of less than 100 nucleotides in length. An oligonucleotide may be single-stranded or double-stranded. An oligonucleotide may or may not have duplex regions. As a set of non-limiting examples, an oligonucleotide may be, but is not limited to, a small interfering RNA (siRNA), microRNA (miRNA), short hairpin RNA (shRNA), dicer substrate interfering RNA (dsiRNA), antisense oligonucleotide, short siRNA, or single-stranded siRNA. In some embodiments, a double-stranded oligonucleotide is an RNAi oligonucleotide.

[0072] Overhang: As used herein, the term “overhang” refers to terminal non-base pairing nucleotide(s) resulting from one strand or region extending beyond the terminus of a complementary strand with which the one strand or region forms a duplex. In some embodiments, an overhang comprises one or more unpaired nucleotides extending from a duplex region at the 5' terminus or 3' terminus of a double-stranded oligonucleotide. In certain embodiments, the overhang is a 3' or 5' overhang on the antisense strand or sense strand of a double-stranded oligonucleotides.

[0073] Phosphate analog: As used herein, the term “phosphate analog” refers to a chemical moiety that mimics the electrostatic and/or steric properties of a phosphate group. In some embodiments, a phosphate analog is positioned at the 5' terminal nucleotide of an oligonucleotide in place of a 5'-phosphate, which is often susceptible to enzymatic removal. In some embodiments, a 5' phosphate analogs contain a phosphatase-resistant linkage. Examples of phosphate analogs include 5' phosphonates, such as 5' methylenephosphonate (5'-MP) and 5'-(E)-vinylphosphonate (5'-VP). In some embodiments, an oligonucleotide has a phosphate analog at a 4'-carbon position of the sugar (referred to as a “4'-phosphate analog”) at a 5'-terminal nucleotide. An example of a 4'-phosphate analog is oxymethylphosphonate, in which the oxygen atom of the oxymethyl group is bound to the sugar moiety (e.g., at its 4'-carbon) or analog thereof (see, e.g., International patent publication WO/2018/045317, the contents of which relating to phosphate analogs is incorporated herein by reference. Other modifications have been developed for the 5' end of oligonucleotides (see, e.g., WO 2011/133871; U.S. Patent No. 8,927,513; and Prakash et al., *Nucleic Acids Res.*, 2015, 43(6):2993-3011, the contents of each of which relating to phosphate analogs are incorporated herein by reference).

[0074] Reduced expression: As used herein, the term “reduced expression” of a gene refers to a decrease in the amount of RNA transcript or protein encoded by the gene and/or a decrease in the amount of activity of the gene in a cell or subject, as compared to an appropriate reference cell or subject. For example, the act of treating a cell with a double-stranded oligonucleotide (e.g., one having an antisense strand that is complementary to HMGB1 mRNA sequence) may result in a decrease in the amount of RNA transcript, protein and/or activity (e.g., encoded by the HMGB1 gene) compared to a cell that is not treated with the double-stranded oligonucleotide. Similarly, “reducing expression” as used herein refers to an act that results in reduced expression of a gene (e.g., HMGB1).

[0075] Region of Complementarity: As used herein, the term “region of complementary” refers to a sequence of nucleotides of a nucleic acid (e.g., a double-stranded oligonucleotide) that is sufficiently complementary to an antiparallel sequence of nucleotides to permit hybridization between the two sequences of nucleotides under appropriate hybridization conditions, e.g., in a phosphate buffer, in a cell, etc.

[0076] Ribonucleotide: As used herein, the term “ribonucleotide” refers to a nucleotide having a ribose as its pentose sugar, which contains a hydroxyl group at its 2' position. A modified ribonucleotide is a ribonucleotide having one or more modifications or substitutions of atoms other than at the 2' position, including modifications or substitutions in or of the ribose, phosphate group or base.

[0077] RNAi Oligonucleotide: As used herein, the term “RNAi oligonucleotide” refers to either (a) a double stranded oligonucleotide having a sense strand (passenger) and antisense strand (guide), in which the antisense strand or part of the antisense strand is used by the Argonaute 2 (Ago2) endonuclease in the cleavage of a target mRNA or (b) a single stranded oligonucleotide having a single antisense strand, where that antisense strand (or part of that antisense strand) is used by the Ago2 endonuclease in the cleavage of a target mRNA.

[0078] Strand: As used herein, the term “strand” refers to a single contiguous sequence of nucleotides linked together through internucleotide linkages (e.g., phosphodiester linkages, phosphorothioate linkages). In some embodiments, a strand has two free ends, e.g., a 5'-end and a 3'-end.

[0079] Subject: As used herein, the term “subject” means any mammal, including mice, rabbits, and humans. In some embodiments, the subject is a human or non-human primate. The terms “individual” or “patient” may be used interchangeably with “subject.”

[0080] Synthetic: As used herein, the term “synthetic” refers to a nucleic acid or other molecule that is artificially synthesized (e.g., using a machine (e.g., a solid-state nucleic acid synthesizer)) or that is otherwise not derived from a natural source (e.g., a cell or organism) that normally produces the molecule.

[0081] Targeting ligand: As used herein, the term “targeting ligand” refers to a molecule (e.g., a carbohydrate, amino sugar, cholesterol, polypeptide or lipid) that selectively binds to a cognate molecule (e.g., a receptor) of a tissue or cell of interest and that is conjugatable to another substance for purposes of targeting the other substance to the tissue or cell of interest. For example, in some embodiments, a targeting ligand may be conjugated to an oligonucleotide for purposes of targeting the oligonucleotide to a specific tissue or cell of interest. In some embodiments, a targeting ligand selectively binds to a cell surface receptor. Accordingly, in some embodiments, a targeting ligand when conjugated to an oligonucleotide facilitates delivery of the oligonucleotide into a particular cell

through selective binding to a receptor expressed on the surface of the cell and endosomal internalization by the cell of the complex comprising the oligonucleotide, targeting ligand and receptor. In some embodiments, a targeting ligand is conjugated to an oligonucleotide via a linker that is cleaved following or during cellular internalization such that the oligonucleotide is released from the targeting ligand in the cell.

[0082] Tetraloop: As used herein, the term “tetraloop” refers to a loop that increases stability of an adjacent duplex formed by hybridization of flanking sequences of nucleotides. The increase in stability is detectable as an increase in melting temperature (T_m) of an adjacent stem duplex that is higher than the T_m of the adjacent stem duplex expected, on average, from a set of loops of comparable length consisting of randomly selected sequences of nucleotides. For example, a tetraloop can confer a melting temperature of at least 50°C, at least 55°C., at least 56°C, at least 58°C, at least 60°C, at least 65°C or at least 75°C in 10 mM NaHPO₄ to a hairpin comprising a duplex of at least 2 base pairs in length. In some embodiments, a tetraloop may stabilize a base pair in an adjacent stem duplex by stacking interactions. In addition, interactions among the nucleotides in a tetraloop include but are not limited to non-Watson-Crick base pairing, stacking interactions, hydrogen bonding, and contact interactions (Cheong et al., *Nature*, 1990, 346(6285):680-2; Heus and Pardi, *Science*, 1991, 253(5016):191-4). In some embodiments, a tetraloop comprises or consists of 3 to 6 nucleotides, and is typically 4 to 5 nucleotides. In certain embodiments, a tetraloop comprises or consists of three, four, five, or six nucleotides, which may or may not be modified (e.g., which may or may not be conjugated to a targeting moiety). In one embodiment, a tetraloop consists of four nucleotides. Any nucleotide may be used in the tetraloop and standard IUPAC-IUB symbols for such nucleotides may be used, as described in Cornish-Bowden, *Nucleic Acids Res.*, 1985, 13:3021-3030. For example, the letter “N” may be used to mean that any base may be in that position, the letter “R” may be used to show that A (adenine) or G (guanine) may be in that position, and “B” may be used to show that C (cytosine), G (guanine), or T (thymine) may be in that position. Examples of tetraloops include the UNCG family of tetraloops (e.g., UUCG), the GNRA family of tetraloops (e.g., GAAA), and the CUUG tetraloop (Woese et al., *Proc Natl Acad Sci USA.*, 1990, 87(21):8467-71; Antao et al., *Nucleic Acids Res.*, 1991, 19(21):5901-5). Examples of DNA tetraloops include the d(GNNA) family of tetraloops (e.g., d(GTTA), the d(GNRA)) family of tetraloops, the d(GNAB) family of tetraloops, the d(CNNG) family of tetraloops, and the d(TNCG) family of tetraloops (e.g., d(TTCG)). See, for example, Nakano et al., *Biochemistry*, 2002, 41(48):14281-14292; Shinji et al., *Nippon Kagakkai Koen Yokoshu*, 2000, 78(2):731; which are incorporated by reference herein for their relevant disclosures. In some embodiments, the tetraloop is contained within a nicked tetraloop structure.

[0083] Treat: As used herein, the term “treat” refers to the act of providing care to a subject in need thereof, e.g., through the administration a therapeutic agent (e.g., an oligonucleotide) to the subject, for purposes of improving the health and/or well-being of the subject with respect to an existing

condition (e.g., a disease, disorder) or to prevent or decrease the likelihood of the occurrence of a condition. In some embodiments, treatment involves reducing the frequency or severity of at least one sign, symptom or contributing factor of a condition (e.g., disease, disorder) experienced by a subject.

II. Oligonucleotide-based inhibitors of HMGB1 expression

i. HMGB1 Target Sequences

[0084] In some embodiments, oligonucleotide-based inhibitors of HMGB1 expression are provided herein that can be used to achieve a therapeutic benefit. Through examination of the HMGB1 mRNA, including mRNAs of multiple different species (human, rhesus monkey, and mouse (see, e.g., Example 1) and in vitro and in vivo testing, it has been discovered that certain sequences of HMGB1 mRNA are useful as targeting sequences because they are more amenable than others to oligonucleotide-based inhibition. In some embodiments, a HMGB1 target sequence comprises, or consists of, a sequence as forth in any one of SEQ ID NOs: 1-13. These regions of HMGB1 mRNA may be targeted using oligonucleotides as discussed herein for purposes of inhibiting HMGB1 mRNA expression.

[0085] Accordingly, in some embodiments, oligonucleotides provided herein are designed so as to have regions of complementarity to HMGB1 mRNA (e.g., within a target sequence of HMGB1 mRNA) for purposes of targeting the mRNA in cells and inhibiting its expression. The region of complementarity is generally of a suitable length and base content to enable annealing of the oligonucleotide (or a strand thereof) to HMGB1 mRNA for purposes of inhibiting its expression. In some embodiments, the region of complementarity is at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19 or at least 20 nucleotides in length. In some embodiments, an oligonucleotide provided herein has a region of complementarity to HMGB1 that is in the range of 12 to 30 (e.g., 12 to 30, 12 to 22, 15 to 25, 17 to 21, 18 to 27, 19 to 27, or 15 to 30) nucleotides in length. In some embodiments, an oligonucleotide provided herein has a region of complementarity to HMGB1 that is 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 nucleotides in length.

[0086] In some embodiments, an oligonucleotide disclosed herein comprises a region of complementarity (e.g., on an antisense strand of a double-stranded oligonucleotide) that is at least partially complementary to a sequence as set forth in any one of SEQ ID NOs: 1-13. In some embodiments, an oligonucleotide disclosed herein comprises a region of complementarity (e.g., on an antisense strand of a double-stranded oligonucleotide) that is fully complementary to a sequence as set forth in any one of SEQ ID NOs: 1-13. In some embodiments, a region of complementarity of an oligonucleotide (e.g., on an antisense strand of a double-stranded oligonucleotide) is complementary to a contiguous sequence of nucleotides of a sequence as set forth in any one of SEQ ID NOs: 1-13 that is in the range of 12 to 20 nucleotides (e.g., 12 to 20, 12 to 18, 12 to 16, 12 to 14, 14 to 20, 14 to

18, 14 to 16, 16 to 20, 16 to 18, or 18 to 20) in length. In some embodiments, a region of complementarity of an oligonucleotide (e.g., on an antisense strand of a double-stranded oligonucleotide) is complementary to a contiguous sequence of nucleotides of a sequence as set forth in any one of SEQ ID NOs: 11-13 that is 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 contiguous nucleotides in length.

[0087] In some embodiments, a region of complementarity of an oligonucleotide that is complementary to contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 1-13 spans the entire length of an antisense strand. In some embodiments, a region of complementarity of an oligonucleotide that is complementary to contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 1-13 spans a portion of the entire length of an antisense strand. In some embodiments, an oligonucleotide disclosed herein comprises a region of complementarity (e.g., on an antisense strand of a double-stranded oligonucleotide) that is at least partially (e.g., fully) complementary to a contiguous stretch of nucleotides spanning nucleotides 1-20 of a sequence as set forth in any one of SEQ ID NOs: 1-13.

[0088] In some embodiments, a region of complementarity to HMGB1 may have one or more mismatches compared with a corresponding sequence of HMGB1 mRNA. A region of complementarity on an oligonucleotide may have up to 1, up to 2, up to 3, up to 4, up to 5, etc. mismatches provided that it maintains the ability to form complementary base pairs with HMGB1 mRNA under appropriate hybridization conditions. Alternatively, a region of complementarity on an oligonucleotide may have no more than 1, no more than 2, no more than 3, no more than 4, or no more than 5 mismatches provided that it maintains the ability to form complementary base pairs with HMGB1 mRNA under appropriate hybridization conditions. In some embodiments, if there are more than one mismatches in a region of complementarity, they may be positioned consecutively (e.g., 2, 3, 4, or more in a row), or interspersed throughout the region of complementarity provided that the oligonucleotide maintains the ability to form complementary base pairs with HMGB1 mRNA under appropriate hybridization conditions.

ii. Types of Oligonucleotides

[0089] There are a variety of structures of oligonucleotides that are useful for targeting HMGB1 in the methods of the present disclosure, including RNAi, antisense, miRNA, etc. Any of the structures described herein or elsewhere may be used as a framework to incorporate or target a sequence described herein (e.g., a hotspot sequence of HMGB1 such as those illustrated in SEQ ID NOs: 1-13).

[0090] In some embodiments, oligonucleotides for reducing the expression of HMGB1 expression engage RNA interference (RNAi) pathways upstream or downstream of dicer involvement. For example, RNAi oligonucleotides have been developed with each strand having sizes of 19-25 nucleotides with at least one 3' overhang of 1 to 5 nucleotides (see, e.g., U.S. Patent No. 8,372,968).

Longer oligonucleotides have also been developed that are processed by Dicer to generate active RNAi products (see, e.g., U.S. Patent No. 8,883,996). Further work produced extended double-stranded oligonucleotides where at least one end of at least one strand is extended beyond a duplex targeting region, including structures where one of the strands includes a thermodynamically-stabilizing tetraloop structure (see, e.g., U.S. Patent Nos. 8,513,207 and 8,927,705, as well as International patent publication WO2010033225, which are incorporated by reference herein for their disclosure of the structures and form of these oligonucleotides). Such structures may include single-stranded extensions (on one or both sides of the molecule) as well as double-stranded extensions.

[0091] In some embodiments, oligonucleotides provided herein are designed to engage in the RNA interference pathway downstream of the involvement of dicer (e.g., dicer cleavage). Such oligonucleotides may have an overhang (e.g., of 1, 2, or 3 nucleotides in length) in the 3' end of the sense strand. Such oligonucleotides (e.g., siRNAs) may comprise a 21 nucleotide guide strand that is antisense to a target RNA and a complementary passenger strand, in which both strands anneal to form a 19-bp duplex and 2 nucleotide overhangs at either or both 3' ends. Longer oligonucleotide designs are also available including oligonucleotides having a guide strand of 23 nucleotides and a passenger strand of 21 nucleotides, where there is a blunt end on the right side of the molecule (3'-end of passenger strand/5'-end of guide strand) and a two nucleotide 3'-guide strand overhang on the left side of the molecule (5'-end of the passenger strand/3'-end of the guide strand). In such molecules, there is a 21 base pair duplex region. See, for example, U.S. Patent Nos. 9,012,138; 9,012,621; and 9,193,753, each of which are incorporated herein for their relevant disclosures.

[0092] In some embodiments, oligonucleotides as disclosed herein may comprise sense and antisense strands that are both in the range of 17 to 26 (e.g., 17 to 26, 20 to 25, or 21-23) nucleotides in length. In some embodiments, an oligonucleotide as disclosed herein comprises a sense and antisense strand that are both in the range of 19-22 nucleotide in length. In some embodiments, the sense and antisense strands are of equal length. In some embodiments, an oligonucleotide comprises sense and antisense strands, such that there is a 3'-overhang on either the sense strand or the antisense strand, or both the sense and antisense strand. In some embodiments, for oligonucleotides that have sense and antisense strands that are both in the range of 21-23 nucleotides in length, a 3' overhang on the sense, antisense, or both sense and antisense strands is 1 or 2 nucleotides in length. In some embodiments, the oligonucleotide has a guide strand of 22 nucleotides and a passenger strand of 20 nucleotides, where there is a blunt end on the right side of the molecule (3'-end of passenger strand/5'-end of guide strand) and a two nucleotide 3'-guide strand overhang on the left side of the molecule (5'-end of the passenger strand/3'-end of the guide strand). In such molecules, there is a 20 base pair duplex region.

[0093] Other oligonucleotides designs for use with the compositions and methods disclosed herein include: 16-mer siRNAs (see, e.g., *Nucleic Acids in Chemistry and Biology*, Blackburn (ed.), Royal Society of Chemistry, 2006), shRNAs (e.g., having 19 bp or shorter stems; see, e.g., Moore et al.

Methods Mol. Biol., 2010, 629:141-158), blunt siRNAs (e.g., of 19 bps in length; see, e.g., Kraynack and Baker, RNA, 2006, 12:163-176), asymmetrical siRNAs (aiRNA; see, e.g., Sun et al., Nat. Biotechnol., 2008, 26:1379-1382), asymmetric shorter-duplex siRNA (see, e.g., Chang et al., Mol Ther., 2009, 17(4):725-32), fork siRNAs (see, e.g., Hohjoh, FEBS Letters, 2004, 557(1-3):193-198), single-stranded siRNAs (Elsner, Nature Biotechnology, 2012, 30:1063), dumbbell-shaped circular siRNAs (see, e.g., Abe et al., J Am Chem Soc., 2007, 129:15108-15109), and small internally segmented interfering RNA (siRNA; see, e.g., Bramsen et al., Nucleic Acids Res., 2007, 35(17):5886-5897). Each of the foregoing references is incorporated by reference in its entirety for the related disclosures therein. Further non-limiting examples of oligonucleotide structures that may be used in some embodiments to reduce or inhibit the expression of HMGB1 are microRNA (miRNA), short hairpin RNA (shRNA), and short siRNA (see, e.g., Hamilton et al., EMBO J., 2002, 21(17):4671-4679; see also U.S. patent publication no. 20090099115).

[0094] Still, in some embodiments, an oligonucleotide for reducing HMGB1 expression as described herein is single-stranded. Such structures may include, but are not limited to single-stranded RNAi molecules. Recent efforts have demonstrated the activity of single-stranded RNAi molecules (see, e.g., Matsui et al., Molecular Therapy, 2016, 24(5):946-955). However, in some embodiments, oligonucleotides provided herein are antisense oligonucleotides (ASOs). An antisense oligonucleotide is a single-stranded oligonucleotide that has a nucleobase sequence which, when written in the 5' to 3' direction, comprises the reverse complement of a targeted segment of a particular nucleic acid and is suitably modified (e.g., as a gapmer) so as to induce RNaseH mediated cleavage of its target RNA in cells or (e.g., as a mixmer) so as to inhibit translation of the target mRNA in cells. Antisense oligonucleotides for use in the instant disclosure may be modified in any suitable manner known in the art including, for example, as shown in U.S. Patent No. 9,567,587, which is incorporated by reference herein for its disclosure regarding modification of antisense oligonucleotides (including, e.g., length, sugar moieties of the nucleobase (pyrimidine, purine), and alterations of the heterocyclic portion of the nucleobase). Further, antisense molecules have been used for decades to reduce expression of specific target genes (see, e.g., Bennett et al., "Pharmacology of Antisense Drugs," Ann Rev Pharmacol Toxicol., 2017, 57:81-105).

iii. Double-Stranded Oligonucleotides

[0095] Double-stranded oligonucleotides for targeting HMGB1 expression (e.g., via the RNAi pathway) generally have a sense strand and an antisense strand that form a duplex with one another. In some embodiments, the sense and antisense strands are not covalently linked. However, in some embodiments, the sense and antisense strands are covalently linked. In some embodiments, a duplex formed between a sense and antisense strand is at least 15 (e.g., at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, or at least 21) nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is in the range of 15-30 nucleotides in length (e.g., 15 to

30, 15 to 27, 15 to 22, 18 to 22, 18 to 25, 18 to 27, 18 to 30, or 21 to 30 nucleotides in length). In some embodiments, a duplex formed between a sense and antisense strand is 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. In some embodiments, the duplex region is 20 nucleotides in length. In some embodiments a duplex formed between a sense and antisense strand does not span the entire length of the sense strand and/or antisense strand. In some embodiments, a duplex between a sense and antisense strand spans the entire length of either the sense or antisense strands. In certain embodiments, a duplex between a sense and antisense strand spans the entire length of both the sense strand and the antisense strand.

[0096] In some embodiments, an oligonucleotide provided herein comprises a sense strand having a sequence as set forth in any one of SEQ ID NOs: 1-13 and an antisense strand comprising a complementary sequence selected from SEQ ID NOs: 14-26, as is arranged Table 1.

[0097] In some embodiments, the sense strand comprising a sequence as set forth in SEQ ID NO: 1 and the antisense strand comprising a sequence as set forth in SEQ ID NO: 14. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 2 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 15. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 3 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 16. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 4 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 17. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 5 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 18. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 6 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 19. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 7 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 20. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 8 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 21. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 9 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 22. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 10 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 23. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 11 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 24. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 12 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 25. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 13 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 26.

[0098] In some embodiments, an oligonucleotide provided herein comprises a sense strand comprising a sequence as set forth in any one of SEQ ID NOs: 27-39 and an antisense strand

comprising a complementary sequence selected from SEQ ID NOs: 14-26, as is also arranged in Table 2, including modifications to the sense sequence and antisense sequences. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 27 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 14. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 28 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 15. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 29 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 16. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 30 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 17. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 31 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 18. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 32 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 19. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 33 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 20. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 34 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 21. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 35 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 22. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 36 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 23. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 37 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 24. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 38 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 25. In some embodiments, the sense strand comprises a sequence as set forth in SEQ ID NO: 39 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 26.

[0099] It should be appreciated that, in some embodiments, sequences presented in the sequence listing may be referred to in describing the structure of an oligonucleotide or other nucleic acid. In such embodiments, the actual oligonucleotide or other nucleic acid may have one or more alternative nucleotides (e.g., an RNA counterpart of a DNA nucleotide or a DNA counterpart of an RNA nucleotide) and/or one or more modified nucleotides and/or one or more modified internucleotide linkages and/or one or more other modification compared with the specified sequence while retaining essentially same or similar complementary properties as the specified sequence.

[0100] In some embodiments, a double-stranded oligonucleotide comprises a 25-nucleotide sense strand and a 27-nucleotide antisense strand that when acted upon by a dicer enzyme results in an antisense strand that is incorporated into the mature RISC. In some embodiments, a sense strand of an oligonucleotide is longer than 27 nucleotides (e.g., 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 or 40

nucleotides). In some embodiments, a sense strand of an oligonucleotide is longer than 25 nucleotides (e.g., 26, 27, 28, 29 or 30 nucleotides).

[0101] In some embodiments, the length of a duplex formed between a sense and antisense strand of an oligonucleotide may be 12 to 30 nucleotides (e.g., 12 to 30, 12 to 27, 15 to 25, 18 to 30 or 19 to 30 nucleotides) in length. In some embodiments, the length of a duplex formed between a sense and antisense strand of an oligonucleotide is at least 12 nucleotides long (e.g., at least 12, at least 15, at least 20, or at least 25 nucleotides long). In some embodiments, the length of a duplex formed between a sense and antisense strand of an oligonucleotide is 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length.

[0102] In some embodiments, oligonucleotides provided herein have one 5' end that is thermodynamically less stable compared to the other 5' end. In some embodiments, an asymmetry oligonucleotide is provided that includes a blunt end at the 3' end of a sense strand and an overhang at the 3' end of an antisense strand. In some embodiments, a 3' overhang on an antisense strand is 1-8 nucleotides in length (e.g., 1, 2, 3, 4, 5, 6, 7 or 8 nucleotides in length). Typically, an oligonucleotide for RNAi has a two-nucleotide overhang on the 3' end of the antisense (guide) strand. However, other overhangs are possible. In some embodiments, an overhang is a 3' overhang comprising a length of between one and six nucleotides, optionally one to five, one to four, one to three, one to two, two to six, two to five, two to four, two to three, three to six, three to five, three to four, four to six, four to five, five to six nucleotides, or one, two, three, four, five or six nucleotides. However, in some embodiments, the overhang is a 5' overhang comprising a length of between one and six nucleotides, optionally one to five, one to four, one to three, one to two, two to six, two to five, two to four, two to three, three to six, three to five, three to four, four to six, four to five, five to six nucleotides, or one, two, three, four, five or six nucleotides.

[0103] In some embodiments, two terminal nucleotides on the 3' end of an antisense strand are modified. In some embodiments, the two terminal nucleotides on the 3' end of the antisense strand are complementary with the target. In some embodiments, the two terminal nucleotides on the 3' end of the antisense strand are not complementary with the target. In some embodiments, two terminal nucleotides on each 3' end of an oligonucleotide in the nicked tetraloop structure are GG. Typically, one or both of the two terminal GG nucleotides on each 3' end of an oligonucleotide is not complementary with the target.

[0104] In some embodiments, there is one or more (e.g., 1, 2, 3, 4, 5) mismatches between a sense and antisense strand. If there is more than one mismatch between a sense and antisense strand, they may be positioned consecutively (e.g., 2, 3 or more in a row), or interspersed throughout the region of complementarity. In some embodiments, the 3'-terminus of the sense strand contains one or more mismatches. In one embodiment, two mismatches are incorporated at the 3' terminus of the sense

strand. In some embodiments, base mismatches or destabilization of segments at the 3'-end of the sense strand of the oligonucleotide improved the potency of synthetic duplexes in RNAi, possibly through facilitating processing by Dicer.

a. Antisense Strands

[0105] In some embodiments, an antisense strand of an oligonucleotide may be referred to as a “guide strand.” For example, if an antisense strand can engage with RNA-induced silencing complex (RISC) and bind to an Argonaut protein, or engage with or bind to one or more similar factors, and direct silencing of a target gene, it may be referred to as a guide strand. In some embodiments a sense strand complementary with a guide strand may be referred to as a “passenger strand.”

[0106] In some embodiments, an oligonucleotide provided herein comprises an antisense strand that is up to 50 nucleotides in length (e.g., up to 30, up to 27, up to 25, up to 21, or up to 19 nucleotides in length). In some embodiments, an oligonucleotide provided herein comprises an antisense strand is at least 12 nucleotides in length (e.g., at least 12, at least 15, at least 19, at least 21, at least 25, or at least 27 nucleotides in length). In some embodiments, an antisense strand of an oligonucleotide disclosed herein is in the range of 12 to 50 or 12 to 30 (e.g., 12 to 30, 11 to 27, 11 to 25, 15 to 21, 15 to 27, 17 to 21, 17 to 25, 19 to 27, or 19 to 30) nucleotides in length. In some embodiments, an antisense strand of any one of the oligonucleotides disclosed herein is 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 nucleotides in length.

[0107] In some embodiments an oligonucleotide disclosed herein comprises an antisense strand comprising a sequence as set forth in any one of SEQ ID NOs: 14-26. In some embodiments, an oligonucleotide comprises an antisense strand comprising a contiguous sequence of nucleotides that is in the range of 12 to 20 nucleotides (e.g., 12 to 20, 12 to 18, 12 to 16, 12 to 14, 14 to 20, 14 to 18, 14 to 16, 16 to 20, 16 to 18, or 18 to 20 nucleotides) in length of any of the sequences as set forth in any one of SEQ ID NOs: 14-26. In some embodiments, an oligonucleotide comprises an antisense strand comprising a contiguous sequence of nucleotides of a sequence as set forth in any one of SEQ ID NOs: 14-26 that is 12, 13, 14, 15, 16, 17, 18, 19, or 20 contiguous nucleotides in length. In some embodiments, an oligonucleotide comprises an antisense strand that consists of a sequence as set forth in any one of SEQ ID NOs: 14-26.

b. Sense Strands

[0108] In some embodiments, a double-stranded oligonucleotide may have a sense strand of up to 40 nucleotides in length (e.g., up to 40, up to 35, up to 30, up to 27, up to 25, up to 21, up to 19 up to 17, or up to 12 nucleotides in length). In some embodiments, an oligonucleotide may have a sense strand of at least 12 nucleotides in length (e.g., at least 12, at least 15, at least 19, at least 21, at least 25, at least 27, at least 30, at least 35, or at least 38 nucleotides in length). In some embodiments, an

oligonucleotide may have a sense strand in a range of 12 to 50 (e.g., 12 to 40, 12 to 36, 12 to 32, 12 to 28, 15 to 40, 15 to 36, 15 to 32, 15 to 28, 17 to 21, 17 to 25, 19 to 27, 19 to 30, 20 to 40, 22 to 40, 25 to 40, or 32 to 40) nucleotides in length. In some embodiments, an oligonucleotide may have a sense strand of 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 nucleotides in length. In some embodiments, a sense strand of an oligonucleotide is longer than 27 nucleotides (e.g., 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 or 40 nucleotides). In some embodiments, a sense strand of an oligonucleotide is longer than 25 nucleotides (e.g., 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 nucleotides). In some embodiments, the sense strand is 20 nucleotides in length. In some embodiments, the sense strand is 36 nucleotides in length.

[0109] In some embodiments, an oligonucleotide disclosed herein comprises a sense strand sequence as set forth in in any one of SEQ ID NOs: 1-13 and 27-39. In some embodiments, an oligonucleotide has a sense strand that comprises at least 12 (e.g., at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23) contiguous nucleotides of a sequence as set forth in in any one of SEQ ID NOs: 1-13 and 27-39. In some embodiments, an oligonucleotide has a sense strand that comprises a contiguous sequence of nucleotides that is in the range of 7 to 36 nucleotides (e.g., 12 to 30, 12 to 27, 12 to 22, 15 to 25, 17 to 21, 18 to 27, 19-27, 20-36, or 15 to 36 nucleotides) in length of any of the sequences as set forth in any one of SEQ ID NOs: 1-13 and 27-39. In some embodiments, an oligonucleotide has a sense strand that comprises a contiguous sequence of nucleotides of a sequence as set forth in any one of SEQ ID NOs: 1-13 and 27-39 that is 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 nucleotides in length. In some embodiments, an oligonucleotide has a sense strand that consists of a sequence as set forth in any one of SEQ ID NOs: 1-13 and 27-39.

[0110] In some embodiments, a sense strand comprises a stem-loop at its 3'-end. In some embodiments, a sense strand comprises a stem-loop at its 5'-end. In some embodiments, a strand comprising a stem loop is in the range of 2 to 66 nucleotides long (e.g., 2 to 66, 10 to 52, 14 to 40, 2 to 30, 4 to 26, 8 to 22, 12 to 18, 10 to 22, 14 to 26, or 14 to 30 nucleotides long). In some embodiments, a strand comprising a stem loop is 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. In some embodiments, a stem comprises a duplex of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 nucleotides in length. In some embodiments, a stem-loop provides the molecule better protection against degradation (e.g., enzymatic degradation) and facilitates targeting characteristics for delivery to a target cell. For example, in some embodiments, a loop provides added nucleotides on which modification can be made without substantially affecting the gene expression inhibition activity of an oligonucleotide. In certain embodiments, an oligonucleotide is provided herein in which the sense strand comprises (e.g., at its 3'-end) a stem-loop set forth as: S_1 -L- S_2 , in which S_1 is complementary to S_2 , and in which L forms a

loop between S_1 and S_2 of up to 10 nucleotides in length (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length).

[0111] In some embodiments, a loop (L) of a stem-loop is a tetraloop (e.g., within a nicked tetraloop structure). A tetraloop may contain ribonucleotides, deoxyribonucleotides, modified nucleotides, and combinations thereof. Typically, a tetraloop has 4 to 5 nucleotides. However, in some embodiments, a tetraloop comprises or consists of 3 to 6 nucleotides, and typically consists of 4 to 5 nucleotides. In certain embodiments, a tetraloop comprises or consists of three, four, five, or six nucleotides.

iv. Oligonucleotide Modifications

[0112] Oligonucleotides may be modified in various ways to improve or control specificity, stability, delivery, bioavailability, resistance from nuclease degradation, immunogenicity, base-pairing properties, RNA distribution and cellular uptake and other features relevant to therapeutic or research use (see, e.g., Bramsen et al., *Nucleic Acids Res.*, 2009, 37:2867-2881; Bramsen and Kjems, *Frontiers in Genetics*, 2012, 3:1-22). Accordingly, in some embodiments, oligonucleotides of the present disclosure may include one or more suitable modifications. In some embodiments, a modified nucleotide has a modification in its base (or nucleobase), the sugar (e.g., ribose, deoxyribose), or the phosphate group.

[0113] The number of modifications on an oligonucleotide and the positions of those nucleotide modifications may influence the properties of an oligonucleotide. For example, oligonucleotides may be delivered in vivo by conjugating them to or encompassing them in a lipid nanoparticle (LNP) or similar carrier. However, when an oligonucleotide is not protected by an LNP or similar carrier, it may be advantageous for at least some of the nucleotides to be modified. Accordingly, in certain embodiments of any of the oligonucleotides provided herein, all or substantially all the nucleotides of an oligonucleotide are modified. In certain embodiments, more than half of the nucleotides are modified. In certain embodiments, less than half of the nucleotides are modified. Typically, with naked delivery, every sugar is modified at the 2'-position. These modifications may be reversible or irreversible. In some embodiments, an oligonucleotide as disclosed herein has a number and type of modified nucleotides sufficient to cause the desired characteristic (e.g., protection from enzymatic degradation, capacity to target a desired cell after in vivo administration, and/or thermodynamic stability).

a. Sugar Modifications

[0114] In some embodiments, a modified sugar (also referred herein to a sugar analog) includes a modified deoxyribose or ribose moiety, e.g., in which one or more modifications occur at the 2', 3', 4', and/or 5' carbon position of the sugar. In some embodiments, a modified sugar may also include non-natural alternative carbon structures such as those present in locked nucleic acids ("LNA") (see, e.g., Koshkin et al., *Tetrahedron*, 1998, 54:3607-3630), unlocked nucleic acids ("UNA") (see, e.g., Snead

et al., *Molecular Therapy – Nucleic Acids*, 2013, 2, e103), and bridged nucleic acids (“BNA”) (see, e.g., Imanishi and Obika, *The Royal Society of Chemistry, Chem. Commun.*, 2002, 16:1653-1659). Koshkin et al., Snead et al., and Imanishi and Obika are incorporated by reference herein for their disclosures relating to sugar modifications.

[0115] In some embodiments, a nucleotide modification in a sugar comprises a 2'-modification. A 2'-modification may be 2'-aminoethyl, 2'-fluoro, 2'-O-methyl, 2'-O-methoxyethyl, and 2'-deoxy-2'-fluoro- β -d-arabinonucleic acid. Typically, the modification is 2'-fluoro, 2'-O-methyl, or 2'-O-methoxyethyl. In some embodiments a modification in a sugar comprises a modification of the sugar ring, which may comprise modification of one or more carbons of the sugar ring. For example, a modification of a sugar of a nucleotide may comprise a 2'-oxygen of a sugar is linked to a 1'-carbon or 4'-carbon of the sugar, or a 2'-oxygen is linked to the 1'-carbon or 4'-carbon via an ethylene or methylene bridge. In some embodiments, a modified nucleotide has an acyclic sugar that lacks a 2'-carbon to 3'-carbon bond. In some embodiments, a modified nucleotide has a thiol group, e.g., in the 4' position of the sugar.

[0116] In some embodiments, the oligonucleotide described herein comprises at least one modified nucleotide (e.g., at least 1, at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, or more). In some embodiments, the sense strand of the oligonucleotide comprises at least one modified nucleotide (e.g., at least 1, at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, or more). In some embodiments, the antisense strand of the oligonucleotide comprises at least one modified nucleotide (e.g., at least 1, at least 5, at least 10, at least 15, at least 20, or more).

[0117] In some embodiments, all the nucleotides of the sense strand of the oligonucleotide are modified. In some embodiments, all the nucleotides of the antisense strand of the oligonucleotide are modified. In some embodiments, all the nucleotides of the oligonucleotide (i.e., both the sense strand and the antisense strand) are modified. In some embodiments, the modified nucleotide comprises a 2'-modification (e.g., a 2'-fluoro or 2'-O-methyl).

[0118] The present disclosure provides oligonucleotides having different modification patterns. In some embodiments, the modified oligonucleotides comprise a sense strand sequence having a sequence as set forth in any one of SEQ ID NOs: 27-39, and an antisense strand sequence having a sequence as set forth in any one of SEQ ID NOs: 14-26. In some embodiments, for these oligonucleotides, one or more of positions 1, 2, 4, 6, 7, 12, 14, 16, 18-27, and 31-36 of the sense strand, and/or one or more of positions 1, 4, 6, 8, 9, 11, 13, 15, 18, and 20-22 of the antisense strand are modified with a 2'-O-methyl. In some embodiments, all of positions 1, 2, 4, 6, 7, 12, 14, 16, 18-27, and 31-36 of the sense strand, and all of positions 1, 4, 6, 8, 9, 11, 13, 15, 18, and 20-22 of the antisense strand are modified with a 2'-O-methyl. In some embodiments, one or more of positions 3,

5, 8-11, 13, 15, and 17 of the sense strand, and/or one or more of positions 2, 3, 5, 7, 10, 12, 14, 16, 17, and 19 of the antisense strand are modified with a 2'-fluoro. In some embodiments, all of positions 3, 5, 8-11, 13, 15, and 17 of the sense strand, and all of positions 2, 3, 5, 7, 10, 12, 14, 16, 17, and 19 of the antisense strand are modified with a 2'-fluoro. In some embodiments, all of positions 1, 2, 4, 6, 7, 12, 14, 16, 18-27, and 31-36 of the sense strand, all of positions 1, 4, 6, 8, 9, 11, 13, 15, 18, and 20-22 of the antisense strand are modified with a 2'-O-methyl, all of positions 3, 5, 8-11, 13, 15, and 17 of the sense strand, and all of positions 2, 3, 5, 7, 10, 12, 14, 16, 17, and 19 of the antisense strand are modified with a 2'-fluoro.

[0119] In some embodiments, for oligonucleotides comprising a sense strand having a sequence as set forth in any one of SEQ ID NOs: 27-39, and an antisense strand having a sequence as set forth in any one of SEQ ID NOs: 14-26, one or more of positions 1-7, 12-27, and 31-36 of the sense strand, and/or one or more of positions 1, 4, 6, 8, 9, 11-13, and 15-22 of the antisense strand are modified with a 2'-O-methyl. In some embodiments, all of positions 1-7, 12-27, and 31-36 of the sense strand, and all of positions 1, 4, 6, 8, 9, 11-13, and 15-22 of the antisense strand are modified with a 2'-O-methyl. In some embodiments, one or more of positions 8-11 of the sense strand, and/or one or more of positions 2, 3, 5, 7, 10, and 14 of the antisense strand are modified with a 2'-fluoro. In some embodiments, all of positions 8-11 of the sense strand, and all of positions 2, 3, 5, 7, 10, and 14 of the antisense strand are modified with a 2'-fluoro. In some embodiments, all of positions 1-7, 12-27, and 31-36 of the sense strand, all of positions 1, 4, 6, 8, 9, 11-13, and 15-22 of the antisense strand are modified with a 2'-O-methyl, all of positions 8-11 of the sense strand, and all of positions 2, 3, 5, 7, 10, and 14 of the antisense strand are modified with a 2'-fluoro.

[0120] In some embodiments, for oligonucleotides comprising a sense strand having a sequence as set forth in any one of SEQ ID NOs: 27-39, and an antisense strand having a sequence as set forth in any one of SEQ ID NOs: 14-26, one or more of positions 1, 2, 4-7, 9, 11, 14-16, 18-27, and 31-36 of the sense strand, and/or one or more of positions 1, 6, 8, 9, 11, 13, 15, 18, and 20-22 of the antisense strand are modified with a 2'-O-methyl. In some embodiments, all of positions 1, 2, 4-7, 9, 11, 14-16, 18-27, and 31-36 of the sense strand, and all of positions 1, 6, 8, 9, 11, 13, 15, 18, and 20-22 of the antisense strand are modified with a 2'-O-methyl. In some embodiments, one or more of positions 3, 8, 10, 12, 13, and 17 of the sense strand, and/or one or more of positions 2-5, 7, 10, 12, 14, 16, 17, and 19 of the antisense strand are modified with a 2'-fluoro. In some embodiments, all of positions 3, 8, 10, 12, 13, and 17 of the sense strand, and all of positions 2-5, 7, 10, 12, 14, 16, 17, and 19 of the antisense strand are modified with a 2'-fluoro.

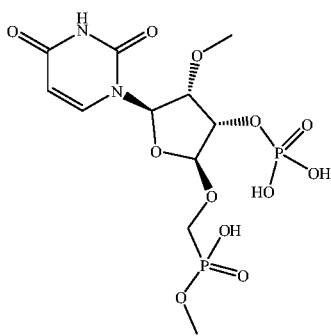
[0121] In some embodiments, the terminal 3'-end group (e.g., a 3'-hydroxyl) with a phosphate group or other group, which can be used, for example, to attach linkers, adapters or labels or for the direct ligation of an oligonucleotide to another nucleic acid.

b. 5' Terminal Phosphates

[0122] In some embodiments, 5'-terminal phosphate groups of oligonucleotides enhance the interaction with Argonaute 2. However, oligonucleotides comprising a 5'-phosphate group may be susceptible to degradation via phosphatases or other enzymes, which can limit their bioavailability in vivo. In some embodiments, oligonucleotides include analogs of 5' phosphates that are resistant to such degradation. In some embodiments, a phosphate analog may be oxymethylphosphonate, vinylphosphonate, or malonylphosphonate. In certain embodiments, the 5' end of an oligonucleotide strand is attached to chemical moiety that mimics the electrostatic and steric properties of a natural 5'-phosphate group ("phosphate mimic") (see, e.g., Prakash et al., *Nucleic Acids Res.*, 2015, 43(6):2993–3011, the contents of which relating to phosphate analogs are incorporated herein by reference). Many phosphate mimics have been developed that can be attached to the 5' end (see, e.g., U.S. Patent No. 8,927,513, the contents of which relating to phosphate analogs are incorporated herein by reference). Other modifications have been developed for the 5' end of oligonucleotides (see, e.g., International patent publication WO2011133871, the contents of which relating to phosphate analogs are incorporated herein by reference). In certain embodiments, a hydroxyl group is attached to the 5' end of the oligonucleotide.

[0123] In some embodiments, an oligonucleotide has a phosphate analog at a 4'-carbon position of the sugar (referred to as a "4'-phosphate analog") (see, e.g., International patent publication WO2018045317, entitled 4'-Phosphate Analogs and Oligonucleotides Comprising the Same, which content relating to phosphate analogs is incorporated herein by reference). In some embodiments, an oligonucleotide provided herein comprise a 4'-phosphate analog at a 5'-terminal nucleotide. In some embodiments, a phosphate analog is an oxymethylphosphonate in which the oxygen atom of the oxymethyl group is bound to the sugar moiety (e.g., at its 4'-carbon) or analog thereof. In other embodiments, a 4'-phosphate analog is a thiomethylphosphonate or an aminomethylphosphonate in which the sulfur atom of the thiomethyl group or the nitrogen atom of the aminomethyl group is bound to the 4'-carbon of the sugar moiety or analog thereof. In certain embodiments, a 4'-phosphate analog is an oxymethylphosphonate. In some embodiments, an oxymethylphosphonate is represented by the formula $-O-CH_2-PO(OH)_2$ or $-O-CH_2-PO(OR)_2$, in which R is independently selected from H, CH_3 , an alkyl group, CH_2CH_2CN , $CH_2OCOC(CH_3)_3$, $CH_2OCH_2CH_2Si(CH_3)_3$, or a protecting group. In certain embodiments, the alkyl group is CH_2CH_3 . More typically, R is independently selected from H, CH_3 , or CH_2CH_3 .

[0124] In certain embodiments, a phosphate analog attached to the oligonucleotide is a methoxy phosphonate (MOP). In certain embodiments, a phosphate analog attached to the oligonucleotide is a 5' mono-methyl protected MOP. In some embodiments, the following uridine nucleotide comprising a phosphate analog may be used, e.g., at the first position of a guide (antisense) strand:



which modified nucleotide is referred to as [MePhosphonate-4O-mU] or 5'-Methoxy, Phosphonate-4'oxy- 2'-O-methyluridine.

c. Modified Intranucleotide Linkages

[0125] In some embodiments, phosphate modifications or substitutions may result in an oligonucleotide comprises at least one (e.g., at least 1, at least 2, at least 3 or at least 5) comprising a modified internucleotide linkage. In some embodiments, any one of the oligonucleotides disclosed herein comprises 1 to 10 (e.g., 1 to 10, 2 to 8, 4 to 6, 3 to 10, 5 to 10, 1 to 5, 1 to 3 or 1 to 2) modified internucleotide linkages. In some embodiments, any one of the oligonucleotides disclosed herein comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 modified internucleotide linkages.

[0126] A modified internucleotide linkage may be a phosphorodithioate linkage, a phosphorothioate linkage, a phosphotriester linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a phosphoramidite linkage, a phosphonate linkage or a boranophosphate linkage. In some embodiments, at least one modified internucleotide linkage of any one of the oligonucleotides as disclosed herein is a phosphorothioate linkage.

[0127] In some embodiments, the oligonucleotide described herein has a phosphorothioate linkage between one or more of: positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 3 and 4 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand. In some embodiments, the oligonucleotide described herein has a phosphorothioate linkage between each of: positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand.

d. Base modifications

[0128] In some embodiments, oligonucleotides provided herein have one or more modified nucleobases. In some embodiments, modified nucleobases (also referred to herein as base analogs) are linked at the 1' position of a nucleotide sugar moiety. In certain embodiments, a modified nucleobase is a nitrogenous base. In certain embodiments, a modified nucleobase does not contain nitrogen atom (see, e.g., U.S. patent publication 20080274462). In some embodiments, a modified

nucleotide comprises a universal base. However, in certain embodiments, a modified nucleotide does not contain a nucleobase (abasic).

[0129] In some embodiments a universal base is a heterocyclic moiety located at the 1' position of a nucleotide sugar moiety in a modified nucleotide, or the equivalent position in a nucleotide sugar moiety substitution, that, when present in a duplex, can be positioned opposite more than one type of base without substantially altering structure of the duplex. In some embodiments, compared to a reference single-stranded nucleic acid (e.g., oligonucleotide) that is fully complementary to a target nucleic acid, a single-stranded nucleic acid containing a universal base forms a duplex with the target nucleic acid that has a lower T_m than a duplex formed with the complementary nucleic acid. However, in some embodiments, compared to a reference single-stranded nucleic acid in which the universal base has been replaced with a base to generate a single mismatch, the single-stranded nucleic acid containing the universal base forms a duplex with the target nucleic acid that has a higher T_m than a duplex formed with the nucleic acid comprising the mismatched base.

[0130] Non-limiting examples of universal-binding nucleotides include inosine, 1- β -D-ribofuranosyl-5-nitroindole, and/or 1- β -D-ribofuranosyl-3-nitropyrrole (U.S. patent publication no. 20070254362; Van Aerschot et al., *Nucleic Acids Res.* 1995, 23(21):4363-70; Loakes et al., *Nucleic Acids Res.* 1995, 23(13):2361-6; Loakes and Brown, *Nucleic Acids Res.*, 1994, 22(20):4039-43. Each of the foregoing is incorporated by reference herein for their disclosures relating to base modifications).

e. Reversible Modifications

[0131] While certain modifications to protect an oligonucleotide from the in vivo environment before reaching target cells can be made, they can reduce the potency or activity of the oligonucleotide once it reaches the cytosol of the target cell. Reversible modifications can be made such that the molecule retains desirable properties outside of the cell, which are then removed upon entering the cytosolic environment of the cell. Reversible modification can be removed, for example, by the action of an intracellular enzyme or by the chemical conditions inside of a cell (e.g., through reduction by intracellular glutathione).

[0132] In some embodiments, a reversibly modified nucleotide comprises a glutathione-sensitive moiety. Typically, nucleic acid molecules have been chemically modified with cyclic disulfide moieties to mask the negative charge created by the internucleotide diphosphate linkages and improve cellular uptake and nuclease resistance (see, e.g., U.S. patent publication 20110294869, International patent publication WO2015188197; Meade et al., *Nature Biotechnology*, 2014, 32:1256-1263; International patent publication WO2014088920; each of which are incorporated by reference for their disclosures of such modifications). This reversible modification of the internucleotide diphosphate linkages is designed to be cleaved intracellularly by the reducing environment of the

cytosol (e.g., glutathione). Earlier examples include neutralizing phosphotriester modifications that were reported to be cleavable inside cells (Dellinger et al., J. Am. Chem. Soc., 2003, 125:940-950).

[0133] In some embodiments, such a reversible modification allows protection during in vivo administration (e.g., transit through the blood and/or lysosomal/endosomal compartments of a cell) where the oligonucleotide will be exposed to nucleases and other harsh environmental conditions (e.g., pH). When released into the cytosol of a cell where the levels of glutathione are higher compared to extracellular space, the modification is reversed and the result is a cleaved oligonucleotide. Using reversible, glutathione sensitive moieties, it is possible to introduce sterically larger chemical groups into the oligonucleotide of interest as compared to the options available using irreversible chemical modifications. This is because these larger chemical groups will be removed in the cytosol and, therefore, should not interfere with the biological activity of the oligonucleotides inside the cytosol of a cell. As a result, these larger chemical groups can be engineered to confer various advantages to the nucleotide or oligonucleotide, such as nuclease resistance, lipophilicity, charge, thermal stability, specificity, and reduced immunogenicity. In some embodiments, the structure of the glutathione-sensitive moiety can be engineered to modify the kinetics of its release.

[0134] In some embodiments, a glutathione-sensitive moiety is attached to the sugar of the nucleotide. In some embodiments, a glutathione-sensitive moiety is attached to the 2' carbon of the sugar of a modified nucleotide. In some embodiments, the glutathione-sensitive moiety is located at the 5'-carbon of a sugar, particularly when the modified nucleotide is the 5'-terminal nucleotide of the oligonucleotide. In some embodiments, the glutathione-sensitive moiety is located at the 3'-carbon of sugar, particularly when the modified nucleotide is the 3'-terminal nucleotide of the oligonucleotide. In some embodiments, the glutathione-sensitive moiety comprises a sulfonyl group (see, e.g., International patent publication WO2018039364, the contents of which are incorporated by reference herein for its relevant disclosures).

v. Targeting Ligands

[0135] In some embodiments, it may be desirable to target the oligonucleotides of the disclosure to one or more cells or one or more organs. Such a strategy may help to avoid undesirable effects in other organs or may avoid undue loss of the oligonucleotide to cells, tissue or organs that would not benefit for the oligonucleotide. Accordingly, in some embodiments, oligonucleotides disclosed herein may be modified to facilitate targeting of a particular tissue, cell or organ, e.g., to facilitate delivery of the oligonucleotide to the liver. In certain embodiments, oligonucleotides disclosed herein may be modified to facilitate delivery of the oligonucleotide to the hepatocytes of the liver. In some embodiments, an oligonucleotide comprises a nucleotide that is conjugated to one or more targeting ligand.

[0136] A targeting ligand may comprise a carbohydrate, amino sugar, cholesterol, peptide, polypeptide, protein or part of a protein (e.g., an antibody or antibody fragment) or lipid. In some embodiments, a targeting ligand is an aptamer. For example, a targeting ligand may be an RGD peptide that is used to target tumor vasculature or glioma cells, CREKA peptide to target tumor vasculature or stoma, transferring, lactoferrin, or an aptamer to target transferrin receptors expressed on CNS vasculature, or an anti-EGFR antibody to target EGFR on glioma cells. In certain embodiments, the targeting ligand is one or more GalNAc moieties.

[0137] In some embodiments, 1 or more (e.g., 1, 2, 3, 4, 5 or 6) nucleotides of an oligonucleotide are each conjugated to a separate targeting ligand. In some embodiments, 2 to 4 nucleotides of an oligonucleotide are each conjugated to a separate targeting ligand. In some embodiments, targeting ligands are conjugated to 2 to 4 nucleotides at either ends of the sense or antisense strand (e.g., ligands are conjugated to a 2 to 4 nucleotide overhang or extension on the 5' or 3' end of the sense or antisense strand) such that the targeting ligands resemble bristles of a toothbrush and the oligonucleotide resembles a toothbrush. For example, an oligonucleotide may comprise a stem-loop at either the 5' or 3' end of the sense strand and 1, 2, 3 or 4 nucleotides of the loop of the stem may be individually conjugated to a targeting ligand.

[0138] In some embodiments, it is desirable to target an oligonucleotide that reduces the expression of HMGB1 to the hepatocytes of the liver of the subject. Any suitable hepatocyte targeting moiety may be used for this purpose.

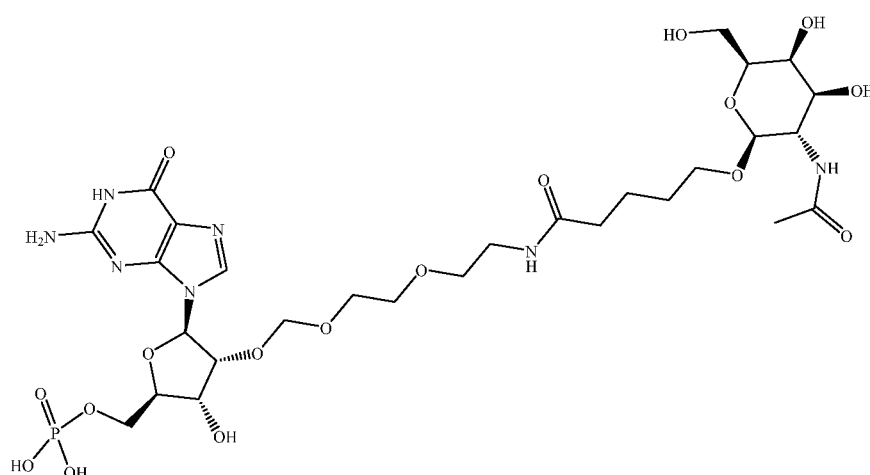
[0139] GalNAc is a high affinity ligand for asialoglycoprotein receptor (ASGPR), which is primarily expressed on the sinusoidal surface of hepatocyte cells and has a major role in binding, internalization, and subsequent clearance of circulating glycoproteins that contain terminal galactose or N-acetylgalactosamine residues (asialoglycoproteins). Conjugation (either indirect or direct) of GalNAc moieties to oligonucleotides of the instant disclosure may be used to target these oligonucleotides to the ASGPR expressed on these hepatocyte cells.

[0140] In some embodiments, an oligonucleotide of the instant disclosure is conjugated directly or indirectly to a monovalent GalNAc. In some embodiments, the oligonucleotide is conjugated directly or indirectly to more than one monovalent GalNAc (e.g., is conjugated to 2, 3, or 4 monovalent GalNAc moieties, and is typically conjugated to 3 or 4 monovalent GalNAc moieties). In some embodiments, an oligonucleotide of the instant disclosure is conjugated to a one or more bivalent GalNAc, trivalent GalNAc, or tetravalent GalNAc moieties.

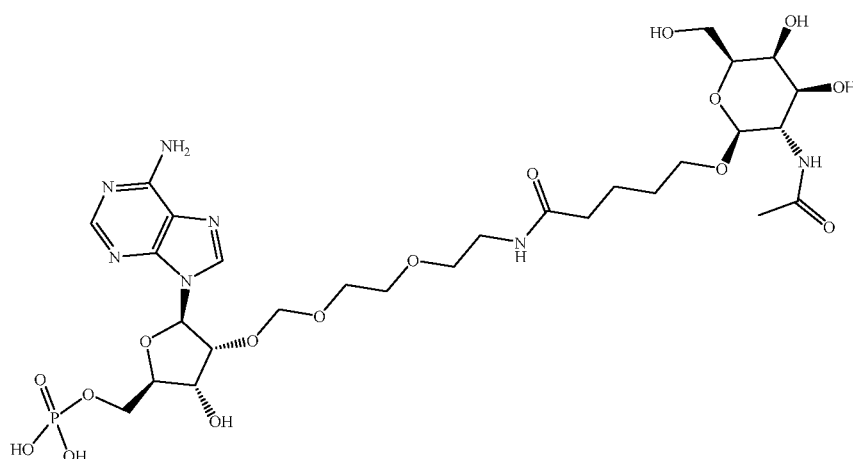
[0141] In some embodiments, 1 or more (e.g., 1, 2, 3, 4, 5 or 6) nucleotides of an oligonucleotide are each conjugated to a GalNAc moiety. In some embodiments, 2 to 4 nucleotides of the loop (L) of the stem-loop are each conjugated to a separate GalNAc. In some embodiments, targeting ligands are conjugated to 2 to 4 nucleotides at either ends of the sense or antisense strand (e.g., ligands are

conjugated to a 2 to 4 nucleotide overhang or extension on the 5' or 3' end of the sense or antisense strand) such that the GalNAc moieties resemble bristles of a toothbrush and the oligonucleotide resembles a toothbrush. For example, an oligonucleotide may comprise a stem-loop at either the 5' or 3' end of the sense strand and 1, 2, 3 or 4 nucleotides of the loop of the stem may be individually conjugated to a GalNAc moiety. In some embodiments, GalNAc moieties are conjugated to a nucleotide of the sense strand. For example, four GalNAc moieties can be conjugated to nucleotides in the tetraloop of the sense strand where each GalNAc moiety is conjugated to one nucleotide.

[0142] In some embodiments, an oligonucleotide herein comprises a monovalent GalNAc attached to a Guanine nucleotide, referred to as [ademG-GalNAc] or 2'-aminodiethoxymethanol-Guanidine-GalNAc, as depicted below:

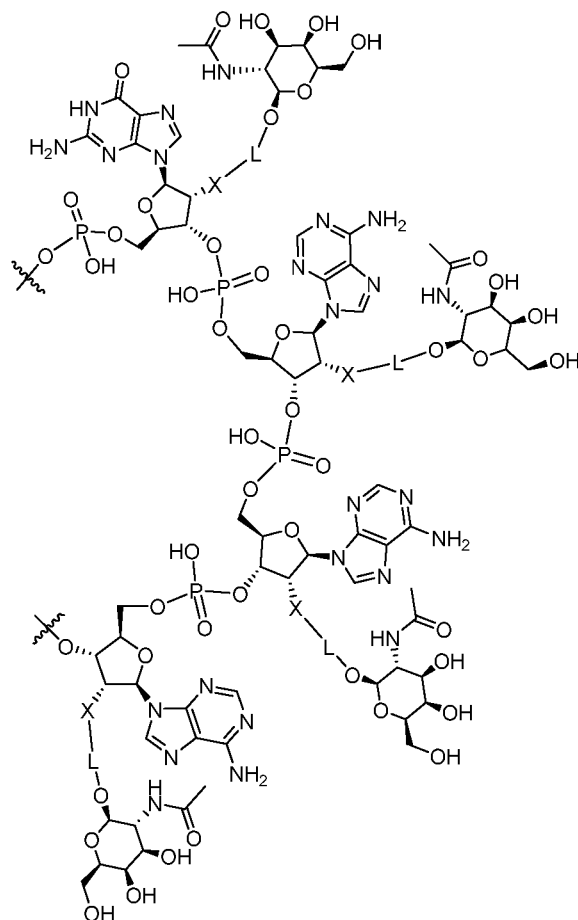


[0143] In some embodiments, an oligonucleotide herein comprises a monovalent GalNAc attached to an adenine nucleotide, referred to as [ademA-GalNAc] or 2'-aminodiethoxymethanol-Adenine-GalNAc, as depicted below.



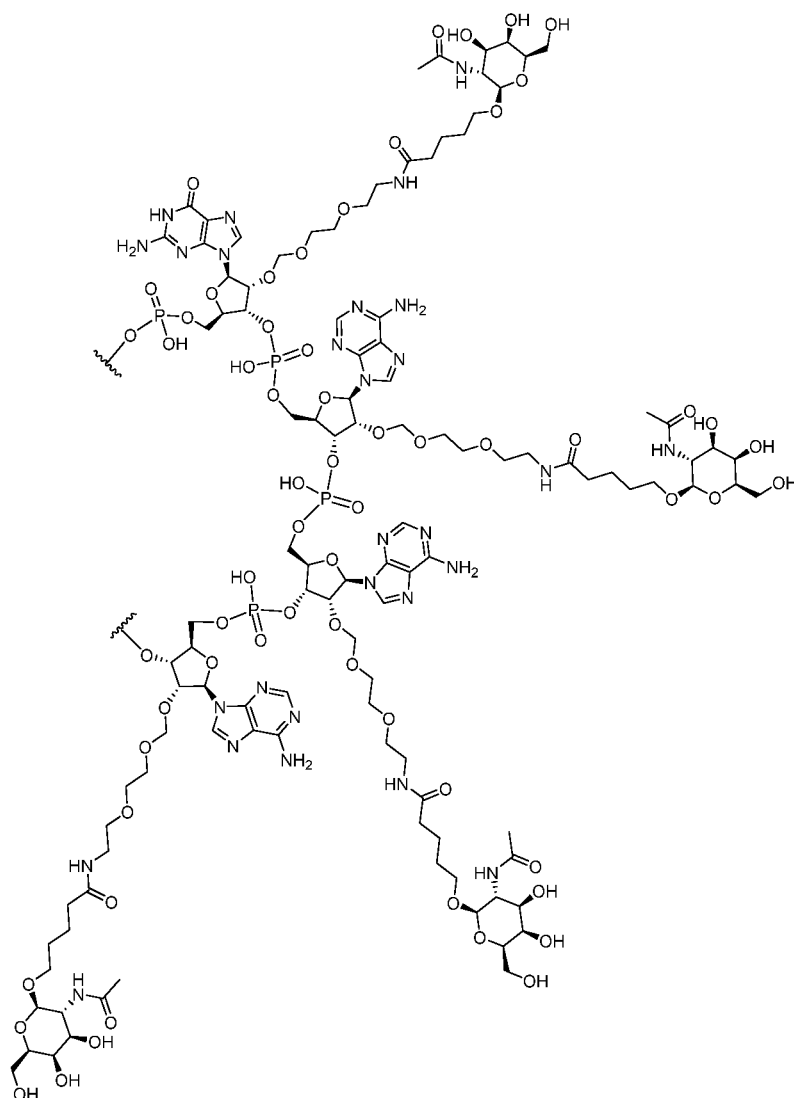
[0144] An example of such conjugation is shown below for a loop comprising from 5' to 3' the nucleotide sequence GAAA (L = linker, X = heteroatom) stem attachment points are shown. Such a

loop may be present, for example, at positions 27-30 of the molecules shown in FIG. 1B. In the chemical formula,  is used to describe an attachment point to the oligonucleotide strand.



[0145] Appropriate methods or chemistry (e.g., click chemistry) can be used to link a targeting ligand to a nucleotide. In some embodiments, a targeting ligand is conjugated to a nucleotide using a click linker. In some embodiments, an acetal-based linker is used to conjugate a targeting ligand to a nucleotide of any one of the oligonucleotides described herein. Acetal-based linkers are disclosed, for example, in International patent publication WO2016100401, the contents of which relating to such linkers are incorporated herein by reference. In some embodiments, the linker is a labile linker. However, in other embodiments, the linker is stable. A “labile linker” refers to a linker that can be cleaved, e.g., by acidic pH. A “stable linker” refers to a linker that cannot be cleaved.

[0146] An example is shown below for a loop comprising from 5' to 3' the nucleotides GAAA, in which GalNAc moieties are attached to nucleotides of the loop using an acetal linker. Such a loop may be present, for example, at positions 27-30 of the molecules described in FIG. 10. In the chemical formula,  is an attachment point to the oligonucleotide strand.



[0147] Any appropriate method or chemistry (e.g., click chemistry) can be used to link a targeting ligand to a nucleotide. In some embodiments, a targeting ligand is conjugated to a nucleotide using a click linker. In some embodiments, an acetal-based linker is used to conjugate a targeting ligand to a nucleotide of any one of the oligonucleotides described herein. Acetal-based linkers are disclosed, for example, in International patent publication WO2016100401, the contents of which relating to such linkers are incorporated herein by reference. In some embodiments, the linker is a labile linker. In other embodiments, the linker is stable.

[0148] In some embodiments, a duplex extension (e.g., of up to 3, 4, 5, or 6 base pairs in length) is provided between a targeting ligand (e.g., a GalNAc moiety) and a double-stranded oligonucleotide.

III. Formulations

[0149] Various formulations have been developed to facilitate oligonucleotide use. For example, oligonucleotides can be delivered to a subject or a cellular environment using a formulation that

minimizes degradation, facilitates delivery and/or uptake, or provides another beneficial property to the oligonucleotides in the formulation. In some embodiments, provided herein are compositions comprising oligonucleotides (e.g., single-stranded or double-stranded oligonucleotides) to reduce the expression of HMGB1. Such compositions can be suitably formulated such that when administered to a subject, either into the immediate environment of a target cell or systemically, a sufficient portion of the oligonucleotides enter the cell to reduce HMGB1 expression. Any of a variety of suitable oligonucleotide formulations can be used to deliver oligonucleotides for the reduction of HMGB1 as disclosed herein. In some embodiments, an oligonucleotide is formulated in buffer solutions such as phosphate buffered saline solutions, liposomes, micellar structures, and capsids.

[0150] Formulations of oligonucleotides with cationic lipids can be used to facilitate transfection of the oligonucleotides into cells. For example, cationic lipids, such as lipofectin, cationic glycerol derivatives, and polycationic molecules (e.g., polylysine, can be used. Suitable lipids include Oligofectamine, Lipofectamine (Life Technologies), NC388 (Ribozyme Pharmaceuticals, Inc., Boulder, Colo.), or FuGene 6 (Roche) all of which can be used according to the manufacturer's instructions.

[0151] Accordingly, in some embodiments, a formulation comprises a lipid nanoparticle. In some embodiments, an excipient comprises a liposome, a lipid, a lipid complex, a microsphere, a microparticle, a nanosphere, or a nanoparticle, or may be otherwise formulated for administration to the cells, tissues, organs, or body of a subject in need thereof (see, e.g., Remington: The Science and Practice of Pharmacy, 22nd Ed., Pharmaceutical Press, 2013).

[0152] In some embodiments, formulations as disclosed herein comprise an excipient. In some embodiments, an excipient confers to a composition improved stability, improved absorption, improved solubility and/or therapeutic enhancement of the active ingredient. In some embodiments, an excipient is a buffering agent (e.g., sodium citrate, sodium phosphate, a tris base, or sodium hydroxide) or a vehicle (e.g., a buffered solution, petrolatum, dimethyl sulfoxide, or mineral oil). In some embodiments, an oligonucleotide is lyophilized for extending its shelf-life and then made into a solution before use (e.g., administration to a subject). Accordingly, an excipient in a composition comprising any one of the oligonucleotides described herein may be a lyoprotectant (e.g., mannitol, lactose, polyethylene glycol, or polyvinyl pyrrolidone), or a collapse temperature modifier (e.g., dextran, ficoll, or gelatin).

[0153] In some embodiments, a pharmaceutical composition is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), transmucosal, and rectal administration.

[0154] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL.TM. (BASF, Parsippany, N.J., USA) or phosphate buffered saline (PBS). The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, sodium chloride in the composition. Sterile injectable solutions can be prepared by incorporating the oligonucleotides in a required amount in a selected solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization.

[0155] In some embodiments, a composition may contain at least about 0.1% of the therapeutic agent (e.g., an oligonucleotide for reducing HMGB1 expression) or more, although the percentage of the active ingredient(s) may be about 1% to about 80% or more of the weight or volume of the total composition. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

[0156] Even though a number of embodiments are directed to liver-targeted delivery of any of the oligonucleotides disclosed herein, targeting of other tissues is also contemplated.

IV. Methods of Use

i. Reducing HMGB1 Expression in Cells

[0157] In some embodiments, methods are provided for delivering to a cell an effective amount any one of oligonucleotides disclosed herein for purposes of reducing expression of HMGB1 in the cell. Methods provided herein are useful in any appropriate cell type. In some embodiments, a cell is any cell that expresses HMGB1 (e.g., hepatocytes, macrophages, monocyte-derived cells, prostate cancer cells, cells of the brain, endocrine tissue, bone marrow, lymph nodes, lung, gall bladder, liver, duodenum, small intestine, pancreas, kidney, gastrointestinal tract, bladder, adipose and soft tissue and skin). In some embodiments, the cell is a primary cell that has been obtained from a subject and that may have undergone a limited number of passages, such that the cell substantially maintains its natural phenotypic properties. In some embodiments, a cell to which the oligonucleotide is delivered is ex vivo or in vitro (e.g., can be delivered to a cell in culture or to an organism in which the cell resides). In specific embodiments, methods are provided for delivering to a cell an effective amount any one of oligonucleotides disclosed herein for purposes of reducing expression of HMGB1 solely in hepatocytes.

[0158] In some embodiments, oligonucleotides disclosed herein can be introduced using appropriate nucleic acid delivery methods including injection of a solution containing the oligonucleotides, bombardment by particles covered by the oligonucleotides, exposing the cell or organism to a solution containing the oligonucleotides, or electroporation of cell membranes in the presence of the oligonucleotides. Other appropriate methods for delivering oligonucleotides to cells may be used, such as lipid-mediated carrier transport, chemical-mediated transport, and cationic liposome transfection such as calcium phosphate, and others.

[0159] The consequences of inhibition can be confirmed by an appropriate assay to evaluate one or more properties of a cell or subject, or by biochemical techniques that evaluate molecules indicative of HMGB1 expression (e.g., RNA, protein). In some embodiments, the extent to which an oligonucleotide provided herein reduces levels of expression of HMGB1 is evaluated by comparing expression levels (e.g., mRNA or protein levels of HMGB1 to an appropriate control (e.g., a level of HMGB1 expression in a cell or population of cells to which an oligonucleotide has not been delivered or to which a negative control has been delivered). In some embodiments, an appropriate control level of HMGB1 expression may be a predetermined level or value, such that a control level need not be measured every time. The predetermined level or value can take a variety of forms. In some embodiments, a predetermined level or value can be single cut-off value, such as a median or mean.

[0160] In some embodiments, administration of an oligonucleotide as described herein results in a reduction in the level of HMGB1 expression in a cell. In some embodiments, the reduction in levels of HMGB1 expression may be a reduction to 1% or lower, 5% or lower, 10% or lower, 15% or lower, 20% or lower, 25% or lower, 30% or lower, 35% or lower, 40% or lower, 45% or lower, 50% or lower, 55% or lower, 60% or lower, 70% or lower, 80% or lower, or 90% or lower compared with an appropriate control level of HMGB1. The appropriate control level may be a level of HMGB1 expression in a cell or population of cells that has not been contacted with an oligonucleotide as described herein. In some embodiments, the effect of delivery of an oligonucleotide to a cell according to a method disclosed herein is assessed after a finite period of time. For example, levels of HMGB1 may be analyzed in a cell at least 8 hours, 12 hours, 18 hours, 24 hours; or at least one, two, three, four, five, six, seven, or fourteen days after introduction of the oligonucleotide into the cell.

[0161] In some embodiments, an oligonucleotide is delivered in the form of a transgene that is engineered to express in a cell the oligonucleotides (e.g., its sense and antisense strands). In some embodiments, an oligonucleotide is delivered using a transgene that is engineered to express any oligonucleotide disclosed herein. Transgenes may be delivered using viral vectors (e.g., adenovirus, retrovirus, vaccinia virus, poxvirus, adeno-associated virus or herpes simplex virus) or non-viral vectors (e.g., plasmids or synthetic mRNAs). In some embodiments, transgenes can be injected directly to a subject.

ii. Treatment Methods

[0162] Aspects of the disclosure relate to methods for reducing HMGB1 expression in for attenuating the onset or progression of liver fibrosis in a subject. In some embodiments, the methods may comprise administering to a subject in need thereof an effective amount of any one of the oligonucleotides disclosed herein. Such treatments could be used, for example, to slow or halt any type of liver fibrosis. The present disclosure provides for both prophylactic and therapeutic methods of treating a subject at risk of (or susceptible to) a disease or disorder associated with liver fibrosis and/or liver inflammation.

[0163] The compounds of the invention selectively target HMGB1 mRNA exclusively in the liver. Compared to other NASH therapies, this selectivity is expected to increase the potency of the HMGB1 inhibitors of the inventions while decreasing off-target interactions and potential side effects.

[0164] In certain aspects, the disclosure provides a method for preventing in a subject, a disease or disorder as described herein by administering to the subject a therapeutic agent (e.g., an oligonucleotide or vector or transgene encoding same). In some embodiments, the subject to be treated is a subject who will benefit therapeutically from a reduction in the amount of HMGB1 protein, e.g., in the liver. Subjects at risk for the disease or disorder can be identified by, for example, one or a combination of diagnostic or prognostic assays known in the art (e.g., identification of liver fibrosis and/or liver inflammation). Administration of a prophylactic agent can occur prior to the detection of or the manifestation of symptoms characteristic of the disease or disorder, such that the disease or disorder is prevented or, alternatively, delayed in its progression.

[0165] In some embodiments, the disclosure provides methods for using RNAi oligonucleotides of the invention for treating subjects having or suspected of having liver conditions such as, for example, cholestatic liver disease, nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH).

[0166] In some embodiments, the disclosure provides RNAi oligonucleotides described herein for use in treating subjects having or suspected of having liver conditions such as, for example, cholestatic liver disease, NAFLD and NASH.

[0167] In some embodiments, the disclosure provides RNAi for the preparation of a medicament for treatment of subjects having or suspected of having liver conditions such as, for example, cholestatic liver disease, NAFLD and nonalcoholic steatohepatitis NASH.

[0168] Methods described herein are typically involve administering to a subject in an effective amount of an oligonucleotide, that is, an amount capable of producing a desirable therapeutic result. A therapeutically acceptable amount may be an amount that is capable of treating a disease or disorder. The appropriate dosage for any one subject will depend on certain factors, including the subject's size, body surface area, age, the particular composition to be administered, the active

ingredient(s) in the composition, time and route of administration, general health, and other drugs being administered concurrently.

[0169] In some embodiments, a subject is administered any one of the compositions disclosed herein either enterally (e.g., orally, by gastric feeding tube, by duodenal feeding tube, via gastrostomy or rectally), parenterally (e.g., subcutaneous injection, intravenous injection or infusion, intra-arterial injection or infusion, intraosseous infusion, intramuscular injection, intracerebral injection, intracerebroventricular injection, intrathecal), topically (e.g., epicutaneous, inhalational, via eye drops, or through a mucous membrane), or by direct injection into a target organ (e.g., the liver of a subject). Typically, oligonucleotides disclosed herein are administered intravenously or subcutaneously.

[0170] As a non-limiting set of examples, the oligonucleotides of the instant disclosure would typically be administered quarterly (once every three months), bi-monthly (once every two months), monthly, or weekly. For example, the oligonucleotides may be administered every week or at intervals of two, or three weeks. In some embodiments, the oligonucleotides may be administered daily.

[0171] In some embodiments, the subject to be treated is a human or non-human primate or other mammalian subject. Other exemplary subjects include domesticated animals such as dogs and cats; livestock such as horses, cattle, pigs, sheep, goats, and chickens; and animals such as mice, rats, guinea pigs, and hamsters.

EXAMPLES

Example 1: In vivo Activity of GalNAc-conjugated HMGB1 oligonucleotides

[0172] HMGB1 oligonucleotides used in this example were designed to bind to conserved sequences identified by the algorithm in the human, monkey (both rhesus), and mouse sequences (“triple common” sequences). In this study, three triple-common oligonucleotide sequences (S31-AS18, S35-AS22, and S36-AS23) were tested in 3 different modification patterns (M1, M2 and M3, see FIGs. 1A and 1B). Oligonucleotides were subcutaneously administered to CD-1 mice at 1 mg/kg and mice were euthanized on day 5 following administration. Liver samples were obtained and RNA was extracted to evaluate HMGB1 mRNA levels by qPCR (normalized to HPRT1-F576 (Housekeeping gene)). The levels of remaining HMGB1 mRNA were interrogated using TAQMAN®-based qPCR assays.

[0173] The qPCR was performed using two different primers specific to different regions in the HMGB1 mRNA. The qPCR performed using the primer at the 5' end relative to the other primer was designated “5' qPCR.” Similarly, the qPCR performed using the primer at the 3' end relative to the other primer was designated “3' qPCR.” In this experiment, a 3' qPCR assay (using primer MmHMGB1-F1541) was used. The data showed that all tested HMGB1 oligonucleotides were potent

in knockdown HMGB1 5 days after administration, as indicated by the reduced amount of HMGB1 mRNA remaining in mice liver (normalized to a PBS control treatment) (FIG. 1A).

[0174] Two GalNAc-conjugated HMGB1 oligonucleotides with different modification patterns (S31-AS18-M3 and S35-AS22-M2) were further tested in a dose response analysis, using the tool compound S36-AS23-M2 as control. The three oligonucleotides were subcutaneously administered to CD-1 mice at three different dosages (0.5 mg/kg, 1 mg/kg, and 2 mg/kg). Mice were euthanized on day 5 following administration. Liver samples were obtained, and RNA was extracted to evaluate HMGB1 mRNA levels by qPCR (normalized to HPRT1-F576 (Housekeeping gene)). The levels of remaining HMGB1 mRNA were interrogated using TAQMAN®-based qPCR assays (a 3' assay as described above was used). The results show that the two tested GalNAc-conjugated HMGB1 oligonucleotides, in both modification patterns, reduced liver HMGB1 mRNA level in mice liver (FIG. 2). All oligonucleotides showed ED₅₀s of ~0.5 – 1.0 mg/kg, especially if non-hepatocyte 'floor' is considered.

[0175] The two GalNAc-conjugated HMGB1 oligonucleotides with different modification patterns (S31-AS18-M3 and S35-AS22-M2) were then tested in vivo in a duration study to evaluate their activity in inhibiting HMGB1 expression in mice. PBS was used as negative control, and the tool compound S36-AS23-M2 was used as positive control in this experiment. Oligonucleotides were subcutaneously administered to CD-1 mice at 1 mg/kg and mice were euthanized on days 7, 14, 21, and 28 following administration. Liver samples were obtained and RNA was extracted to evaluate HMGB1 mRNA levels by qPCR (normalized to HPRT1-F576 housekeeping gene). A 3' assay as described above was used. The data showed that all tested HMGB1 oligonucleotides were potent in knockdown HMGB1 3 weeks after injection, even with 1 mg/kg single dose, as indicated by the reduced amount of HMGB1 mRNA remaining in mice liver at days 7, 14, 21, and 28 (normalized to a PBS control treatment) (FIG. 3).

Example 2: Additional In vitro screening of new HMGB1 RNAi oligonucleotides sequences to identify additional RNAi oligonucleotides that inhibit HMGB1 expression

[0176] Additional 288 triple commons HMGB1 RNAi oligonucleotides (see Table 4 for sequences) were screened in an in vitro activity assay to identify additional RNAi oligonucleotides sequences that are effective at inhibiting HMGB1 expression (FIGs. 4A-4F). In this assay, Huh-7 cells were transfected with the indicated oligonucleotides. Cells were maintained for 24h following transfection, RNAs were isolated using the iScript RT-qPCR sample preparation buffer. HMGB1 mRNA were interrogated using TAQMAN®-based qPCR assays. Two qPCR assays, a 5' assay and a 3' assay, were used to determine mRNA levels as measured by HEX (housekeeping gene – HPRT-F576/SFRS9-F594) and FAM probes, respectively.

[0177] The percent mRNA remaining is shown for each of the 5' assay (red) and the 3' assay (blue). Oligonucleotides with the lowest percentage of mRNA remaining compared to mock transfection controls were considered hits. Oligonucleotides with low complementarity to the human genome were used as negative controls.

[0178] Twenty-two (22) new sequences identified in the screen were made into GalNAc-conjugated tetraloop oligonucleotides (see Table 2 and Table 5 for sequences) with two different modification patterns (M2 and M3, respectively) and their in vivo activities in reduce liver HMGB1 mRNA level were tested. PBS was used as negative control, and the tool compound in two different modification patterns (S36-AS23-M2 and S36-AS23-M3) were used as positive control in this experiment. Oligonucleotides were subcutaneously administered to CD-1 mice at 1 mg/kg, and mice were euthanized on day 5 following administration. Liver samples were obtained and RNA was extracted to evaluate HMGB1 mRNA levels by qPCR (normalized to HPRT1-F576 (Housekeeping gene)). The levels of remaining HMGB1 mRNA were interrogated using TAQMAN®-based qPCR assays (3' assay was used). The results show that the new GalNAc-conjugated oligonucleotides had different levels of activity in inhibiting liver HMGB1 and 7 new GalNAc-conjugated HMGB1 oligonucleotides (as indicated by the arrow, S27-AS14, S28-AS15, S29-AS16, S30-AS17, S32-AS19, S33-AS20, and S34-AS21) were selected to be included in knockdown duration study, if at least 50% suppression of HMGB1 mRNA is achieved 3 weeks after a single dose of 3 to 5 mg/kg in mice (FIG. 5).

[0179] For the knockdown duration assay, the 7 new GalNAc-conjugated HMGB1 oligonucleotides (S27-AS14, S28-AS15, S29-AS16, S30-AS17, S32-AS19, S33-AS20, and S34-AS21) with different modification patterns (M2 or M3) were tested and compared with two previously identified GalNAc-conjugated HMGB1 oligonucleotides (S31-AS18-M3 and S35-AS22-M2). PBS was used as negative control, and the tool compound S36-AS23-M2 was used as positive control. Oligonucleotides were subcutaneously administered to CD-1 mice at 4 mg/kg and mice were euthanized on day 21 following administration. Liver samples were obtained and RNA was extracted to evaluate HMGB1 mRNA levels by qPCR (normalized to HPRT1-F576 (Housekeeping gene)). The levels of remaining HMGB1 mRNA were interrogated using TAQMAN®-based qPCR assays (3' assay was used). The percent remaining HMGB1 mRNA in the liver 21 days after the administration of the oligonucleotides, normalized to PBS control treatment, is shown in FIG. 6. All tested HMGB1 oligonucleotides were potent in knockdown HMGB1 3 weeks after injection.

Example 3: Testing GalNAc-conjugated HMGB1 oligonucleotides in primary monkey or human hepatocytes

[0180] The GalNAc-conjugated HMGB1 oligonucleotides tested in this experiment were shown in FIG. 7. Also shown in FIG. 7 is a GalNAc-conjugated LDHA oligonucleotide for using as positive control. In this assay, GalNAc-conjugates HMGB1 oligonucleotides were delivered by ASGPR

receptor-mediated uptake into the monkey primary hepatocyte (FIGs. 8A and 8B) or the human hepatocyte (FIG. 8C) cells.

[0181] Cells were maintained for 24h following oligonucleotides delivery. RNA was extracted to evaluate HMGB1 mRNA levels by qPCR (normalized to RhPPIB (Housekeeping gene) for monkey hepatocytes and HPRT1-F576 (Housekeeping gene) for human hepatocytes). The levels of remaining HMGB1 mRNA were interrogated using TAQMAN®-based qPCR assays. RhMHGB1-F457 qPCR assay (FIGs. 8A and 8B) and HsHMGB1-F81 assay (FIG. 8C) were used. GalNAc-conjugate LDHA-1360 oligonucleotide was used as assay control (FIG. 8D) and the level of remaining LDHA mRNA was measured by RhLDHA-F887 qPCR assay. IC50 curves of RhHMGB1, normalized to Mock treatment, are shown.

[0182] Four exemplary GalNAc-conjugated HMGB1 oligonucleotides (S27-AS14-M2, S33-AS20-M2, S35-AS22-M2, and S37-AS24-M2) were further tested in vivo in non-human primates (monkeys) for their activity in HMGB1 knockdown. PBS was used as negative control, and the tool compound S36-AS23-M2 was used as positive control in this experiment. The structures of S27-AS14-M2, S33-AS20-M2, S35-AS22-M2, and S36-AS23-M2 are depicted in FIG. 7.

[0183] Oligonucleotides were subcutaneously administered to non-human primate at 4 mg/kg, one single dose, or 2 mg/kg, 4 repeat doses. Monkey liver biopsies were taken each time point following administration. Liver samples were obtained and RNA was extracted to evaluate HMGB1 mRNA levels by qPCR. The percentages of remaining HMGB1 mRNA in monkey liver 7, 14, 25, 54, 81 and 112 days after the administration, normalized to PBS control treatment, are shown (FIGs. 9A-9B). The results show that all oligonucleotides tested significantly reduced liver HMGB1 mRNA level at 25 days post administration. With 4 repeated 2 mg/kg doses, the HMGB1 knockdown effect lasted through 112 days (FIG. 9B).

Example 4: Comparing HMGB1 RNAi oligonucleotides in primary monkey/human hepatocytes

[0184] The activity of five HMGB1 double strand RNAi oligonucleotides (S866-AS887, S869-AS878, S116-AS490, S117-AS491, S871-AS880, and S872-AS881 in Table 4) were compared in mouse, monkey, and human cell lines. PBS was used as negative control, and the tool compound S36-AS23-M2 was used as positive control in this experiment. In this assay, mouse cells (Hepa1-6 cells, FIGs. 10A and 10B), monkey cells (LLC-MK2 cells, FIGs. 10C and 10D), and human cells (Huh-7, FIGs. 10E and 10F) were transfected with the indicated oligonucleotides, respectively. Cells were maintained for 24 h following transfection, RNAs were isolated using the iScript RT-qPCR sample preparation buffer. HMGB1 mRNA were interrogated using TAQMAN®-based qPCR assays. Two qPCR assays, a 5' assay (FIGs. 10A, 10C, and 10E) and a 3' assay (FIGs. 10B, 10D, and 10F), were used to determine mRNA levels as measured by HEX (housekeeping gene – HPRT-F576) and

FAM probes, respectively. Oligonucleotides 210, 840, 852, 853 show more than 80% knockdown at 0.1 nM and 1 nM concentrations in both assays in mouse cell line (FIGs. 10A and 10B). All RNAi oligonucleotides display more than 80% KD at 0.1 nM and 1 nM concentrations (FIGs. 10C and 10D). Oligonucleotides 210, 840, 852, 853, 932 show better potency with more than ~90% KD at 0.1 nM and 1 nM concentrations in human cell line (FIGs. 10E and 10F).

Example 5: Testing GalXC-HMGB1 for HMGB1 selectivity

[0185] The selectivity of GalNAc-conjugated HMGB1 oligonucleotides S27-AS14-M2, S33-AS20-M2, S35-AS22-M2, and S36-AS23-M2 against HMGB1, HMGB2, and HMGB3 were tested in human hepatocytes. The structures of S27-AS14-M2, S33-AS20-M2, S35-AS22-M2, and S36-AS23-M2 are depicted in FIG. 7. A GalNAc-conjugated LDHA oligonucleotide for using as positive control. Huh-7 cells were transfected with the indicated oligonucleotides with 8 different concentration (4-fold dilution with 8-points, highest concentration is 1 nM). Cells were maintained for 24h following transfection, RNAs were isolated using the iScript RT-qPCR sample preparation buffer. HMGB1 mRNA were interrogated using TAQMAN®-based qPCR assays. 5' qPCR assay used to determine mRNA levels as measured by HEX (housekeeping gene – SFRS9) and FAM probes, respectively. IC50 curves of HMGB1 (FIG. 11A), HMGB2 (FIG. 11B) and HMGB3 (FIG. 11C), normalized to mock treatment, are shown. All four tested conjugates had similar IC50 value for HMGB1 (FIG. 11A). None of the conjugates (including the LDHA control oligonucleotide) had any effect of HMGB2 mRNA level (FIG. 11B) or HMGB3 mRNA level (FIG. 11C).

Example 6: Materials and Methods

Transfection

[0186] For the first screen, Lipofectamine RNAiMAX™ was used to complex the oligonucleotides for efficient transfection. Oligonucleotides, RNAiMAX and Opti-MEM were added to a plate and incubated at room temperature for 20 minutes prior to transfection. Media was aspirated from a flask of actively passaging cells and the cells are incubated at 37°C in the presence of trypsin for 3-5 minutes. After cells no longer adhered to the flask, cell growth media (lacking penicillin and streptomycin) was added to neutralize the trypsin and to suspend the cells. A 10 µL aliquot was removed and counted with a hemocytometer to quantify the cells on a per millimeter basis. For HeLa cells, 20,000 cells were seeded per well in 100 µL of media. The suspension was diluted with the known cell concentration to obtain the total volume required for the number of cells to be transfected. The diluted cell suspension was added to the 96 well transfection plates, which already contained the oligonucleotides in Opti-MEM. The transfection plates were then incubated for 24 hours at 37°C. After 24 hours of incubation, media was aspirated from each well. Cells were lysed using the lysis buffer from the Promega RNA Isolation kit. The lysis buffer was added to each well. The lysed cells

were then transferred to the Corbett XtractorGENE (QIAxtractor) for RNA isolation or stored at -80°C.

[0187] For subsequent screens and experiments, e.g., the secondary screen, Lipofectamine RNAiMAX was used to complex the oligonucleotides for reverse transfection. The complexes were made by mixing RNAiMAX and siRNAs in OptiMEM medium for 15 minutes. The transfection mixture was transferred to multi-well plates and cell suspension was added to the wells. After 24 hours incubation the cells were washed once with PBS and then lysed using lysis buffer from the Promega SV96 kit. The RNA was purified using the SV96 plates in a vacuum manifold. Four microliters of the purified RNA was then heated at 65°C for 5 minutes and cooled to 4°C. The RNA was then used for reverse transcription using the High Capacity Reverse Transcription kit (Life Technologies) in a 10-microliter reaction. The cDNA was then diluted to 50 µL with nuclease free water and used for quantitative PCR with multiplexed 5'-endonuclease assays and SSoFast qPCR mastermix (Bio-Rad laboratories).

cDNA Synthesis

[0188] RNA was isolated from mammalian cells in tissue culture using the Corbett X-tractor Gene™ (QIAxtractor). A modified SuperScript II protocol was used to synthesize cDNA from the isolated RNA. Isolated RNA (approximately 5 ng/µL) was heated to 65°C for five minutes and incubated with dNPs, random hexamers, oligo dTs and water. The mixture was cooled for 15 seconds. An “enzyme mix,” consisting of water, 5X first strand buffer, DTT, SUPERase•In™ (an RNA inhibitor), and SuperScript II RTase was added to the mixture. The contents were heated to 42°C for one hour, then to 70°C for 15 minutes, and then cooled to 4°C using a thermocycler. The resulting cDNA was then subjected to SYBR®-based qPCR. The qPCR reactions were multiplexed, containing two 5' endonuclease assays per reaction.

qPCR Assays

[0189] Primer sets were initially screened using SYBR®-based qPCR. Assay specificity was verified by assessing melt curves as well as “minus RT” controls. Dilutions of cDNA template (10-fold serial dilutions from 20 ng and to 0.02 ng per reaction) from HeLa and Hepa1-6 cells are used to test human (Hs) and mouse (Mm) assays, respectively. qPCR assays were set up in 384-well plates, covered with MicroAmp film, and run on the 7900HT from Applied Biosystems. Reagent concentrations and cycling conditions included the following: 2x SYBR mix, 10 µM forward primer, 10 µM reverse primer, DD H₂O, and cDNA template up to a total volume of 10 µL.

[0190] In some cases, as noted, qPCR was performed using TAQMAN®-based qPCR assays. TAQMAN® probes target two different positions (5' and 3' to one another) within the coding region of the target mRNA (e.g., HMGB1) were generally used to provide additional confirmation of mRNA levels in the analysis.

Cloning

[0191] PCR amplicons that displayed a single melt-curve were ligated into the pGEM®-T Easy vector kit from Promega according to the manufacturer's instructions. Following the manufacturer's protocol, JM109 High Efficiency cells were transformed with the newly ligated vectors. The cells were then plated on LB plates containing ampicillin and incubated at 37°C overnight for colony growth.

PCR Screening and Plasmid Mini-Prep

[0192] PCR was used to identify colonies of *E. coli* that had been transformed with a vector containing the ligated amplicon of interest. Vector-specific primers that flank the insert were used in the PCR reaction. All PCR products were then run on a 1% agarose gel and imaged by a transilluminator following staining. Gels were assessed qualitatively to determine which plasmids appeared to contain a ligated amplicon of the expected size (approximately 300 bp, including the amplicon and the flanking vector sequences specific to the primers used).

[0193] The colonies that were confirmed transformants by PCR screening were then incubated overnight in cultures consisting of 2 mL LB broth with ampicillin at 37°C with shaking. *E. coli* cells were then lysed, and the plasmids of interest were isolated using Promega's Mini-Prep kit. Plasmid concentration was determined by UV absorbance at 260 nm.

Plasmid Sequencing and Quantification

[0194] Purified plasmids were sequenced using the BigDye® Terminator sequencing kit. The vector-specific primer, T7, was used to give read lengths that span the insert. The following reagents were used in the sequencing reactions: water, 5X sequencing buffer, BigDye terminator mix, T7 primer, and plasmid (100 ng/μL) to a volume of 10 μL. The mixture was held at 96°C for one minute, then subjected to 15 cycles of 96°C for 10 seconds, 50°C for 5 seconds, 60°C for 1 minute, 15 seconds; 5 cycles of 96°C for 10 seconds, 50°C for 5 seconds, 60°C for 1 minute, 30 seconds; and 5 cycles of 96°C for 10 seconds, 50°C for 5 seconds, and 60°C for 2 minutes. Dye termination reactions were then sequenced using Applied Biosystems' capillary electrophoresis sequencers.

[0195] Sequence-verified plasmids were then quantified. They were linearized using a single cutting restriction endonuclease. Linearity was confirmed using agarose gel electrophoresis. All plasmid dilutions were made in TE buffer (pH 7.5) with 100 μg of tRNA per mL buffer to reduce non-specific binding of plasmid to the polypropylene vials.

[0196] The linearized plasmids were then serially diluted from 1,000,000 to 01 copies per μL and subjected to qPCR. Assay efficiency was calculated, and the assays were deemed acceptable if the efficiency was in the range of 90-110%.

Multi-Plexing Assays

[0197] For each target, mRNA levels were quantified by two 5' nuclease assays. In general, several assays are screened for each target. The two assays selected displayed a combination of good efficiency, low limit of detection, and broad 5'→3' coverage of the gene of interest (GOI). Both assays against one GOI could be combined in one reaction when different fluorophores were used on the respective probes. Thus, the final step in assay validation was to determine the efficiency of the selected assays when they were combined in the same qPCR or "multi-plexed".

[0198] Linearized plasmids for both assays in 10-fold dilutions were combined and qPCR was performed. The efficiency of each assay was determined as described above. The accepted efficiency rate was 90-110%.

[0199] While validating multi-plexed reactions using linearized plasmid standards, C_q values for the target of interest were also assessed using cDNA as the template. For human or mouse targets, HeLa and Hepa1-6 cDNA were used, respectively. The cDNA, in this case, was derived from RNA isolated on the Corbett (~5 ng/μL in water) from untransfected cells. In this way, the observed C_q values from this sample cDNA were representative of the expected C_q values from a 96-well plate transfection. In cases where C_q values were greater than 30, other cell lines were sought that exhibit higher expression levels of the gene of interest. A library of total RNA isolated from via high-throughput methods on the Corbett from each human and mouse line was generated and used to screen for acceptable levels of target expression.

Description of oligonucleotide nomenclature

[0200] All oligonucleotides described herein are designated either SN₁-ASN₂-MN₃. The following designations apply:

- N₁: sequence identifier number of the sense strand sequence
- N₂: sequence identifier number of the antisense strand sequence
- N₃: reference number of modification pattern, in which each number represents a pattern of modified nucleotides in the oligonucleotide.

[0201] For example, S1-AS14-M1 represents an oligonucleotide with a sense sequence that is set forth by SEQ ID NO: 1, an antisense sequence that is set forth by SEQ ID NO: 14, and which is adapted to modification pattern number 1.

Table 1: Lead HMGB1 RNAi Oligonucleotide Sequences

Sense (S) – Antisense (A) Designation	Sense Sequence/mRNA Sequence	S SEQ ID NO:	Antisense Sequence	AS SEQ ID NO:
S1-AS14	UGGGCAAAGGAGAUCCUAAA	1	UUUAGGAUCUCCUUUGCCCAG G	14
S2-AS15	AAAGAGAAAUGAAAACCUAA	2	UUAGGUUUUCAUUUCUCUUUG G	15
S3-AS16	AAGAAGAUGAUGAUGAUGAA	3	UUCAUCAUCAUCAUCUUCUUG G	16
S4-AS17	AUGAUGAUGAUGAAUAAGUA	4	UACUUAUUCAUCAUCAUCAUG G	17
S5-AS18	GAUGAUGAAUAAGUUGGUUC	5	GAACCAACUUAUUCAUCAUCG G	18
S6-AS19	UGAAUAAGUUGGUUCUAGCA	6	UGCUAGAACCAACUUAUUCAG G	19
S7-AS20	AAUAAGUUGGUUCUAGCGCA	7	UGCGCUAGAACCAACUUAUUG G	20
S8-AS21	AUAAGUUGGUUCUAGCGCAA	8	UUGCGCUAGAACCAACUUAUG G	21
S9-AS22	AGAAAAAAAUUGAAAUGUAA	9	UUACAUUUCAAUUUUUUUCUG G	22
S10-AS23	UUGUUGUUCUGUUAACUGAA	10	UUCAGUUAACAGAACAACAAG G	23
S11-AS24	UUCUGAAUGCUUCUAAGUAA	11	UUACUUAGAAGCAUUCAGAAG G	24
S12-AS25	CUGAAUGCUUCUAAGUAAAA	12	UUUUACUUAGAAGCAUUCAGG G	25
S13-AS26	GAAUGCUUCUAAGUAAAUAA	13	UUUUUUACUUAGAAGCAUUCG G	26

[0202] Table 2: Lead GalNAc-conjugated HMGB1 oligonucleotide sequences with modifications

GalNAc- conjugated oligonucleotides	Sense sequence (unmodified)	Sense sequence (modified)	Antisense sequence (unmodified)	Antisense sequence (modified)
S27- AS14- M2	UGGGCAA AGGAGAU CCUAAAG CAGCCGA AAGGCUG C (SEQ ID NO: 27)	[mUs][mG][mG][mG][mC][mA][mA][fA][fG][fG][fA][mG][mA][mU][mC][mC][mU][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 788)	UUUAGGA UCUCCUU UGCCCAG G (SEQ ID NO: 14)	[MePhosphonate-4O-mUs][fUs][fU][mA][fG][mG][fA][mU][mC][fU][mC][mC][mU][fU][mU][mG][mC][mC][mC][mAs][mGs][mG] (SEQ ID NO: 814)
S27- AS14- M3	UGGGCAA AGGAGAU CCUAAAG CAGCCGA AAGGCUG C (SEQ ID NO: 27)	[mUs][mG][fG][mG][mC][mA][mA][fA][mG][fG][mA][fG][fA][mU][mC][mC][fU][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	UUUAGGA UCUCCUU UGCCCAG G (SEQ ID NO: 14)	[MePhosphonate-4O-mUs][fUs][fU][fA][fG][mG][fA][mU][mC][fU][mC][fC][mU][fU][mU][fG][fC][mC][fC][mAs][mGs][mG]

	NO: 27)	(SEQ ID NO: 789)		(SEQ ID NO: 815)
S28- AS15- M2	AAAGAGA AAUGAAA ACCUAAG CAGCCGA AAGGCUG C (SEQ ID NO: 28)	[mAs][mA][mA][mG][mA][mG][mA][fA][fA][fU][fG][mA][mA][mA][mA][mC][mC][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 790)	UUAGGUU UUCAUUU CUCUUUG G (SEQ ID NO: 15)	[MePhosphonate-4O-mUs][fUs][fA][mG][fG][mU][fU][mU][mU][fC][mA][mU][mU][fU][mC][mU][mC][mU][mU][mUs][mGs][mG] (SEQ ID NO: 816)
S28- AS15- M3	AAAGAGA AAUGAAA ACCUAAG CAGCCGA AAGGCUG C (SEQ ID NO: 28)	[mAs][mA][fA][mG][mA][mG][mA][fA][mA][fU][mG][fA][fA][mA][mA][mC][fC][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 791)	UUAGGUU UUCAUUU CUCUUUG G (SEQ ID NO: 15)	[MePhosphonate-4O-mUs][fUs][fA][fG][fG][mU][fU][mU][mU][fC][mA][fU][mU][fU][mC][fU][fC][mU][fU][mUs][mGs][mG] (SEQ ID NO: 817)
S29- AS16- M2	AAGAAGA UGAUGAU GAUGAAG CAGCCGA AAGGCUG C (SEQ ID NO: 29)	[mAs][mA][mG][mA][mA][mG][mA][fU][fG][fA][fU][mG][mA][mU][mG][mA][mU][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 792)	UUCAUCA UCAUCAU CUUCUUG G (SEQ ID NO: 16)	[MePhosphonate-4O-mUs][fUs][fC][mA][fU][mC][fA][mU][mC][mA][fU][mC][mU][mU][mC][mU][mUs][mGs][mG] (SEQ ID NO: 818)
S29- AS16- M3	AAGAAGA UGAUGAU GAUGAAG CAGCCGA AAGGCUG C (SEQ ID NO: 29)	[mAs][mA][fG][mA][mA][mG][mA][fU][mG][fA][mU][fG][fA][mU][mG][mA][fU][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 793)	UUCAUCA UCAUCAU CUUCUUG G (SEQ ID NO: 16)	[MePhosphonate-4O-mUs][fUs][fC][fA][fU][mC][fA][mU][mC][fA][mU][fC][mA][fU][mC][fU][fU][mC][fU][mUs][mGs][mG] (SEQ ID NO: 819)
S30- AS17- M2	AUGAUGA UGAUGAA UAAGUAG CAGCCGA AAGGCUG C (SEQ ID NO: 30)	[mAs][mU][mG][mA][mU][mG][mA][fU][fG][fA][fU][mG][mA][mA][mU][mA][mA][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 794)	UACUUAU UCAUCAU CAUCAUG G (SEQ ID NO: 17)	[MePhosphonate-4O-mUs][fAs][fC][mU][fU][mA][fU][mU][mC][fA][mU][mC][mA][fU][mC][mA][mU][mC][mA][mUs][mGs][mG] (SEQ ID NO: 820)
S30- AS17- M3	AUGAUGA UGAUGAA UAAGUAG CAGCCGA AAGGCUG C (SEQ ID NO: 30)	[mAs][mU][fG][mA][mU][mG][mA][fU][mG][fA][mU][fG][fA][mA][mU][mA][fA][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 795)	UACUUAU UCAUCAU CAUCAUG G (SEQ ID NO: 17)	[MePhosphonate-4O-mUs][fAs][fC][fU][fU][mA][fU][mU][mC][fA][mU][fC][mA][fU][mC][fA][fU][mC][fA][mUs][mGs][mG] (SEQ ID NO: 821)
S31- AS18- M1	GAUGAUG AAUAAGU UGGUUAG CAGCCGA AAGGCUG C (SEQ ID NO: 31)	[mGs][mA][fU][mG][fA][mU][mG][fA][fA][fU][fA][mA][fG][mU][fU][mG][fG][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 796)	GAACCAA CUUAUUC AUCAUCG G (SEQ ID NO: 18)	[MePhosphonate-4O-mUs][fAs][fA][mC][fC][mA][fA][mC][mU][fU][mA][fU][mU][fC][mA][fU][fC][mA][fU][mCs][mGs][mG] (SEQ ID NO: 822)
S31- AS18- M2	GAUGAUG AAUAAGU UGGUUAG CAGCCGA AAGGCUG C (SEQ ID NO: 31)	[mGs][mA][mU][mG][mA][mU][mG][fA][fA][fU][fA][mA][mG][mU][mU][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 797)	GAACCAA CUUAUUC AUCAUCG G (SEQ ID NO: 18)	[MePhosphonate-4O-mUs][fAs][fA][mC][fC][mA][fA][mC][mU][fU][mA][mU][mU][fC][mA][mU][mC][mA][mU][mCs][mGs][mG] (SEQ ID NO: 823)
S31-	GAUGAUG	[mGs][mA][fU][mG][mA][mU][mG][fA]	GAACCAA	[MePhosphonate-4O-

AS18-M3	AAUAAGU UGGUUAG CAGCCGA AAGGCUG C (SEQ ID NO: 31)	[[mA][fU][mA][fA][fG][mU][mU][mG][fG][mU][mU][mA][mG][mC][mA][mG] [mC][mC][mG][ademA- GalNAc][ademA-GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 798)	CUUAUUC AUCAUCG G (SEQ ID NO: 18)	mUs][fAs][fA][fC][fC][m A][fA][mC][mU][fU][mA] [fU][mU][fC][mA][fU][fC]][mA][fU][mCs][mGs][m G] (SEQ ID NO: 824)
S32- AS19- M2	UGAAUAA GUUGGUU CUAGCAG CAGCCGA AAGGCUG C (SEQ ID NO: 32)	[mUs][mG][mA][mA][mU][mA][mA][f G][fU][fU][fG][mG][mU][mU][mC][mU]][mA][mG][mC][mA][mG][mC][mA][m G][mC][mC][mG][ademA- GalNAc][ademA-GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 799)	UGCUAGA ACCAACU UAUUCAG G (SEQ ID NO: 19)	[MePhosphonate-4O- mUs][fGs][fC][mU][fA][m G][fA][mA][mC][fC][mA] [mA][mC][fU][mU][mA][mU][mU][mC][mAs][mGs][mG] (SEQ ID NO: 825)
S32- AS19- M3	UGAAUAA GUUGGUU CUAGCAG CAGCCGA AAGGCUG C (SEQ ID NO: 32)	[mUs][mG][fA][mA][mU][mA][mA][fG]][mU][fU][mG][fG][fU][mU][mC][mU][fA][mG][mC][mA][mG][mC][mA][mG][mC][mC][mG][ademA- GalNAc][ademA-GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 800)	UGCUAGA ACCAACU UAUUCAG G (SEQ ID NO: 19)	[MePhosphonate-4O- mUs][fGs][fC][fU][fA][m G][fA][mA][mC][fC][mA] [fA][mC][fU][mU][fA][fU]][mU][fC][mAs][mGs][m G] (SEQ ID NO: 826)
S33- AS20- M2	AAUAAGU UGGUUCU AGCGCAG CAGCCGA AAGGCUG C (SEQ ID NO: 33)	[mAs][mA][mU][mA][mA][mG][mU][f U][fG][fG][fU][mU][mC][mU][mA][mG]][mC][mG][mC][mA][mG][mC][mA][m G][mC][mC][mG][ademA- GalNAc][ademA-GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 801)	UGCGCUA GAACCAA CUUAUUG G (SEQ ID NO: 20)	[MePhosphonate-4O- mUs][fGs][fC][mG][fC][m U][fA][mG][mA][fA][mC] [mC][mA][fA][mC][mU][mU][mA][mU][mUs][mGs][mG] (SEQ ID NO: 827)
S33- AS20- M3	AAUAAGU UGGUUCU AGCGCAG CAGCCGA AAGGCUG C (SEQ ID NO: 33)	[mAs][mA][fU][mA][mA][mG][mU][fU]][mG][fG][mU][fU][fC][mU][mA][mG][fC][mG][mC][mA][mG][mC][mA][mG][mC][mC][mG][ademA- GalNAc][ademA-GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 802)	UGCGCUA GAACCAA CUUAUUG G (SEQ ID NO: 20)	[MePhosphonate-4O- mUs][fGs][fC][fG][fC][m U][fA][mG][mA][fA][mC] [fC][mA][fA][mC][fU][fU]][mA][fU][mUs][mGs][m G] (SEQ ID NO: 828)
S34- AS21- M2	AUAAGUU GGUUCUA GCGCAAG CAGCCGA AAGGCUG C (SEQ ID NO: 34)	[mAs][mU][mA][mA][mG][mU][mU][f G][fG][fU][fU][mC][mU][mA][mG][mC]][mG][mC][mA][mA][mG][mC][mA][m G][mC][mC][mG][ademA- GalNAc][ademA-GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 803)	UUGCGCU AGAACCA ACUUAUG G (SEQ ID NO: 21)	[MePhosphonate-4O- mUs][fUs][fG][mC][fG][m C][fU][mA][mG][fA][mA] [mC][mC][fA][mA][mC][mU][mU][mA][mUs][mGs][mG] (SEQ ID NO: 829)
S34- AS21- M3	AUAAGUU GGUUCUA GCGCAAG CAGCCGA AAGGCUG C (SEQ ID NO: 34)	[mAs][mU][fA][mA][mG][mU][mU][fG]][mG][fU][mU][fC][fU][mA][mG][mC][fG][mC][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA- GalNAc][ademA-GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 804)	UUGCGCU AGAACCA ACUUAUG G (SEQ ID NO: 21)	[MePhosphonate-4O- mUs][fUs][fG][fC][fG][m C][fU][mA][mG][fA][mA] [fC][mC][fA][mA][fC][fU] [mU][fA][mUs][mGs][mG] (SEQ ID NO: 830)
S35- AS22- M1	AGAAAAA AAUUGAA AUGUAAG CAGCCGA AAGGCUG C (SEQ ID NO: 35)	[mAs][mG][fA][mA][fA][mA][mA][fA][fA][fU][fU][mG][fA][mA][fA][mU][fG] [mU][mA][mA][mG][mC][mA][mG][m C][mC][mG][ademA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 805)	UUACAUU UCAAUUU UUUUCUG G (SEQ ID NO: 22)	[MePhosphonate-4O- mUs][fUs][fA][mC][fA][m U][fU][mU][mC][fA][mA] [fU][mU][fU][mU][fU][fU]][mU][fC][mUs][mGs][m G] (SEQ ID NO: 831)
S35- AS22- M2	AGAAAAA AAUUGAA AUGUAAG CAGCCGA AAGGCUG	[mAs][mG][mA][mA][mA][mA][mA][f A][fA][fU][fU][mG][mA][mA][mA][mU]][mG][mU][mA][mA][mG][mC][mA][m G][mC][mC][mG][ademA- GalNAc][ademA-GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 805)	UUACAUU UCAAUUU UUUUCUG G (SEQ ID NO: 22)	[MePhosphonate-4O- mUs][fUs][fA][mC][fA][m U][fU][mU][mC][fA][mA] [mU][mU][fU][mU][mU][mU][mU][mC][mUs][mGs]

	C (SEQ ID NO: 35)	GalNAc[mG][mG][mC][mU][mG][mC] (SEQ ID NO: 806)	NO: 22)	][mG] (SEQ ID NO: 832)
S35-AS22-M3	AGAAAAA AAUUGAA AUGUAAG CAGCCGA AAGGCUG C (SEQ ID NO: 35)	[mAs][mG][fA][mA][mA][mA][fA][mA][fU][mU][fG][fA][mA][mA][mU][fG][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 807)	UUACAUU UCAAUUU UUUUCUG G (SEQ ID NO: 22)	[MePhosphonate-4O-mUs][fUs][fA][fC][fA][mU][fU][mU][mC][fA][mA][fU][mU][fU][mU][fU][fU][mU][fC][mUs][mGs][mG] (SEQ ID NO: 833)
S36-AS23-M1	UUGUUGU UCUGUUA ACUGAAG CAGCCGA AAGGCUG C (SEQ ID NO: 36)	[mUs][mU][fG][mU][fU][mG][mU][fU][fC][fU][fG][mU][fU][mA][fA][mC][fU][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 808)	UUCAGUU AACAGAA CAACAAG G (SEQ ID NO: 23)	[MePhosphonate-4O-mUs][fUs][fC][mA][fG][mU][fU][mA][mA][fC][mA][fG][mA][fA][mC][fA][fA][mC][fA][mAs][mGs][mG] (SEQ ID NO: 834)
S36-AS23-M2	UUGUUGU UCUGUUA ACUGAAG CAGCCGA AAGGCUG C (SEQ ID NO: 36)	[mUs][mU][mG][mU][mU][mG][mU][fU][fC][fU][fG][mU][mU][mA][mA][mC][mU][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 809)	UUCAGUU AACAGAA CAACAAG G (SEQ ID NO: 23)	[MePhosphonate-4O-mUs][fUs][fC][mA][fG][mU][fU][mA][mA][fC][mA][mG][mA][fA][mC][mA][mA][mC][mA][mAs][mGs][mG] (SEQ ID NO: 835)
S36-AS23-M3	UUGUUGU UCUGUUA ACUGAAG CAGCCGA AAGGCUG C (SEQ ID NO: 36)	[mUs][mU][fG][mU][mU][mG][mU][fU][mC][fU][mG][fU][fU][mA][mA][mC][fU][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 810)	UUCAGUU AACAGAA CAACAAG G (SEQ ID NO: 23)	[MePhosphonate-4O-mUs][fUs][fC][fA][fG][mU][fU][mA][mA][fC][mA][fG][mA][fA][mC][fA][fA][mC][fA][mAs][mGs][mG] (SEQ ID NO: 836)
S37-AS24-M2	UUCUGAA UGCUCU AAGUAAG CAGCCGA AAGGCUG C (SEQ ID NO: 37)	[mUs][mU][mC][mU][mG][mA][mA][fU][fG][fC][fU][mU][mC][mU][mA][mA][mG][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 811)	UUACUUA GAAGCAU UCAGAAG G (SEQ ID NO: 24)	[MePhosphonate-4O-mUs][fUs][fA][mC][fU][mU][fA][mG][mA][fA][mG][mC][mA][fU][mU][mC][mA][mG][mA][mAs][mGs][mG] (SEQ ID NO: 837)
S38-AS25-M2	CUGAAUG CUUCUAA GUAAAAG CAGCCGA AAGGCUG C (SEQ ID NO: 38)	[mCs][mU][mG][mA][mA][mU][mG][fC][fU][fU][fC][mU][mA][mA][mG][mU][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 812)	UUUUACU UAGAAGC AUUCAGG G (SEQ ID NO: 25)	[MePhosphonate-4O-mUs][fUs][fU][mU][fA][mC][fU][mU][mA][fG][mA][mA][mG][fC][mA][mU][mU][mC][mA][mGs][mGs][mG] (SEQ ID NO: 838)
S39-AS26-M2	GAAUGCU UCUAAAG AAAUAAAG CAGCCGA AAGGCUG C (SEQ ID NO: 39)	[mGs][mA][mA][mU][mG][mC][mU][fU][fC][fU][fA][mA][mG][mU][mA][mA][mA][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 813)	UUUUUUA CUUAGAA GCAUUCG G (SEQ ID NO: 26)	[MePhosphonate-4O-mUs][fUs][fA][mU][fU][mU][fA][mC][mU][fU][mA][mG][mA][fA][mG][mC][mA][mU][mU][mCs][mGs][mG] (SEQ ID NO: 839)

[0203] Table 3: Modification Key for RNAi Oligonucleotides

Symbol	Modification Description
ademA-GalNAc	2'-aminodiethoxymethanol-GalNAc adenosine
fA	2'-fluoro-deoxyadenosine

fAs	2'-fluoro-deoxyadenosine followed by a phosphorothioate linkage
fC	2'-fluoro-deoxycytosine
fG	2'-fluoro-deoxyguanosine
fGs	2'-fluoro-deoxyguanosine followed by a phosphorothioate linkage
fU	2'-fluoro-uridine
fUs	2'-fluoro-uridine followed by a phosphorothioate linkage
mA	2'-O-methyl adenosine
mAs	2'-O-methyl adenosine followed by a phosphorothioate linkage
mC	2'-O-methyl cytosine
mCs	2'-O-methyl cytosine followed by a phosphorothioate linkage
MePhosphonate-4O-mU	Methyl-4'-O-methylphosphonate-2'-O-methyl uridine
MePhosphonate-4O-mUs	Methyl-4'-O-methylphosphonate-2'-O-methyl uridine followed by a phosphorothioate linkage
mG	2'-O-methyl guanosine
mGs	2'-O-methyl guanosine followed by a phosphorothioate linkage
mU	2'-O-methyl uridine
mUs	2'-O-methyl uridine followed by a phosphorothioate linkage
s	Phosphorothioate linkage

[0204] Table 4: HMGB1 RNAi Oligonucleotide Sequences Included in Screen

RNAi oligonucleotides	Sense Sequence/mRNA seq	S SEQ ID NO	Antisense Sequence	AS SEQ ID NO
S40-AS414	AACUAAACAUGGGCAAAGGAGAUCC	40	GGAUCUCCUUUGCCCAUGUUUAGUUUAU	414
S41-AS415	ACUAAACAUGGGCAAAGGAAAUCCT	41	AGGAUUUCCUUUGCCCAUGUUUAGUUA	415
S42-AS416	CUAAACAUGGGCAAAGGAGAUCCTA	42	UAGGAUCUCCUUUGCCCAUGUUUAGUU	416
S43-AS417	UAAACAUGGGCAAAGGAGAACCUGA	43	UUAGGUUCUCCUUUGCCCAUGUUUAGU	417
S44-AS418	AAACAUGGGCAAAGGAGAUACUAAAG	44	CUUAGUAUCUCCUUUGCCCAUGUUUAG	418
S45-AS419	AACAUGGGCAAAGGAGAUCAUAAGA	45	UCUUAUGAUCUCCUUUGCCCAUGUUUA	419
S46-AS420	ACAUGGGCAAAGGAGAUCCAAAGAA	46	UUCUUUGGAUCUCCUUUGCCCAUGUUU	420
S47-AS421	CAUGGGCAAAGGAGAUCCUAAGAAG	47	CUUCUUAGGAUCUCCUUUGCCCAUGUU	421
S48-AS422	AUGGGCAAAGGAGAUCCUAAGAAGC	48	GCUUCUUAGGAUCUCCUUUGCCCAUGU	422
S49-AS423	AAGCCGAGAGGCAAAAUGUAAUCAT	49	AUGAUUACAUUUUGCCUCUCGGCUUCU	423
S50-AS424	AGCCGAGAGGCAAAAUGUCAUCATA	50	UAUGAUGACAUUUUGCCUCUCGGCUUC	424
S51-AS425	AAAUGUCAUCAUAUGCAUUAUUUGT	51	ACAAAUAUUGCAUAUGAUGACAUUUUG	425

S52- AS426	CAUCAUAUGCAUUUUUU GUACAAAC	52	GUUUGUACAAAAAUGCAU AUGAUGAC	426
S53- AS427	AUCAUAUGCAUUUUUUG UGAAAACT	53	AGUUUUCACAAAAAUGCA UAUGAUGA	427
S54- AS428	AUAUGCAUUUUUUGUGC AAACUUGT	54	ACAAGUUUGCACAAAAAU GCAUAUGA	428
S55- AS429	GUCAACUUCUCAGAGUU UUAUAAGA	55	UCUUAUAAAACUCUGAGAA GUUGACUG	429
S56- AS430	AAGAAGUGCUCAGAGAG GUAGAAGA	56	UCUUCUACCUCUCUGAGCAC UUCUUAG	430
S57- AS431	AGAAGUGCUCAGAGAGG UGAAAGAC	57	GUCUUUCACCUCUCUGAGCA CUUCUUA	431
S58- AS432	GAAGUGCUCAGAGAGGU GGAAGACC	58	GGUCUUCACCUCUCUGAGC ACUUCUU	432
S59- AS433	AAGUGCUCAGAGAGGUG GAAGACCA	59	UGGUCUUCACCUCUCUGAG CACUUCU	433
S60- AS434	AGUGCUCAGAGAGGUGG AAAACCAT	60	AUGGUUUUCCACCUCUCUGA GCACUUC	434
S61- AS435	GUGCUCAGAGAGGUGGA AGACCATG	61	CAUGGUCUUCACCUCUCUG AGCACUU	435
S62- AS436	UGCUCAGAGAGGUGGAA GAACAUGT	62	ACAUGUUCUUCACCUCUCU GAGCACU	436
S63- AS437	GCUCAGAGAGGUGGAAG ACAAUGTC	63	GACAUUGUCUUCACCUCUC UGAGCAC	437
S64- AS438	CUCAGAGAGGUGGAAGA CCAUGUCT	64	AGACAUGGUCUUCACCUCU CUGAGCA	438
S65- AS439	UCAGAGAGGUGGAAGAC CAAGUCTG	65	CAGACUUGGUCUUCACCUC UCUGAGC	439
S66- AS440	CAGAGAGGUGGAAGACC AUAUCUGC	66	GCAGUAUGGUCUUCACCUC CUCUGAG	440
S67- AS441	AGAGAGGUGGAAGACCA UGACUGCT	67	AGCAGUCAUGGUCUUCACC UCUCUGA	441
S68- AS442	GAGAGGUGGAAGACCAU GUAUGCTA	68	UAGCAUACAUGGUCUUCAC CUCUCUG	442
S69- AS443	AGAGGUGGAAGACCAUG UCAGCUAA	69	UUAGCUGACAUGGUCUUC ACCUCUCU	443
S70- AS444	GAGGUGGAAGACCAUGU CUACUAAA	70	UUUAGUAGACAUGGUCUUC CACCUCUC	444
S71- AS445	AGGUGGAAGACCAUGUC UGAUAAAG	71	CUUUAUCAGACAUGGUCUU CCACCUCU	445
S72- AS446	GGUGGAAGACCAUGUCU GCAAAAGA	72	UCUUUUGCAGACAUGGUCU UCCACCUC	446
S73- AS447	GUGGAAGACCAUGUCUG CUAAAGAG	73	CUCUUUAGCAGACAUGGUC UCCACCU	447
S74- AS448	UGGAAGACCAUGUCUGC UAAAGAGA	74	UCUCUUUAGCAGACAUGGU CUUCCACC	448
S75- AS449	GGAAGACCAUGUCUGCU AAAGAGAA	75	UUCUCUUUAGCAGACAUGG UCUCCAC	449
S76- AS450	GAAGACCAUGUCUGCUA AAAAGAAA	76	UUUCUUUUUAGCAGACAUG GUCUCCA	450
S77- AS451	AAGACCAUGUCUGCUAA AGAGAAAG	77	CUUUCUCUUUAGCAGACAU GGUCUCC	451
S78- AS452	AGACCAUGUCUGCUAAA GAAAAAGG	78	CCUUUUUCUUUAGCAGACA UGGUCUUC	452

S79- AS453	AAAUUUGAAGAU AUGGC AAAAGCGG	79	CCGCUUUUGCCAUAUCUUC AAUUUUC	453
S80- AS454	AAUUUGAAGAU AUGGCA AAAGCGGA	80	UCCGCUUUUGCCAUAUCUUC AAAUUUU	454
S81- AS455	GAAAGAGAAAUGAAAAC CUAUAUCC	81	GGAUAUAGGUUUUCAUUUC UCUUUCAU	455
S82- AS456	AAAAAAGAAGUUCAAGG AUACCAAT	82	AUUGGUAUCCUUGAACUUC UUUUUUGU	456
S83- AS457	CCCAAUGCACCCAAGAG GCAUCCTT	83	AAGGAUGCCUCUUGGGUGC AUUGGGAU	457
S84- AS458	CCAAUGCACCCAAGAGG CCACCUTC	84	GAAGGUGGCCUCUUGGGUG CAUUGGGA	458
S85- AS459	CAAUGCACCCAAGAGGC CUACUUCG	85	CGAAGUAGGCCUCUUGGGU GCAUUGGG	459
S86- AS460	AAUGCACCCAAGAGGCC UCAUUCGG	86	CCGAAUGAGGCCUCUUGGG UGCAUUGG	460
S87- AS461	AUGCACCCAAGAGGCCU CCAUCGGC	87	GCCGAUGGAGGCCUCUUGG GUGCAUUG	461
S88- AS462	UGCACCCAAGAGGCCUCC UACGGCC	88	GGCCGUAGGAGGCCUCUUG GGUGCAU	462
S89- AS463	GCACCCAAGAGGCCUCCU UAGGCCT	89	AGGCCUAAGGAGGCCUCU GGGUGCAU	463
S90- AS464	CACCCAAGAGGCCUCCU CAGCCTT	90	AAGGCUGAAGGAGGCCUCU UGGGUGCA	464
S91- AS465	ACCCAAGAGGCCUCCUUC GACCUTC	91	GAAGGUCGAAGGAGGCCUC UUGGGUGC	465
S92- AS466	CCCAAGAGGCCUCCUUCG GACUUCT	92	AGAAGUCCGAAGGAGGCCU CUUGGGUG	466
S93- AS467	CCAAGAGGCCUCCUUCG GCAUUCTT	93	AAGAAUGCCGAAGGAGGCC UCUUGGGU	467
S94- AS468	CAAGAGGCCUCCUUCGG CCAUCUTC	94	GAAGAUGGCCGAAGGAGGC CUCUUGGG	468
S95- AS469	AAGAGGCCUCCUUCGGC CUACUUC	95	GGAAGUAGGCCGAAGGAGG CCUCUUGG	469
S96- AS470	AGAGGCCUCCUUCGGCC UUAUUCCT	96	AGGAAUAAGGCCGAAGGAG GCCUCUUG	470
S97- AS471	GAGGCCUCCUUCGGCCU UCAUCCTC	97	GAGGAUGAAGGCCGAAGGA GGCCUCU	471
S98- AS472	AGGCCUCCUUCGGCCUUC UACCUCT	98	AGAGGUAGAAGGCCGAAGG AGGCCUCU	472
S99- AS473	GGCCUCCUUCGGCCUUCU UACUCTT	99	AAGAGUAAGAAGGCCGAAG GAGGCCUC	473
S100- AS474	GCCUCCUUCGGCCUUCU CAUCUTC	100	GAAGAUGAAGAAGGCCGAA GGAGGCCU	474
S101- AS475	GGAAUAACACUGCUGCA GAAGACAA	101	UUGUCUUCUGCAGCAGUGU UAUCCAC	475
S102- AS476	GAUGACAAGCAGCCUUA UGAAAAGA	102	UCUUUUCAUAAAGGCUGCU GUCAUCUG	476
S103- AS477	GGAUUUUGCUGCAUAUC GAACUAAA	103	UUUAGUUCGAUAUGCAGCA AUAUCCU	477
S104- AS478	AGCAAGAAAAAGAAGGA AGAGGAGG	104	CCUCCUCUCCUUCUUUUUC UUGCUUU	478
S105- AS479	GCAAGAAAAAGAAGGAA GAAGAGGA	105	UCCUCUUCUCCUUCUUUUU CUUGCUU	479

S106-AS480	CAAGAAAAAGAAGGAAG AGAAGGAA	106	UCCUUCUCUCCUUCUUUU UCUUGC	480
S107-AS481	AAGAAAAAGAAGGAAGA GGAGGAAG	107	CUCCUCCUCUCCUUCUUU UUCUUGC	481
S108-AS482	AGAAAAAGAAGGAAGAG GAAGAAGA	108	UCUUCUCCUCUCCUUCUU UUUCUUG	482
S109-AS483	GAAGAAGAUGAUGAUGA UGAAUAAG	109	CUUAUUCAUCAUCAUCU UCUUCUU	483
S110-AS484	GAUGAUGAUGAUGAAUA AGAUGGTT	110	AACCAUCUUAUUCAUCAU UCAUCUU	484
S111-AS485	GAUGAUGAUGAAUAAGU UGAUUCTA	111	UAGAAUCAACUUAUUCAU CAUCAU	485
S112-AS486	AUGAUGAUGAAUAAGUU GGAUCUAG	112	CUAGAUCCAACUUAUUCAU CAUCAU	486
S113-AS487	GAUGAAUAAGUUGGUUC UAACGCAG	113	CUGCGUUAAGAACCAACUA UUCAUCAU	487
S114-AS488	UGAAUAAGUUGGUUCUA GCACAGTT	114	AACUGUGCUAGAACCAACU UAUUCAU	488
S115-AS489	GAAUAAGUUGGUUCUAG CGAAGUTT	115	AAACUUCGCUAGAACCAACU UAUUCAU	489
S116-AS490	AAUAAGUUGGUUCUAGC GCAGUUTT	116	AAAACUGCGCUAGAACCAAC UUAUUC	490
S117-AS491	AUAAGUUGGUUCUAGCG CAAUUUTT	117	AAAAAUUGCGCUAGAACCA ACUUAUUC	491
S118-AS492	UAAGUUGGUUCUAGCGC AGAUUUTT	118	AAAAAUCUGCGCUAGAACC AACUUAUU	492
S119-AS493	AAGUUGGUUCUAGCGCA GUUUUUTT	119	AAAAAUACUGCGCUAGAAC CAACUUAU	493
S120-AS494	UUUUUCUUGUCUAUAAA GCAUUUAA	120	UUAAAUGCUUUUAUAGACAA GAAAAAAA	494
S121-AS495	UUUUCUUGUCUAUAAAG CAAUUAAC	121	GUUAAUUGCUUUUAUAGACA AGAAAAAA	495
S122-AS496	UUUCUUGUCUAUAAAGC AUUAUACC	122	GGUUAUAUGCUUUUAUAGAC AAGAAAAA	496
S123-AS497	UUCUUGUCUAUAAAGCA UUAACCCC	123	GGGUUUAUUGCUUUUAUAGA CAAGAAAA	497
S124-AS498	UCUUGUCUAUAAAGCAU UUAACCCC	124	GGGGUUAUUGCUUUUAUAG ACAAGAAA	498
S125-AS499	CAACUCACUCCUUUUAA AGAAAAAA	125	UUUUUUCUUUAAAAGGAGU GAGUUGUG	499
S126-AS500	AACUCACUCCUUUUAAA GAAAAAAA	126	UUUUUUUCUUUAAAAGGAG UGAGUUGU	500
S127-AS501	ACUCACUCCUUUUAAAG AAAAAAAT	127	AUUUUUUUCUUUAAAAGGA GUGAGUUG	501
S128-AS502	CUCACUCCUUUUAAAGA AAAAAATT	128	AAUUUUUUUCUUUAAAAGG AGUGAGUU	502
S129-AS503	UCACUCCUUUUAAAGAA AAAAAUTG	129	CAUUUUUUUUUCUUUAAAAG GAGUGAGU	503
S130-AS504	CACUCCUUUUAAAGAAA AAAAUUGA	130	UCAUUUUUUUUUCUUUAAA GGAGUGAG	504
S131-AS505	ACUCCUUUUAAAGAAAA AAAUUGAA	131	UUCAUUUUUUUUUCUUUAAA AGGAGUGA	505
S132-AS506	CUCCUUUUAAAGAAAAA AAAUUGAA	132	UUUCAUUUUUUUUUCUUUAA AAGGAGUG	506

S133-AS507	UCCUUUUAAAGAAAAAA AUAGAAAT	133	AUUUCUAUUUUUUUCUUUA AAAGGAGU	507
S134-AS508	CCUUUUAAAGAAAAAAA UUAATAATG	134	CAUUUUAAUUUUUUUCUUU AAAAGGAG	508
S135-AS509	CUUUUAAAGAAAAAAAU UGAAAUGT	135	ACAUUUCAAUUUUUUUCUU UAAAAGGA	509
S136-AS510	UUUUAAAGAAAAAAAUU GAAAUGTA	136	UACAUUUCAAUUUUUUUCU UAAAAGG	510
S137-AS511	UUUAAAGAAAAAAAUUG AAAUGUAA	137	UUACAUUUCAAUUUUUUUC UUUAAAAG	511
S138-AS512	UUAAAGAAAAAAAUUGA AAAGUAAAG	138	CUUACUUUUCAAUUUUUUU CUUUAAAA	512
S139-AS513	UAAAGAAAAAAAUUGAA AUUAUAGG	139	CCUUAUAUUUCAAUUUUUU UCUUUAAA	513
S140-AS514	AAAGAAAAAAAUUGAAA UGAAAGGC	140	GCCUUUCAUUUCAUUUUUU UUCUUUAA	514
S141-AS515	GAAAAAAAUUGAAAUGU AAAGCUGT	141	ACAGCUUUACAUUUCAAUU UUUUUCUU	515
S142-AS516	AAAAAAAUUGAAAUGUA AGACUGTG	142	CACAGUCUUACAUUUCAAU UUUUUUCU	516
S143-AS517	GUAAGAUUUGUUUUUAA ACAGUACA	143	UGUACUGUUUAAAAACAAA UCUUACAC	517
S144-AS518	UAAGAUUUGUUUUUAAA CUAUACAG	144	CUGUAUAGUUUAAAAACAA AUCUUACA	518
S145-AS519	AAGAUUUGUUUUUAAAC UGAACAGT	145	ACUGUUCAGUUUAAAAACA AAUCUUAC	519
S146-AS520	AUUUGUUUUUAAACUGU ACAGUGTC	146	GACACUGUACAGUUUAAAA ACAAAUCU	520
S147-AS521	UUGUUUUUAAACUGUAC AGAGUCTT	147	AAGACUCUGUACAGUUUAA AAACAAAU	521
S148-AS522	UGUUUUUAAACUGUACA GUAUCUTT	148	AAAGAUACUGUACAGUUUA AAAACAAA	522
S149-AS523	GUUUUUUAAACUGUACAG UGACUUTT	149	AAAAGUCACUGUACAGUUU AAAAACAA	523
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S151-AS525	UUUUAAACUGUACAGUG UCAUUUTT	151	AAAAAUACACUGUACAGU UUAAAAAC	525
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S153-AS527	UUAAACUGUACAGUGUC UUAUUUTG	153	CAAAAUAAAGACACUGUACA GUUUAAAA	527
S154-AS528	UAAACUGUACAGUGUCU UUAUUUGT	154	ACAAAUAAAGACACUGUAC AGUUUAAA	528
S155-AS529	AAACUGUACAGUGUCUU UUAUUGTA	155	UACAAUAAAAAGACACUGUA CAGUUUAA	529
S156-AS530	AACUGUACAGUGUCUUU UUAUGUAT	156	AUACAUAAAAAGACACUGU ACAGUUUA	530
S157-AS531	ACUGUACAGUGUCUUUU UUAGUATA	157	UAUACUAAAAAAGACACUG UACAGUUU	531
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S159-AS533	UGUACAGUGUCUUUUUU UGAAUAGT	159	ACUAUUCAAAAAAGACAC UGUACAGU	533

S160-AS534	UACAGUGUCUUUUUUUG UAAAGUTA	160	UAACUUUACAAAAAAGAC ACUGUACA	534
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S162-AS536	GUGGUUUUUCAAUAGC CAAUAACC	162	GGUUUUUGGCUAUUGAAAA UACCACCA	536
S163-AS537	UGGUUUUUCAAUAGCC ACAAACCT	163	AGGUUUUGGGCUAUUGAAA AUACCACC	537
S164-AS538	GGUAAUUUUCAAUAGCCA CUAACCTT	164	AAGGUUAGUGGGCUAUUGAA AAUACCAC	538
S165-AS539	UAUUUUCAAUAGCCACU AAACUUGC	165	GCAAGUUUAGUGGGCUAUUG AAAAUACC	539
S166-AS540	AUUUUCAAUAGCCACUA ACAUUGCC	166	GGCAAUGUUAGUGGGCUAUU GAAAAUAC	540
S167-AS541	UUUUCAAUAGCCACUAA CCAUGCCT	167	AGGCAUGGUUAGUGGGCUAU UGAAAAUA	541
S168-AS542	UUUCAAUAGCCACUAA CUAGCCTG	168	CAGGCUAGGUUAGUGGGCUA UUGAAAAU	542
S169-AS543	UUCAAUAGCCACUAACC UUACCUGG	169	CCAGGUAAGGUUAGUGGGCU AUUGAAAA	543
S170-AS544	UCAAUAGCCACUAACCU UGACUGGT	170	ACCAGUCAAGGUUAGUGGC UAUUGAAA	544
S171-AS545	CAAUAGCCACUAACCUU GCAUGGTA	171	UACCAUGCAAGGUUAGUGG CUAUUGAA	545
S172-AS546	AAUAGCCACUAACCUUG CCAGGUAC	172	GUACCUGGCAAGGUUAGUG GCUAUUGA	546
S173-AS547	AUAGCCACUAACCUUGC CUAGUACA	173	UGUACUAGGCAAGGUUAGU GGCUAUUG	547
S174-AS548	UAGCCACUAACCUUGCC UGAUACAG	174	CUGUAUCAGGCAAGGUUAG UGGCUAUU	548
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S179-AS553	ACUAACCUUGCCUGGUA CAAUAUGG	179	CCAUUUUGUACCAGGCAAG GUUAGUGG	553
S180-AS554	GGGUUGUAAAUUGGCAU GGAAAUTT	180	AAAUUUCCAUGCCAAUUUA CAACCCCC	554
S181-AS555	GGUUGUAAAUUGGCAUG GAAAUUTA	181	UAAAUUUCCAUGCCAAUUU ACAACCCC	555
S182-AS556	GUUGUAAAUUGGCAUGG AAAUUUAA	182	UUAAAAUUCCAUGCCAAUU UACAACCC	556
S183-AS557	UUGUAAAUUGGCAUGGA AAAUUAAA	183	UUUAAUUUCCAUGCCAAU UUACAACC	557
S184-AS558	UGUAAAUUGGCAUGGAA AUAUAAAG	184	CUUUAUAAUUCCAUGCCAA UUUACAAC	558
S185-AS559	GUAAAUUGGCAUGGAAA UUAAAAGC	185	GCUUUUAAUUCCAUGCCA AUUUACAA	559
S186-AS560	UAAAUUGGCAUGGAAAU UUAAAGCA	186	UGCUUUAAAUUCCAUGCC AAUUUACA	560

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S189- AS563	AUUGGCAUGGAAAUUUA AAACAGGT	189	ACCUGUUUUAAAUUUCCA GCCAAUUU	563
S190- AS564	UUGGCAUGGAAAUUUAA AGAAGGTT	190	AACCUUCUUUAAAUUUCCA UGCCAAUU	564
S191- AS565	UGGCAUGGAAAUUUAAA GCAGGUTC	191	GAACCUUGC UUUAAA UUUCC AUGCCAAU	565
S192- AS566	GGCAUGGAAAUUUAAAG CAAGUUCT	192	AGAACUUGC UUUAAA UUUC CAUGCCAA	566
S193- AS567	GCAUGGAAAUUUAAAGC AGAUUCTT	193	AAGAAUCUGC UUUAAA UU CCAUGCCA	567
S194- AS568	CAUGGAAAUUUAAAGCA GGAUCUTG	194	CAAGAUCCUGC UUUAAA UU UCCAUGCC	568
S195- AS569	AUGGAAAUUUAAAGCAG GUACUUGT	195	ACAAGUACCUGC UUUAAA UCCAUGC	569
S196- AS570	UGGAAAUUUAAAGCAGG UUAUUGTT	196	AACAAUAACCUGC UUUAAA UUCCAUG	570
S197- AS571	GGAAAUUUAAAGCAGGU UCAUGUTG	197	CAACAUGAACCUGC UUUA AUUCCA	571
S198- AS572	GAAAUUUAAAGCAGGUU CUAGUUGG	198	CCAACUAGAACCUGC UUUA AUUCCA	572
S199- AS573	AAAUUUAAAGCAGGUUC UUAUUGGT	199	ACCAAUAAGAACCUGC UU AAAUUCC	573
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S207- AS581	AGCAGGUUCUUGUUGGU GCACAGCA	207	UGCUGUGCACCAACAAGAAC CUGCUUU	581
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S209- AS583	CAGGUUCUUGUUGGUGC ACAGCACA	209	UGUGCUGUGCACCAACAAG AACCUGCU	583
S210- AS584	AGGUUCUUGUUGGUGCA CAACACAA	210	UUGUGUUGUGCACCAACAA GAACCUGC	584
S211- AS585	GGUUCUUGUUGGUGCAC AGAACAAA	211	UUUGUUCUGUGCACCAACA AGAACCUG	585
S212- AS586	GUUCUUGUUGGUGCACA GCACAAAT	212	AUUUGUGCUGUGCACCAAC AAGAACCU	586
S213- AS587	UUCUUGUUGGUGCACAG CAAAAATT	213	AAUUUUUGCUGUGCACCA CAAGAACC	587

S214-AS588	UCUUGUUGGUGCACAGC ACAAUATA	214	UAAUUUGUGCUGUGCACCA ACAAGAAC	588
S215-AS589	CUUGUUGGUGCACAGCA CAAAUAG	215	CUAAUUUGUGCUGUGCACC ACAAGAA	589
S216-AS590	UUGUUGGUGCACAGCAC AAAUUAGT	216	ACUAAUUUGUGCUGUGCAC CAACAAGA	590
S217-AS591	UGUUGGUGCACAGCACA AAAUAGTT	217	AACUAAUUUGUGCUGUGCA CCAACAAG	591
S218-AS592	GUUGGUGCACAGCACAA AUAAGUTA	218	UAACUUAUUUGUGCUGUGC ACCAACAA	592
S219-AS593	UUGGUGCACAGCACAAA UUAGUUAT	219	AUAACUAAUUUGUGCUGUG CACCAACA	593
S220-AS594	UGGUGCACAGCACAAAU UAAUUATA	220	UAUAAUUAAUUUGUGCUGU GCACCAAC	594
S221-AS595	GGUGCACAGCACAAAUU AGAUUAT	221	AUAUAUCUAAUUUGUGCUG UGCACCAA	595
S222-AS596	UUUUUUCAUUCUUCAGUU GUAUCUGA	222	UCAGAUACAACUGAAGAUG AAAAAACU	596
S223-AS597	UUUUUUCAUUCUUCAGUUG UCACUGAT	223	AUCAGUGACAACUGAAGAU GAAAAAAC	597
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S231-AS605	CUGAUGCAGCUUAUACG AAAUUATT	231	AAUUAUUUCGUUAUAGCUG CAUCAGAG	605
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S237-AS611	AUACGAAAUAAUUGUUG UUAUGUTA	237	UAACAUAACAACAAUUAUU UCGUUAUA	611
S238-AS612	UACGAAAUAAUUGUUGU UCAGUUA	238	UUAACUGAACAACAAUUAU UUCGUUA	612
S239-AS613	ACGAAAUAAUUGUUGUU CUAUUAAC	239	GUUAAUAGAACAACAAUUA UUUCGUUA	613
S240-AS614	CGAAAUAAUUGUUGUUC UGAUAACT	240	AGUUAUCAGAACAACAAU AUUUCGUA	614

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S243-AS617	AAUAUUUGUUGUUCUGU UAACUGAA	243	UUCAGUUAACAGAACAAACA AUUAUUUC	617
S244-AS618	AAUUGUUGUUCUGUUAAC CUAAAUAC	244	GUAUUUAGUUAACAGAACAA ACAAUUAU	618
S245-AS619	AUUGUUGUUCUGUUAAC UGAAUACC	245	GGUAUUCAGUUAACAGAAC AACAAUUA	619
S246-AS620	UGUUGUUCUGUUAACUG AAAACCAC	246	GUGGUUUUCAGUUAACAGAA ACAACAAU	620
S247-AS621	GUUGUUCUGUUAACUGA AUACCACT	247	AGUGGUUUUCAGUUAACAG AACAAACA	621
S248-AS622	UGUUCUGUUAACUGAAU ACAACUCT	248	AGAGUUGUAUUCAGUUAAC AGAACAAC	622
S249-AS623	UCUGUUAACUGAAUACC ACACUGTA	249	UACAGUGUGGUUAUUCAGUU AACAGAAC	623
S250-AS624	CUGUUAACUGAAUACCA CUAUGUAA	250	UUACAUAGUGGUUAUUCAGU UAACAGAA	624
S251-AS625	GUUAACUGAAUACCACU CUAUAATT	251	AAUUUAAGAGUGGUUAUUCAG GUUAACAG	625
S252-AS626	AACUGAAUACCACUCUG UAAUUGCA	252	UGCAAUUACAGAGUGGUUAU UCAGUUAU	626
S253-AS627	ACUGAAUACCACUCUGU AAAUGCAA	253	UUGCAUUUACAGAGUGGUUA UUCAGUUA	627
S254-AS628	CUGAAUACCACUCUGUA AUAGCAAA	254	UUUGCUAUUACAGAGUGGU AUUCAGUU	628
S255-AS629	UGAAUACCACUCUGUAA UUACAAAA	255	UUUUGUAAUUACAGAGUGG UAUUCAGU	629
S256-AS630	GAAUACCACUCUGUAAU UGAAAAAA	256	UUUUUCAAUUACAGAGUG GUUUUCAG	630
S257-AS631	AAUACCACUCUGUAAUU GCAAAAAA	257	UUUUUUGCAAUUACAGAGU GGUAUUCA	631
S258-AS632	AAAAAGUUGCAGCUGUU UUAUUGAC	258	GUCAAUAAAACAGCUGCAA CUUUUUUU	632
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S262-AS636	GUUGCAGCUGUUUUUGUU GAAAUUCT	262	AGAAUUUCAACAAAACAGC UGCAACUU	636
S263-AS637	UGCAGCUGUUUUUGUUGA CAAUCUGA	263	UCAGAUUGUCAACAAAACA GCUGCAAC	637
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S267-AS641	GCUGUUUUUGUUGACAUU CUAAAUAGC	267	GCAUUUAGAAUGUCAACAA AACAGCUG	641

S268-AS642	UGUUUUGUUGACAUUCU GAAUGCTT	268	AAGCAUUCAGAAUGUCAAC AAAACAGC	642
S269-AS643	UUUGUUGACAUUCUGAA UGAUUCTA	269	UAGAAUCAUUCAGAAUGUC AACAAAAC	643
S270-AS644	UUGUUGACAUUCUGAAU GCAUCUAA	270	UUAGAUGCAUUCAGAAUGU CAACAAAA	644
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S273-AS647	UUGACAUUCUGAAUGCU UCAAGTA	273	UACUUUGAAGCAUUCAGAA UGUCAACA	647
S274-AS648	UGACAUUCUGAAUGCUU CUAAGUAA	274	UUACUUAGAAGCAUUCAGA AUGUCAAC	648
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S287-AS661	UAUUAGUAUUGUUGUCC UUAUCATA	287	UAUGAUAGGACAACAAUA CUAAUAAA	661
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S289-AS663	UUAGUAUUGUUGUCCUU UUAUUAGG	289	CCUAUUAAAAGGACAACAA UACUAAUA	663
S290-AS664	UAGUAUUGUUGUCCUUU UCAUAGGT	290	ACCUAUGAAAAGGACAACA AUACUAAU	664
S291-AS665	GUUUUGUUGUCCUUUUUC AUAGGUCT	291	AGACCUAUGAAAAGGACAA CAAUACUA	665
S292-AS666	UUGUUGUCCUUUUUCAUA GGACUGAA	292	UUCAGUCCUAUGAAAAGGA CAACAAUA	666
S293-AS667	UGUUGUCCUUUUUCAUAG GUAUGAAA	293	UUUCAUACCUAUGAAAAGG ACAACAAU	667
S294-AS668	UUGUCCUUUUUCAUAGGU CUAAAATT	294	AAUUUUAGACCUAUGAAAA GGACAACA	668

S295- AS669	UGUCCUUUUCAUAGGUC UGAAAUUTT	295	AAAUUUCAGACCUAUGAAA AGGACAAC	669
S296- AS670	GUCCUUUUCAUAGGUCU GAAAUUTT	296	AAAAUUUCAGACCUAUGAA AAGGACAA	670
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S301- AS675	GGGGAAGCUAGUCUUUU GCAUUUGC	301	GCAAAUGCAAAGACUAGC UCCCCUC	675
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S303- AS677	GGAAGCUAGUCUUUUGC UUAUGCCC	303	GGGCAUAAGCAAAGACUA GCUUCCCC	677
S304- AS678	GAAGCUAGUCUUUUGCU UUAGCCCA	304	UGGGCUAAAGCAAAGACU AGCUUCCC	678
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S308- AS682	GCUAAUAAAAAGCUUUU GUUAACAC	308	GUGUAUACAAAAGCUUUUU AUUAGCUA	682
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S320- AS694	UUCAUCCAUAACUGAAC AUACAAAA	320	UUUUGUAUGUUCAGUUAUG GAUGAAAA	694
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S326-AS700	AAACAUUUUUGAAAGUCU GUACUUGA	326	UCAAGUACAGACUUUCAA AUGUUUGA	700
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S339-AS713	GACCUGAGAAUGUAUCC CCAAAAGC	339	GCUUUUGGGGAUACAUCU CAGGUCUU	713
S340-AS714	ACCUGAGAAUGUAUCCC CAAAAGCG	340	CGCUUUUGGGGAUACAUC UCAGGUCU	714
S341-AS715	CCUGAGAAUGUAUCCCC AAAAGCGT	341	ACGCUUUUGGGGAUACAUC CUCAGGUC	715
S342-AS716	CUGAGAAUGUAUCCCCA AAAGCGTG	342	CACGCUUUUGGGGAUACA UCUCAGGU	716
S343-AS717	UGAGAAUGUAUCCCCAA AAACGUGA	343	UCACGUUUUUGGGGAUACA UUCUCAGG	717
S344-AS718	GAGAAUGUAUCCCCAAA AGAGUGAG	344	CUCACUCUUUUGGGGAUAC AUUCUCAG	718
S345-AS719	GCCAUAUUAAAAUUUUU GUAGACAT	345	AUGUCUACAAAAAUUUAA UAUGGCAG	719
S346-AS720	CCAUAUUAAAAUUUUUUG UUAACATT	346	AAUGUUAACAAAAAUUUA AUAUGGCA	720
S347-AS721	CAUAUUAAAAUUUUUUGU UGACAUTA	347	UAAUGUCAACAAAAAUUU AAUAUGGC	721
S348-AS722	AUAUUAAAAUUUUUUGUU GAAAUUAG	348	CUAUUUCAACAAAAAUU UAAUAUGG	722

S349- AS723	AUUAAAUUUUUUGUUGA CAAUAGTC	349	GACUAUUGUCAACAAAAAA UUUAAUUAU	723
S350- AS724	AAAUUUUUUGUUGACAU UAAUCUCA	350	UGAGAUUAAUGUCAACAAA AAAUUUA	724
S351- AS725	AAUUUUUUGUUGACAUU AGACUCAG	351	CUGAGUCUAAUGUCAACAA AAAAUUUA	725
S352- AS726	AUUUUUUUGUUGACAUUA GUAUCAGT	352	ACUGAUACUAAUGUCAACA AAAAUUUU	726
S353- AS727	GAAGACUAUGAAAAUGC UGACUATA	353	UAUAGUCAGCAUUUUAUA GUCUUCAC	727
S354- AS728	AGACUUUCCAUAACAAG UAAUUUTA	354	UAAAAUUACUUGUAAUGGA AAGUCUCG	728
S355- AS729	ACUUUGCAUCUCAGUAU GAAUUATT	355	AAUAAUUCAUACUGAGAUG CAAAGUUU	729
S356- AS730	CUUUGCAUCUCAGUAUG AAUAUTC	356	GAAUAAUUCAUACUGAGAU GCAAAGUU	730
S357- AS731	UUGCAUCUCAGUAUGAA UUAUUCAA	357	UUGAAUAAUUCAUACUGAG AUGCAAAG	731
S358- AS732	GCAUCUCAGUAUGAAUU AUACAATT	358	AAUUGUAUAAUUCAUACUG AGAUGCAA	732
S359- AS733	CAUCUCAGUAUGAAUUA UUAAAUTT	359	AAAUUUAAUAAUUCAUACU GAGAUGCA	733
S360- AS734	GAAUGAUUUUUCUUUAC AAAACAAA	360	UUUGUUUUGUAAAGAAAAA UCAUUCAA	734
S361- AS735	AGUUUAGGGAACAAUUU GGAAAUUTT	361	AAAUUUCCAAAUUGUUCCC UAAACUCC	735
S362- AS736	GUUUAGGGAACAAUUUG GCAAUUTT	362	AAAAUUGCCAAAUUGUUCC CUAAACUC	736
S363- AS737	UUUAGGGAACAAUUUGG CAAUUUTG	363	CAAAAUUGCCAAAUUGUUC CCUAAACU	737
S364- AS738	UUAGGGAACAAUUUGGC AAAUUUGT	364	ACAAAUUUGCCAAAUUGUU CCCUAAAC	738
S365- AS739	UAGGGAACAAUUUGGCA AUUUGTG	365	CACAAUAAUUGCCAAAUUGU UCCCUAAA	739
S366- AS740	AGGGAACAAUUUGGCAA UUAUGUGG	366	CCACAUAAUUGCCAAAUUG UUCCCUAA	740
S367- AS741	GGGAACAAUUUGGCAAU UUAGUGGT	367	ACCACUAAAUUGCCAAAUU GUUCCCUA	741
S368- AS742	GGAACAAUUUGGCAAUU UUAUGGTT	368	AACCAUAAAAUUGCCAAAU UGUUCCCU	742
S369- AS743	GAACAAUUUGGCAAUUU UGAGGUTT	369	AAACCUCAAAAUUGCCAAA UUGUUCCC	743
S370- AS744	AACAAUUUGGCAAUUUU GUAGUUTT	370	AAAACUACAAAUUGCCAA AUUGUUCC	744
S371- AS745	ACAAUUUGGCAAUUUUG UGAUUUTC	371	GAAAAUCACAAAUUGCCA AAUUGUUC	745
S372- AS746	CAAUUUGGCAAUUUUGU GGAUUUCG	372	CGAAAUCCACAAAUUGCCA AAUUGUU	746
S373- AS747	AAAUAGCGUUCUUGUAA UUAUACAC	373	GUGUAUAAUACAAGAACG CUAUUUUA	747
S374- AS748	AAUAGCGUUCUUGUAAU UUAACACG	374	CGUGUUAUUUACAAGAAC GCUAUUUU	748
S375- AS749	GCGUUCUUGUAAUUUUA CAAGCUTT	375	AAAGCUUGUAAAAUACAA GAACGCUA	749

S376- AS750	UAAUUUUACACGCUUUU GUAAUGGA	376	UCCAUUACAAAAGCGUGUA AAAUUACA	750
S377- AS751	CGCUUUUGUGAUGGAGU GCAGUUTT	377	AAAACUGCACUCCAUCACAA AAGCGUG	751
S378- AS752	GCUUUUGUGAUGGAGUG CUAUUUTG	378	CAAAAUAGCACUCCAUCACA AAAGCGU	752
S379- AS753	CUUUUGUGAUGGAGUGC UGAUUUGT	379	ACAAAUCAGCACUCCAUCAC AAAAGCG	753
S380- AS754	UUUUGUGAUGGAGUGCU GUAUUGTT	380	AACAAUACAGCACUCCAUCA CAAAAGC	754
S381- AS755	UUUGUGAUGGAGUGCUG UUAUGUTA	381	UAACAUAAACAGCACUCCAUC ACAAAAG	755
S382- AS756	UGUGAUGGAGUGCUGUU UUAUUATA	382	UAUAAUAAAACAGCACUCC AUCACAAA	756
S383- AS757	UGAUGGAGUGCUGUUUU GUAAUATA	383	UAUAAUACAAAACAGCACU CCAUCACA	757
S384- AS758	GAUGGAGUGCUGUUUUUG UUAUAUAA	384	UUAUAUAACAAAACAGCAC UCCAUCAC	758
S385- AS759	AUGGAGUGCUGUUUUUGU UAAAUAAT	385	AUUUUUUAACAAAACAGCA CUCCAUCA	759
S386- AS760	UGGAGUGCUGUUUUUGUU AUUAUATT	386	AAUUUAUAACAAAACAGC ACUCCAUC	760
S387- AS761	GGAGUGCUGUUUUUGUUA UAAAUTT	387	AAUUUUUAUAACAAAACAG CACUCCA	761
S388- AS762	GAGUGCUGUUUUUGUUAU AUAAUUTA	388	UAAAUUAUAUAACAAAACA GCACUCCA	762
S389- AS763	AGUGCUGUUUUUGUUAUA UAAUUUAG	389	CUAAAUUAUAUAACAAAAC AGCACUCC	763
S390- AS764	GUGCUGUUUUUGUUAUAU AAAUUAGA	390	UCUAAUUUAUAUAACAAA CAGCACUC	764
S391- AS765	UGCUGUUUUUGUUAUAUA AUUAAGAC	391	GUCUAUAUUUAUAUAACAAA ACAGCACU	765
S392- AS766	GCUGUUUUUGUUAUAUAA UUAAGACT	392	AGUCUUAUUUAUAUAACAA AACAGCAC	766
S393- AS767	CUGUUUUUGUUAUAUAU UUAGACTT	393	AAGUCUAAAUUAUAUAACA AAACAGCA	767
S394- AS768	AUUUGCAUUUGUUUAUG UAAUUUCA	394	UGAAAUUACAUAACAAAUA GCAAUUGG	768
S395- AS769	GUUUUAUGUAAUUUCAGG AGAAAUAC	395	GUUUUCUCCUGAAAUUAC AUAAACAA	769
S396- AS770	AUGUAAUUUCAGGAGGA AUACUGAA	396	UUCAGUAUUCUCCUGAAA UUACAUA	770
S397- AS771	GAAUACUGAACAUCUGA GUACUGGA	397	UCCAGUACUCAGAUGUUA GUUUCCU	771
S398- AS772	CAUCUGAGUCCUGGAUG AUACUAAT	398	AUUAGUAUCAUCCAGGACU CAGAUGUU	772
S399- AS773	AUCUGAGUCCUGGAUGA UAAUAATA	399	UAUUUAUAUCAUCCAGGAC UCAGAUGU	773
S400- AS774	UGAGUCCUGGAUGAUAC UAAUAAAC	400	GUUUUAUAGUAUCAUCCAG GACUCAGA	774
S401- AS775	AGUCCUGGAUGAUACUA AUAACTA	401	UAGUUUAUAGUAUCAUCC AGGACUCA	775
S402- AS776	GUCCUGGAUGAUACUAA UAAACUAA	402	UUAGUUUAUAGUAUCAUC CAGGACUC	776

S403- AS777	UCCUGGAUGAUACUAAU AAACUAAT	403	AUUAGUUUAAUAGUAUCAU CCAGGACU	777
S404- AS778	CCUGGAUGAUACUAAUA AAAUAATA	404	UAUUAUUUUAAUAGUAUCA UCCAGGAC	778
S405- AS779	CUGGAUGAUACUAAUAA ACAAAUA	405	UUUUUUUUUUUUUUUUAGUAUC AUCCAGGA	779
S406- AS780	UGGAUGAUACUAAUAAA CUAAUAAT	406	AUUUUUUUUUUUUUUUUAGUAU CAUCCAGG	780
S407- AS781	GGAUGAUACUAAUAAAC UAAUAATT	407	AAUUUUUUUUUUUUUUUUAGUA UCAUCCAG	781
S408- AS782	GAUGAUACUAAUAAACU AAAAAUTG	408	CAUUUUUUUUUUUUUUUUAGU AUCAUCCA	782
S409- AS783	AUGAUACUAAUAAACUA AUAAUUGC	409	GCAUUUUUUUUUUUUUUUUAG UAUCAUCC	783
S410- AS784	UGAUACUAAUAAACUAA UAAUUGCA	410	UGCAUUUUUUUUUUUUUUUA GUAUCAUC	784
S411- AS785	GAUACUAAUAAACUAAU AAAUGCAG	411	CUGCAUUUUUUUUUUUUUUU AGUAUCAU	785
S412- AS786	AUACUAAUAAACUAAUA AUAGCAGA	412	UCUGCUUUUUUUUUUUUUUU UAGUAUCA	786
S413- AS787	UACUAAUAAACUAAUAA UUACAGAG	413	CUCUGUAAUUUUUUUUUUUU UUAGUAUC	787
S866- AS887	UGGGCAAAGGAGAUCU AAAAAGCC	866	GGCUUUUUUUAGGAUCUCCU UGCCCAUG	887
S867- AS876	AAAGAGAAAUGAAAACC UAAAUCCC	867	GGGAUUUUUAGGUUUUCAUU CUCUUUCA	876
S868- AS877	AAGAAGAUGAUGAUGAU GAAUAAGT	868	ACUUAUUUCAUCAUCAUC UUCUUCU	877
S869- AS878	AUGAUGAUGAUGAAUAA GUAGGUTC	869	GAACCUACUUUUUCAUCAUC AUAUCU	878
S870- AS879	GAUGAUGAAUAAGUUGG UUAUAGCG	870	CGCUAUAACCAACUUAUUCA UCAUCAU	879
S871- AS880	AGAAAAAAAUUGAAAUG UAAGGCTG	871	CAGCCUUACAUUUCAAUUU UUUUCUUU	880
S872- AS881	UUGUUGUUCUGUUAACU GAAUACCA	872	UGGUUUUUUUUUUUUUUUUU CAACAAUU	881
S873- AS882	UUCUGAAUGCUUCUAAG UAAAUACA	873	UGUAAUUUUUUUUUUUUUU UCAGAAUG	882
S874- AS883	CUGAAUGCUUCUAAGUA AAAACAAT	874	AUUGUUUUUUUUUUUUUUUU AUUCAGAA	883
S875- AS884	GAAUGCUUCUAAGUAAA UAAAAUTT	875	AAAUUUUUUUUUUUUUUUUU GCAUUCAG	884

[0205] Table 5: Additinoal GalNAc-conjugated HMGB1 oligonucleotide sequences with modifications (tested in FIG. 5).

GalNAc-conjugated oligonucleotides	Sense sequence (unmodified)	Sense sequence (modified)	SEQ ID NO	Antisense sequence (unmodified)	Antisense sequence (unmodified)	SEQ ID NO
S840-AS853-M2	CUAA ACAU GGGC	[mCs][mU][mA][mA][mA][mC][mA][fU][fG][fG][fG][mC][mA][mA]	840	UCUCCU UUGCCC AUGUUU	[MePhosphonate-4O-mUs][fCs][fU][mC][fC][mU][fU][mU][mG][fC][mC][mC]	853

	AAAG GAGA GCAG CCGA AAGG CUGC	[mA][mG][mG][mA][mG][mA][mG][mC][mA][mG][mC][mC][mG][adema-GalNAc][adema-GalNAc][adema-GalNAc][mG][mG][mC][mU][mG][mC]		AGGG	[mA][fU][mG][mU][mU][mU][mA][mGs][mGs][mG]	
S840- AS853- M3	CUAA ACAU GGGC AAAG GAGA GCAG CCGA AAGG CUGC	[mCs][mU][fA][mA][mA][mC][mA][fU][mG][fG][mG][fC][fA][mA][mA][mG][fG][mA][mG][mA][mG][mC][mA][mG][mC][mC][mG][adema-GalNAc][adema-GalNAc][adema-GalNAc][mG][mG][mC][mU][mG][mC]	840	UCUCCU UUGCCC AUGUUU AGGG	[MePhosphonate-4O-mUs][fCs][fU][fC][fC][mU][fU][mU][mG][fC][mC][fC][mA][fU][mG][fU][fU][mU][fA][mGs][mGs][mG]	853
S841- AS854- M2	UAAA CAUG GGCA AAGG AGAA GCAG CCGA AAGG CUGC	[mUs][mA][mA][mA][mC][mA][mU][fG][fG][fG][fC][mA][mA][mA][mG][mG][mA][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][adema-GalNAc][adema-GalNAc][adema-GalNAc][mG][mG][mC][mU][mG][mC]	841	UUCUCC UUUGCC CAUGUU UAGG	[MePhosphonate-4O-mUs][fUs][fC][mU][fC][mC][fU][mU][mU][fG][mC][mC][mC][fA][mU][mG][mU][mU][mU][mAs][mGs][mG]	854
S841- AS854- M3	UAAA CAUG GGCA AAGG AGAA GCAG CCGA AAGG CUGC	[mUs][mA][fA][mA][mC][mA][mU][fG][mG][fG][fG][mC][fA][fA][mA][mG][mG][fA][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][adema-GalNAc][adema-GalNAc][adema-GalNAc][mG][mG][mC][mU][mG][mC]	841	UUCUCC UUUGCC CAUGUU UAGG (SEQ ID NO: 854)	[MePhosphonate-4O-mUs][fUs][fC][fU][fC][mC][fU][mU][mU][fG][mC][fC][mC][fA][mU][fG][fU][mU][fU][mAs][mGs][mG]	854
S842- AS855- M2	AGCC GAGA GGCA AAAU GUCA GCAG CCGA AAGG CUGC	[mAs][mG][mC][mC][mG][mA][mG][fA][fG][fG][fC][mA][mA][mA][mA][mU][mG][mU][mC][mA][mG][mC][mA][mG][mC][mC][mG][adema-GalNAc][adema-GalNAc][adema-GalNAc][mG][mG][mC][mU][mG][mC]	842	UGACAU UUUGCC UCUCGG CUGG	[MePhosphonate-4O-mUs][fGs][fA][mC][fA][mU][fU][mU][mU][fG][mC][mC][mU][fC][mU][mC][mG][mG][mC][mUs][mGs][mG]	855
S842- AS855- M3	AGCC GAGA GGCA AAAU GUCA GCAG CCGA AAGG	[mAs][mG][fC][mC][mG][mA][mG][fA][mG][fG][mC][fA][fA][mA][mA][mU][fG][mU][mC][mA][mG][mC][mA][mG][mC][mC][mG][adema-GalNAc][adema-GalNAc][adema-GalNAc][mG][mG][mC][mU][mG][mC]	842	UGACAU UUUGCC UCUCGG CUGG	[MePhosphonate-4O-mUs][fGs][fA][fC][fA][mU][fU][mU][mU][fG][mC][fC][mU][fC][mU][fC][fG][mG][fC][mUs][mGs][mG]	855

	CUGC	GalNAc][mG][mG][mC][mU][mG][mC]				
S843-AS856-M2	AAGA AGUG CUCA GAGA GGUA GCAG CCGA AAGG CUGC	[mAs][mA][mG][mA][mA][mG][mU][fG][fC][fU][fC][mA][mG][mA][mG][mA][mG][mC][mA][mG][mC][mC][mG][adema-GalNAc][adema-GalNAc][adema-GalNAc][mG][mG][mC][mU][mG][mC]	843	UACCUC UCUGAG CACUUC UUGG	[MePhosphonate-4O-mUs][fAs][fC][mC][fU][mC][fU][mC][mU][fG][mA][mG][mC][fA][mC][mU][mU][mC][mU][mUs][mGs][mG]	856
S843-AS856-M3	AAGA AGUG CUCA GAGA GGUA GCAG CCGA AAGG CUGC	[mAs][mA][fG][mA][mA][mG][mU][fG][mC][fU][mC][fA][fG][mA][mG][mA][fG][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][adema-GalNAc][adema-GalNAc][adema-GalNAc][mG][mG][mC][mU][mG][mC]	843	UACCUC UCUGAG CACUUC UUGG	[MePhosphonate-4O-mUs][fAs][fC][fC][fU][mC][fU][mC][mU][fG][mA][fG][mC][fA][mC][fU][fU][mC][fU][mUs][mGs][mG]	856
S844-AS857-M2	CUCA GAGA GGUG GAAG ACCA GCAG CCGA AAGG CUGC	[mCs][mU][mC][mA][mG][mA][mG][fA][fG][fG][fU][mG][mG][mA][mA][mG][mA][mC][mC][mA][mG][mC][mA][mG][mC][mC][mG][adema-GalNAc][adema-GalNAc][adema-GalNAc][mG][mG][mC][mU][mG][mC]	844	UGGUCU UCCACC UCUCUG AGGG	[MePhosphonate-4O-mUs][fGs][fG][mU][fC][mU][fU][mC][mC][fA][mC][mC][mU][fC][mU][mC][mU][mG][mA][mGs][mGs][mG]	857
S844-AS857-M3	CUCA GAGA GGUG GAAG ACCA GCAG CCGA AAGG CUGC	[mCs][mU][fC][mA][mG][mA][mG][fA][mG][fG][mU][fG][fG][mA][mA][mG][fA][mC][mC][mA][mG][mC][mA][mG][mC][mC][mG][adema-GalNAc][adema-GalNAc][adema-GalNAc][mG][mG][mC][mU][mG][mC]	844	UGGUCU UCCACC UCUCUG AGGG	[MePhosphonate-4O-mUs][fGs][fG][fU][fC][mU][fU][mC][mC][fA][mC][fC][mU][fC][mU][fC][fU][mG][fA][mGs][mGs][mG]	857
S845-AS858-M2	AGGU GGAA GACC AUGU CUGA GCAG CCGA AAGG CUGC	[mAs][mG][mG][mU][mG][mG][mA][fA][fG][fA][fC][mC][mA][mU][mG][mU][mC][mU][mG][mA][mG][mC][mA][mG][mC][mC][mG][adema-GalNAc][adema-GalNAc][adema-GalNAc][mG][mG][mC][mU][mG][mC]	845	UCAGAC AUGGUC UCCAC CUGG	[MePhosphonate-4O-mUs][fCs][fA][mG][fA][mC][fA][mU][mG][fG][mU][mC][mU][fU][mC][mC][mA][mC][mC][mUs][mGs][mG]	858
S845-AS858-	AGGU GGAA	[mAs][mG][fG][mU][mG][mG][mA][fA][mG][f	845	UCAGAC AUGGUC	[MePhosphonate-4O-mUs][fCs][fA][fG][fA][mC][	858

M3	GACC AUGU CUGA GCAG CCGA AAGG CUGC	A][mC][fC][fA][mU][mG][mU][fC][mU][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]		UUCCAC CUGG	fA][mU][mG][fG][mU][fC][mU][fU][mC][fC][fA][mC][fC][mUs][mGs][mG]	
S885- AS886- M2	AAGA CCA GUCU GCUA AAGA GCAG CCGA AAGG CUGC	[mAs][mA][mG][mA][mC][mC][mA][fU][fG][fU][fC][mU][mG][mC][mU][mA][mA][mA][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	885	UCUUUA GCAGAC AUGGUC UUGG	[MePhosphonate-4O-mUs][fCs][fU][mU][fU][mA][fG][mC][mA][fG][mA][mC][mA][fU][mG][mG][mU][mC][mU][mUs][mGs][mG]	886
S885- AS886- M3	AAGA CCA GUCU GCUA AAGA GCAG CCGA AAGG CUGC	[mAs][mA][fG][mA][mC][mC][mA][fU][mG][fU][mC][fU][fG][mC][mU][mA][fA][mA][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	885	UCUUUA GCAGAC AUGGUC UUGG	[MePhosphonate-4O-mUs][fCs][fU][fU][fU][mA][fG][mC][mA][fG][mA][fC][mA][fU][mG][fG][fU][mC][fU][mUs][mGs][mG]	886
S846- AS859- M2	AAAU UUGA AGAU AUGG CAAA GCAG CCGA AAGG CUGC	[mAs][mA][mA][mU][mU][mU][mG][fA][fA][fG][fA][mU][mA][mU][mG][mG][mC][mA][mA][mA][mG][mC][mA][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	846	UUUGCC AUAUCU UCAAAU UUGG	[MePhosphonate-4O-mUs][fUs][fU][mG][fC][mC][fA][mU][mA][fU][mC][mU][mU][fC][mA][mA][mA][mU][mU][mUs][mGs][mG]	859
S846- AS859- M3	AAAU UUGA AGAU AUGG CAAA GCAG CCGA AAGG CUGC	[mAs][mA][fA][mU][mU][mU][mG][fA][mA][fG][mA][fU][fA][mU][mG][mG][fC][mA][mA][mA][mG][mC][mA][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	846	UUUGCC AUAUCU UCAAAU UUGG	[MePhosphonate-4O-mUs][fUs][fU][fG][fC][mC][fA][mU][mA][fU][mC][fU][mU][fC][mA][fA][fA][mU][fU][mUs][mGs][mG]	859
S847- AS860- M2	AGCA AGAA AAAG AAGG AAGA GCAG CCGA	[mAs][mG][mC][mA][mA][mG][mA][fA][fA][fA][fA][mG][mA][mA][mG][mG][mG][mA][mG][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-	847	UCUUCC UUCUUU UUCUUG CUGG	[MePhosphonate-4O-mUs][fCs][fU][mU][fC][mC][fU][mU][mC][fU][mU][mU][mU][fU][mC][mC][mU][mG][mC][mUs][mGs][mG]	860

	AAGG CUGC	GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]				
S847- AS860- M3	AGCA AGAA AAAG AAGG AAGA GCAG CCGA AAGG CUGC	[mAs][mG][fC][mA][m A][mG][mA][fA][mA][f A][mA][fG][fA][mA][m G][mG][fA][mA][mG][mA][mG][mC][mA][m G][mC][mC][mG][adem A-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	847	UCUUC UUUUU UUUUU CUGG	[MePhosphonate-4O- mUs][fCs][fU][fU][fC][mC][fU][mU][mC][fU][mU][fU][mU][fU][mC][fU][fU][mG][f C][mUs][mGs][mG]	860
S848- AS861- M2	CAAG AAAA AGAA GGAA GAGA GCAG CCGA AAGG CUGC	[mCs][mA][mA][mG][mA][mA][mA][fA][fA][fG][fA][mA][mG][mG][mA][mA][mG][mA][m G][mA][mG][mC][mA] [mG][mC][mC][mG][ad emA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	848	UCUCU CCUUC UUUUU UGGG	[MePhosphonate-4O- mUs][fCs][fU][mC][fU][mU][fC][mC][mU][fU][mC][mU][mU][fU][mU][mU][mC][m U][mU][mGs][mGs][mG]	861
S848- AS861- M3	CAAG AAAA AGAA GGAA GAGA GCAG CCGA AAGG CUGC	[mCs][mA][fA][mG][m A][mA][mA][fA][mA][f G][mA][fA][fG][mG][m A][mA][fG][mA][mG][mA][mG][mC][mA][m G][mC][mC][mG][adem A-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	848	UCUCU CCUUC UUUUU UGGG	[MePhosphonate-4O- mUs][fCs][fU][fC][fU][mU][fC][mC][mU][fU][mC][fU][mU][fU][mU][fU][fC][mU][f U][mGs][mGs][mG]	861
S849- AS862- M2	GAUG AUGA UGAA UAAG UUGA GCAG CCGA AAGG CUGC	[mGs][mA][mU][mG][m A][mU][mG][fA][fU][fG][fA][mA][mU][mA][mA][mG][mU][mU][m G][mA][mG][mC][mA] [mG][mC][mC][mG][ad emA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	849	UCAAC UAUUC UCAUC UCGG	[MePhosphonate-4O- mUs][fCs][fA][mA][fC][mU][fU][mA][mU][fU][mC][m A][mU][fC][mA][mU][mC][mA][mU][mCs][mGs][mG]	862
S849- AS862- M3	GAUG AUGA UGAA UAAG UUGA GCAG CCGA AAGG CUGC	[mGs][mA][fU][mG][m A][mU][mG][fA][mU][f G][mA][fA][fU][mA][m A][mG][fU][mU][mG][mA][mG][mC][mA][m G][mC][mC][mG][adem A-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	849	UCAAC UAUUC UCAUC UCGG	[MePhosphonate-4O- mUs][fCs][fA][fA][fC][mU][fU][mA][mU][fU][mC][fA][mU][fC][mA][fU][fC][mA][f U][mCs][mGs][mG]	862
S850-	AUGA	[mAs][mU][mG][mA][	850	UCCAAC	[MePhosphonate-4O-	863

AS863-M2	UGAU GAAU AAGU UGGA GCAG CCGA AAGG CUGC	mU][mG][mA][fU][fG][fA][fA][mU][mA][mA][mG][mU][mU][mG][mG][mA][mG][mC][mA][mG][mC][mG][ad emA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]		UUAUUC AUCAUC AUGG	mUs][fCs][fC][mA][fA][mC][fU][mU][mA][fU][mU][mC][mA][fU][mC][mA][mU][mC][mA][mUs][mGs][mG]	
S850-AS863-M3	AUGA UGAU GAAU AAGU UGGA GCAG CCGA AAGG CUGC (SEQ ID NO: 850)	[mAs][mU][fG][mA][mU][mG][mA][fU][mG][fA][mA][fU][fA][mA][mG][mU][fU][mG][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	850	UCCAAC UUAUUC AUCAUC AUGG	[MePhosphonate-4O-mUs][fCs][fC][fA][fA][mC][fU][mU][mA][fU][mU][fC][mA][fU][mC][fA][fU][mC][fA][mUs][mGs][mG]	863
S851-AS864-M2	AAGU UGGU UCUA GCGC AGUA GCAG CCGA AAGG CUGC	[mAs][mA][mG][mU][mU][mG][mG][fU][fU][fC][fU][mA][mG][mC][mG][mC][mA][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	851	UACUGC GCUAGA ACCAAC UUGG	[MePhosphonate-4O-mUs][fAs][fC][mU][fG][mC][fG][mC][mU][fA][mG][mA][mA][fC][mC][mA][mA][mC][mU][mUs][mGs][mG]	864
S851-AS864-M3	AAGU UGGU UCUA GCGC AGUA GCAG CCGA AAGG CUGC	[mAs][mA][fG][mU][mU][mG][mG][fU][mU][fC][mU][fA][fG][mC][mC][mC][fA][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	851	UACUGC GCUAGA ACCAAC UUGG	[MePhosphonate-4O-mUs][fAs][fC][fU][fG][mC][fG][mC][mU][fA][mG][fA][mA][fC][mC][fA][fA][mC][fU][mUs][mGs][mG]	864
S852-AS865-M2	UUAU AAGU AUUG UUGU CCUA GCAG CCGA AAGG CUGC	[mUs][mU][mA][mU][mU][mA][mG][fU][fA][fU][fU][mG][mU][mU][mU][mG][mU][mC][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	852	UAGGAC AACAAU ACUAAU AAGG	[MePhosphonate-4O-mUs][fAs][fG][mG][fA][mC][fA][mA][mC][fA][mA][mU][mA][fC][mU][mA][mA][mU][mA][mAs][mGs][mG]	865
S852-AS865-M3	UUAU UAGU AUUG UUGU CCUA	[mUs][mU][fA][mU][mU][mA][mG][fU][mU][fU][mU][fG][fU][mU][mG][mU][fC][mC][mU][mA][mG][mC][mA][m]	852	UAGGAC AACAAU ACUAAU AAGG	[MePhosphonate-4O-mUs][fAs][fG][fG][fA][mC][fA][mA][mC][fA][mA][fU][mA][fC][mU][fA][fA][mU][fA][mAs][mGs][mG]	865

	GCAG CCGA AAGG CUGC	G][mC][mC][mG][adem A-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]				

[0206] The disclosure illustratively described herein suitably can be practiced in the absence of any element or elements, limitation or limitations that are not specifically disclosed herein. Thus, for example, in each instance herein any of the terms “comprising”, “consisting essentially of”, and “consisting of” may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments, optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the description and the appended claims.

[0207] In addition, where features or aspects of the invention are described in terms of Markush groups or other grouping of alternatives, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.

[0208] The use of the terms “a” and “an” and “the” and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms “comprising,” “having,” “including,” and “containing” are to be construed as open-ended terms (i.e., meaning “including, but not limited to,”) unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., “such as”) provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[0209] Embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description.

[0210] The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context. Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

CLAIMS

What is claimed is:

1. An oligonucleotide for reducing expression of HMGB1, the oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand of 15 to 30 nucleotides in length, wherein the sense strand forms a duplex region with the antisense strand, wherein the sense strand comprises a sequence as set forth in any one of SEQ ID NOs: 1-13 and wherein the antisense strand comprises a complementary sequence selected from SEQ ID NOs: 14-26.
2. The oligonucleotide of claim 1, wherein the sense strand sequence comprises or consists of a sequence as set forth in any one of SEQ ID NOs: 27-39.
3. The oligonucleotide of claim 1 or claim A2, wherein the antisense strand sequence consists of a sequence as set forth in any one of SEQ ID NOs: 14-26.
4. The oligonucleotide of claim 1, wherein the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 27 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 14.
5. The oligonucleotide of claim 1, wherein the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 28 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 15.
6. The oligonucleotide of claim 1, wherein the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 29 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 16.
7. The oligonucleotide of claim 1, wherein the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 30 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 17.
8. The oligonucleotide of claim 1, wherein the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 31 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 18.
9. The oligonucleotide of claim 1, wherein the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 32 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 19.

10. The oligonucleotide of claim 1, wherein the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 33 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 20.
11. The oligonucleotide of claim 1, wherein the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 34 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 21.
12. The oligonucleotide of claim 1, wherein the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 35 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 22.
13. The oligonucleotide of claim 1, wherein the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 36 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 23.
14. The oligonucleotide of claim 1, wherein the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 37 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 24.
15. The oligonucleotide of claim 1, wherein the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 38 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 25.
16. The oligonucleotide of claim 1, wherein the sense strand sequence comprises a sequence as set forth in SEQ ID NO: 39 and the antisense strand sequence comprises a sequence as set forth in SEQ ID NO: 26.
17. The oligonucleotide of any one of claims 1-16, wherein the oligonucleotide comprises at least one modified nucleotide.
18. The oligonucleotide of claim 17, wherein all the nucleotides of the oligonucleotide are modified.
19. The oligonucleotide of claim 17 or claim 18, wherein the modified nucleotide comprises a 2'-modification.
20. The oligonucleotide of claim 19, wherein the 2'-modification is a 2'-fluoro or 2'-O-methyl.

21. The oligonucleotide of any one of claims 17-20, wherein one or more of positions 1, 2, 4, 6, 7, 12, 14, 16, 18-27, and 31-36 of the sense strand, and/or one or more of positions 1, 4, 6, 8, 9, 11, 13, 15, 18, and 20-22 of the antisense strand are modified with a 2'-O-methyl.
22. The oligonucleotide of claim 21, wherein all of positions 1, 2, 4, 6, 7, 12, 14, 16, 18-27, and 31-36 of the sense strand, and all of positions 1, 4, 6, 8, 9, 11, 13, 15, 18, and 20-22 of the antisense strand are modified with a 2'-O-methyl.
23. The oligonucleotide of any one of claims 17-22, wherein one or more of positions 3, 5, 8-11, 13, 15, and 17 of the sense strand, and/or one or more of positions 2, 3, 5, 7, 10, 12, 14, 16, 17, and 19 of the antisense strand are modified with a 2'-fluoro.
24. The oligonucleotide of claim 23, wherein all of positions 3, 5, 8-11, 13, 15, and 17 of the sense strand, and all of positions 2, 3, 5, 7, 10, 12, 14, 16, 17, and 19 of the antisense strand are modified with a 2'-fluoro.
25. The oligonucleotide of any one of claims 17-20, wherein one or more of positions 1-7, 12-27, and 31-36 of the sense strand, and/or one or more of positions 1, 4, 6, 8, 9, 11-13, and 15-22 of the antisense strand are modified with a 2'-O-methyl.
26. The oligonucleotide of claim 25, wherein all of positions 1-7, 12-27, and 31-36 of the sense strand, and all of positions 1, 4, 6, 8, 9, 11-13, and 15-22 of the antisense strand are modified with a 2'-O-methyl.
27. The oligonucleotide of any one of claims 17-20, 25 and 26, wherein one or more of positions 8-11 of the sense strand, and/or one or more of positions 2, 3, 5, 7, 10, and 14 of the antisense strand are modified with a 2'-fluoro.
28. The oligonucleotide of claim 27, wherein all of positions 8-11 of the sense strand, and all of positions 2, 3, 5, 7, 10, and 14 of the antisense strand are modified with a 2'-fluoro.
29. The oligonucleotide of any one of claims 17-20, wherein one or more of positions 1, 2, 4-7, 9, 11, 14-16, 18-27, and 31-36 of the sense strand, and/or one or more of positions 1, 6, 8, 9, 11, 13, 15, 18, and 20-22 of the antisense strand are modified with a 2'-O-methyl.
30. The oligonucleotide of claim 29, wherein all of positions 1, 2, 4-7, 9, 11, 14-16, 18-27, and 31-36 of the sense strand, and all of positions 1, 6, 8, 9, 11, 13, 15, 18, and 20-22 of the antisense strand are modified with a 2'-O-methyl.

31. The oligonucleotide of any one of claims 17-20, 29, and 30, wherein one or more of positions 3, 8, 10, 12, 13, and 17 of the sense strand, and/or one or more of positions 2-5, 7, 10, 12, 14, 16, 17, and 19 of the antisense strand are modified with a 2'-fluoro.

32. The oligonucleotide of claim 31, wherein all of positions 3, 8, 10, 12, 13, and 17 of the sense strand, and all of positions 2-5, 7, 10, 12, 14, 16, 17, and 19 of the antisense strand are modified with a 2'-fluoro.

33. The oligonucleotide of any one of claims 1-32, wherein the oligonucleotide comprises at least one modified internucleotide linkage.

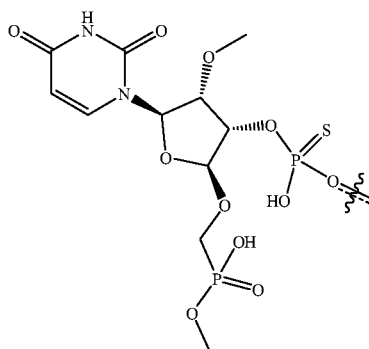
34. The oligonucleotide of claim 33, wherein the at least one modified internucleotide linkage is a phosphorothioate linkage.

35. The oligonucleotide of claim 33 or claim 34, wherein the oligonucleotide has a phosphorothioate linkage between one or more of: positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 3 and 4 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand.

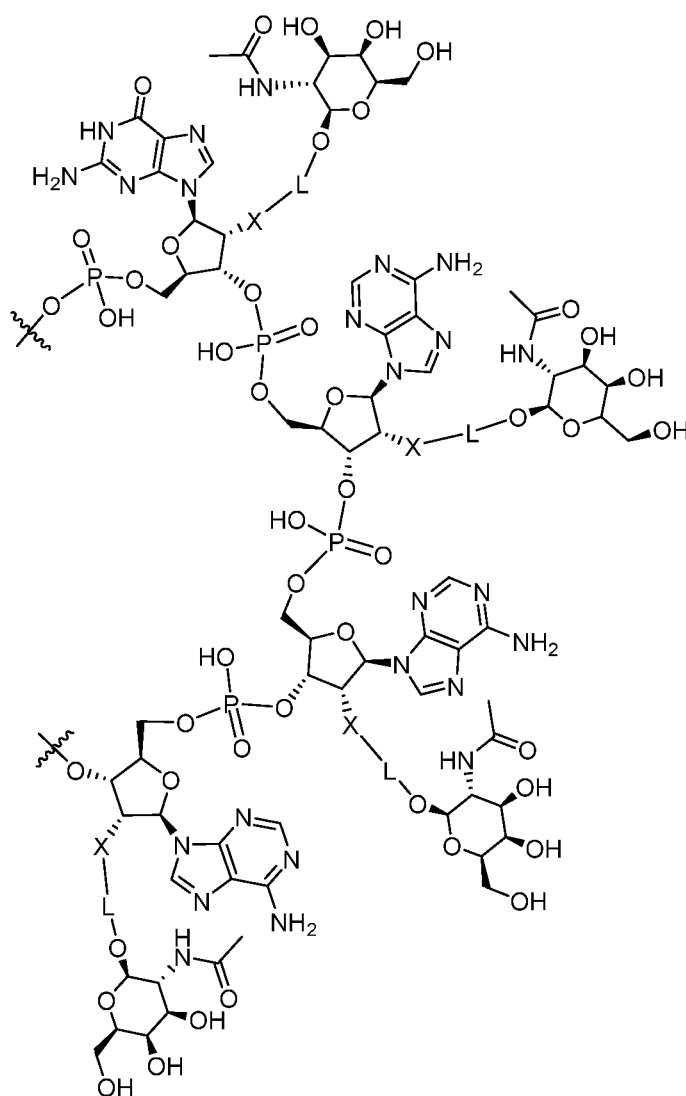
36. The oligonucleotide of claim 35, wherein the oligonucleotide has a phosphorothioate linkage between each of: positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand.

37. The oligonucleotide of any one of claims 1-36, wherein the uridine at the first position of the antisense strand comprises a phosphate analog.

38. The oligonucleotide of claim 37, comprising the following structure at position 1 of the antisense strand:



39. The oligonucleotide of any one claims 1-38, wherein one or more of the nucleotides of the –AAA– sequence at positions 28-30 on the sense strand is conjugated to a monovalent GalNAc moiety.
40. The oligonucleotide of claim 39, wherein each of the nucleotides of the –AAA– sequence at positions 28-30 on the sense strand is conjugated to a monovalent GalNAc moiety.
41. The oligonucleotide of claim 40, wherein the –AAA– motif at positions 28-30 on the sense strand comprises the structure:



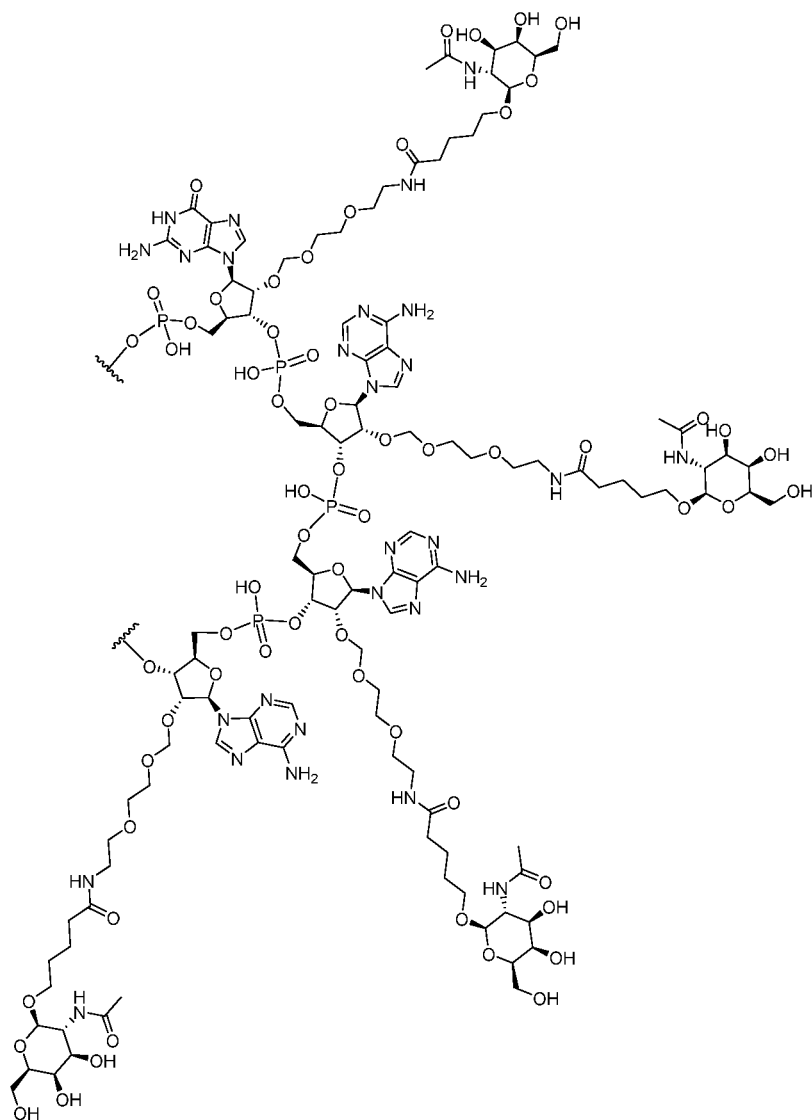
wherein:

L represents a bond, click chemistry handle, or a linker of 1 to 20, inclusive, consecutive, covalently bonded atoms in length, selected from the group consisting of substituted and unsubstituted alkylene, substituted and unsubstituted alkenylene, substituted and unsubstituted alkynylene, substituted and unsubstituted heteroalkylene, substituted and unsubstituted heteroalkenylene,

substituted and unsubstituted heteroalkynylene, and combinations thereof; and

X is O, S, or N.

42. The oligonucleotide of claim 41, wherein L is an acetal linker.
43. The oligonucleotide of claim 41 or claim 42, wherein X is O.
44. The oligonucleotide of any one of claims 41-43, wherein the –AAA– sequence at positions 28-30 on the sense strand comprises the structure:



45. An oligonucleotide for reducing expression of HMGB1, the oligonucleotide comprising an antisense strand of 15 to 30 nucleotides in length, wherein the antisense strand has a region of complementarity to HMGB1 that is complementary to at least 15 contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 1-13.

46. The oligonucleotide of claim 45, wherein the antisense strand is 19 to 27 nucleotides in length.
47. The oligonucleotide of claim 45, wherein the antisense strand is 22 nucleotides in length.
48. The oligonucleotide of any one of claims 45 to 47, further comprising a sense strand of 15 to 50 nucleotides in length, wherein the sense strand forms a duplex region with the antisense strand.
49. The oligonucleotide of claim 48, wherein the sense strand is 19 to 50 nucleotides in length.
50. The oligonucleotide of claim 48 or 49, wherein the duplex region is 20 nucleotides in length.
51. An oligonucleotide for reducing expression of HMGB1 comprising a sense strand and an antisense strand, wherein:
- (a) the sense strand comprises a sequence as set forth in SEQ ID NO: 788 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 814;
 - (b) the sense strand comprises a sequence as set forth in SEQ ID NO: 789 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 815;
 - (c) the sense strand comprises a sequence as set forth in SEQ ID NO: 790 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 816;
 - (d) the sense strand comprises a sequence as set forth in SEQ ID NO: 791 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 817;
 - (e) the sense strand comprises a sequence as set forth in SEQ ID NO: 792 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 818;
 - (f) the sense strand comprises a sequence as set forth in SEQ ID NO: 793 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 819;
 - (g) the sense strand comprises a sequence as set forth in SEQ ID NO: 794 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 820;
 - (h) the sense strand comprises a sequence as set forth in SEQ ID NO: 795 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 821;
 - (i) the sense strand comprises a sequence as set forth in SEQ ID NO: 796 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 822;
 - (j) the sense strand comprises a sequence as set forth in SEQ ID NO: 797 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 823;
 - (k) the sense strand comprises a sequence as set forth in SEQ ID NO: 798 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 824;
 - (l) the sense strand comprises a sequence as set forth in SEQ ID NO: 799 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 825;

- (m) the sense strand comprises a sequence as set forth in SEQ ID NO: 800 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 826;
- (n) the sense strand comprises a sequence as set forth in SEQ ID NO: 801 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 827;
- (o) the sense strand comprises a sequence as set forth in SEQ ID NO: 802 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 828;
- (p) the sense strand comprises a sequence as set forth in SEQ ID NO: 803 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 829;
- (q) the sense strand comprises a sequence as set forth in SEQ ID NO: 804 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 830;
- (r) the sense strand comprises a sequence as set forth in SEQ ID NO: 805 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 831;
- (s) the sense strand comprises a sequence as set forth in SEQ ID NO: 806 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 832;
- (t) the sense strand comprises a sequence as set forth in SEQ ID NO: 807 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 833;
- (u) the sense strand comprises a sequence as set forth in SEQ ID NO: 808 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 834;
- (v) the sense strand comprises a sequence as set forth in SEQ ID NO: 809 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 835;
- (w) the sense strand comprises a sequence as set forth in SEQ ID NO: 810 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 836;
- (x) the sense strand comprises a sequence as set forth in SEQ ID NO: 811 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 837;
- (y) the sense strand comprises a sequence as set forth in SEQ ID NO: 812 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 838; or
- (z) the sense strand comprises a sequence as set forth in SEQ ID NO: 813 and the antisense strand comprises a sequence as set forth in SEQ ID NO: 839.

- 52. A composition comprising the oligonucleotide of any one of claims 1-51 and an excipient.
- 53. A method of delivering an oligonucleotide to a subject, the method comprising administering the composition of claim 52 to the subject.
- 54. The method of claim 53, wherein the subject has or is at risk of having liver fibrosis.
- 55. The method of claim 54, wherein the subject has cholestatic or autoimmune liver disease.

56. The method of any one of claims 53-55, wherein expression of HMGB1 protein is reduced by administering to the subject the oligonucleotide.
57. A method of treating a subject having or at risk of having liver fibrosis, the method comprising administering to the subject an oligonucleotide of any one of claims 1-51.
58. The method of claim 57, wherein the subject has cholestatic or autoimmune liver disease.
59. The method of claim 58, wherein the subject has nonalcoholic steatohepatitis (NASH).
60. The method of any one of claims 57-59, wherein the oligonucleotide is administered prior to exposure of the subject to a hepatotoxic agent.
61. The method of any one of claims 57-59, wherein the oligonucleotide is administered subsequent to exposure of the subject to a hepatotoxic agent.
62. The method of any one of claims 57-59, wherein the oligonucleotide is administered simultaneously with the subject's exposure to a hepatotoxic agent.
63. The method of any one of claims 57-62, wherein the administration results in a reduction in liver HMGB1 levels.
64. The method of any one of claims 57-63, wherein the administration results in a reduction in serum HMGB1 levels.
65. Use of an oligonucleotide of any one of claims 1-51 for treating a subject having or at risk of having liver fibrosis.
66. The use of claim 65, wherein the subject has cholestatic or autoimmune liver disease.
67. The use of claim 65, wherein the subject has nonalcoholic steatohepatitis (NASH).

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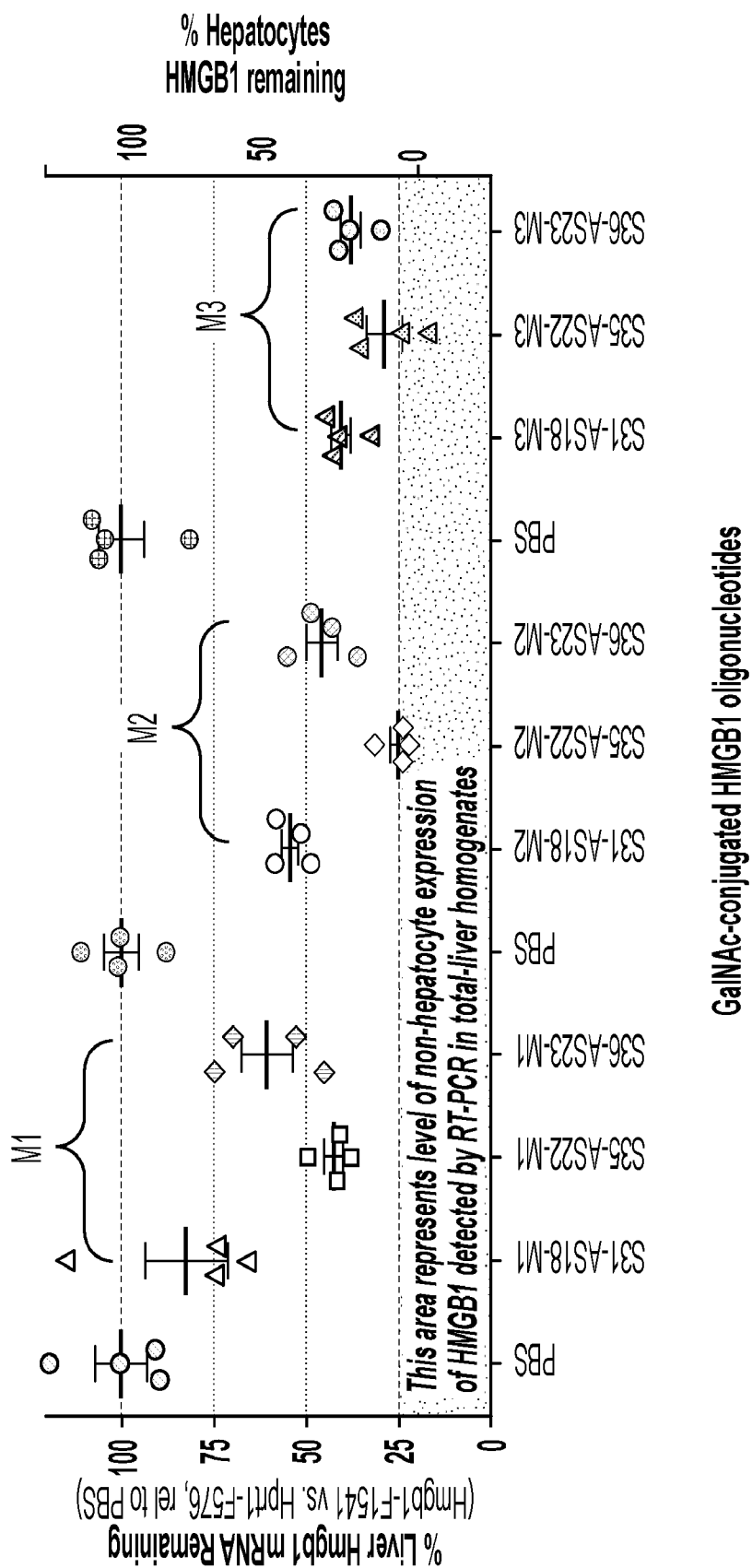


FIG. 1A

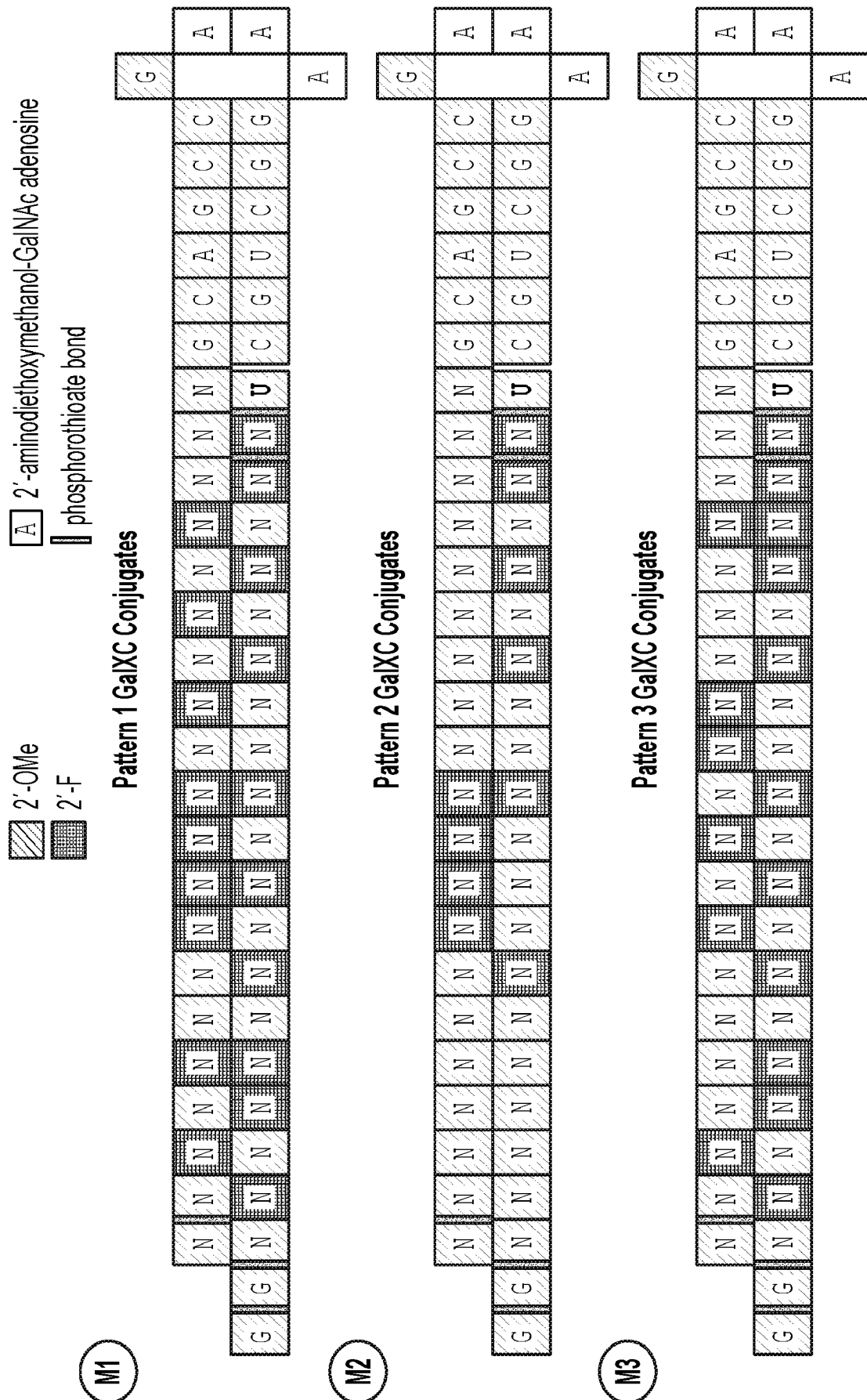


FIG. 1B

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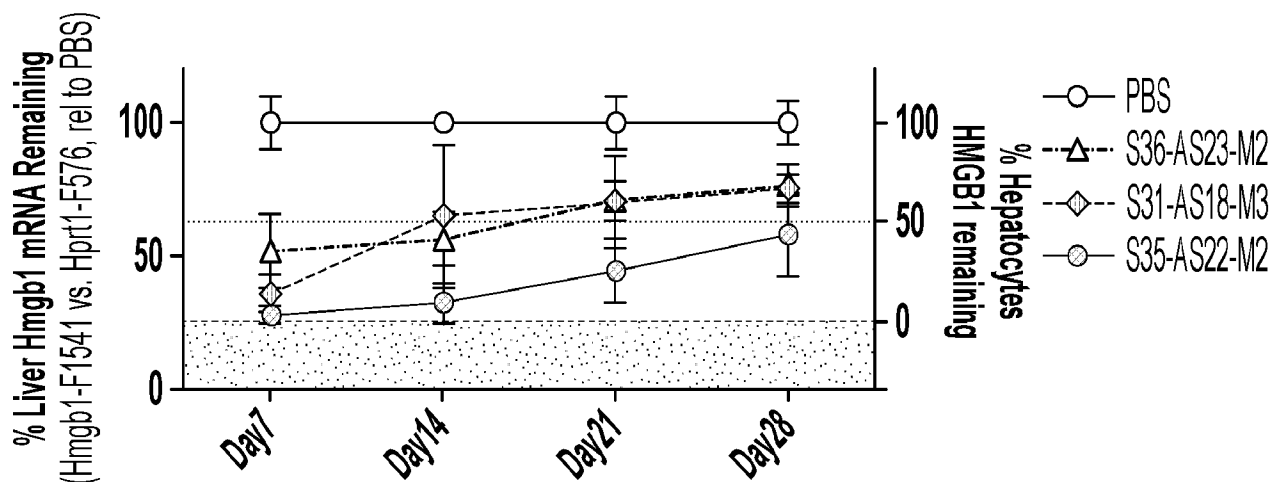
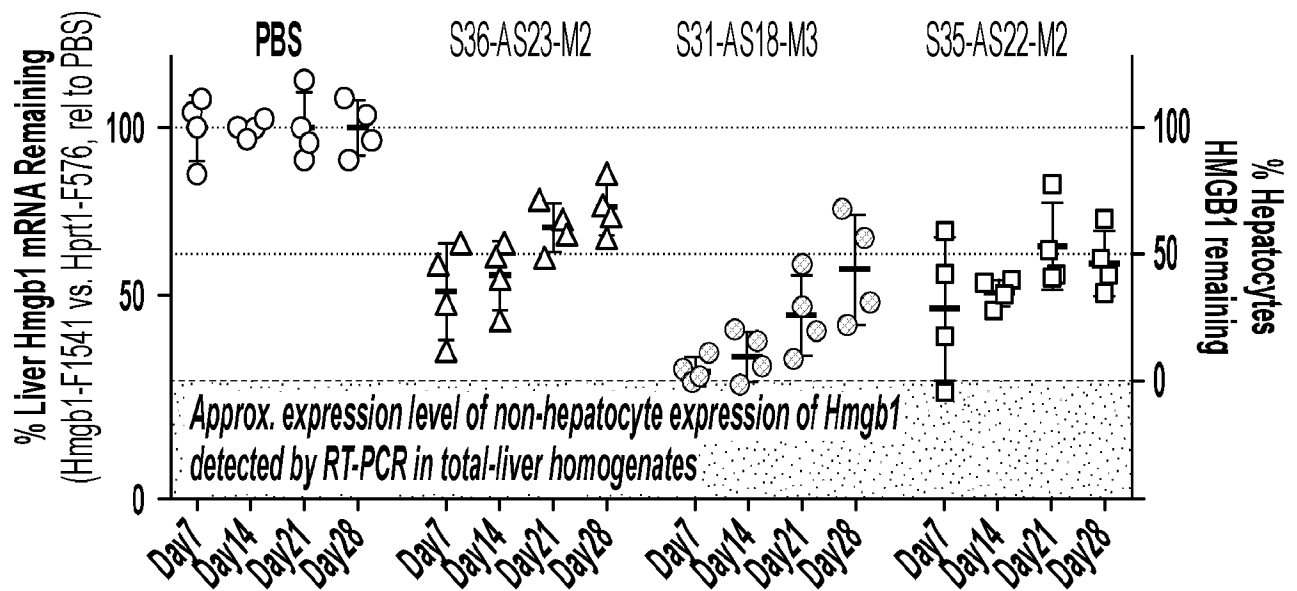
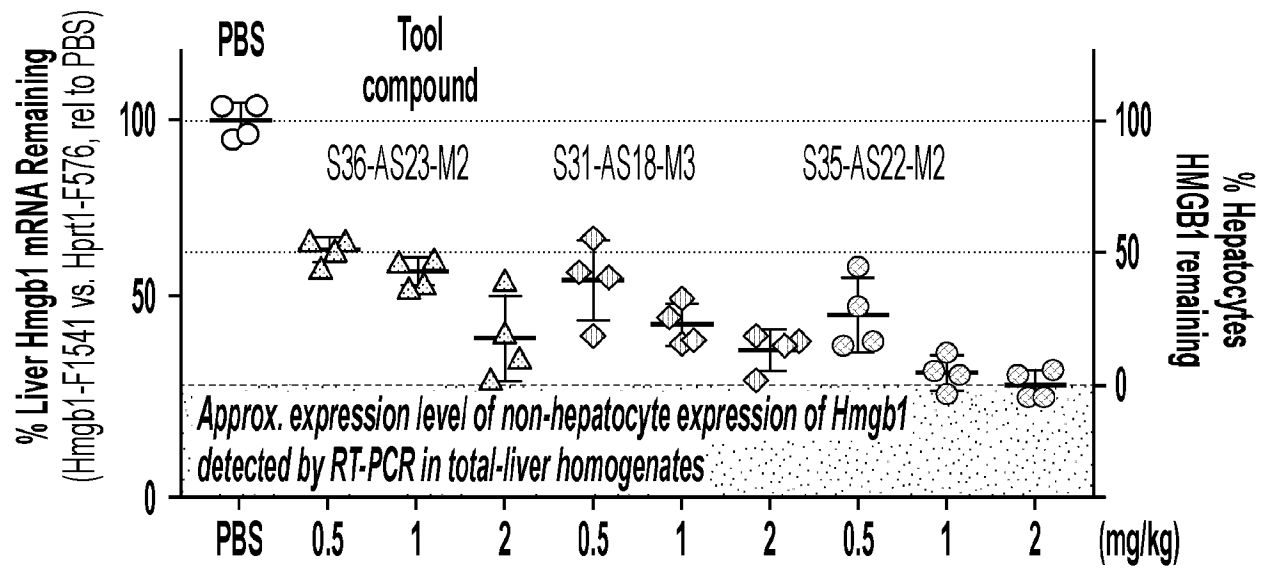


FIG. 3

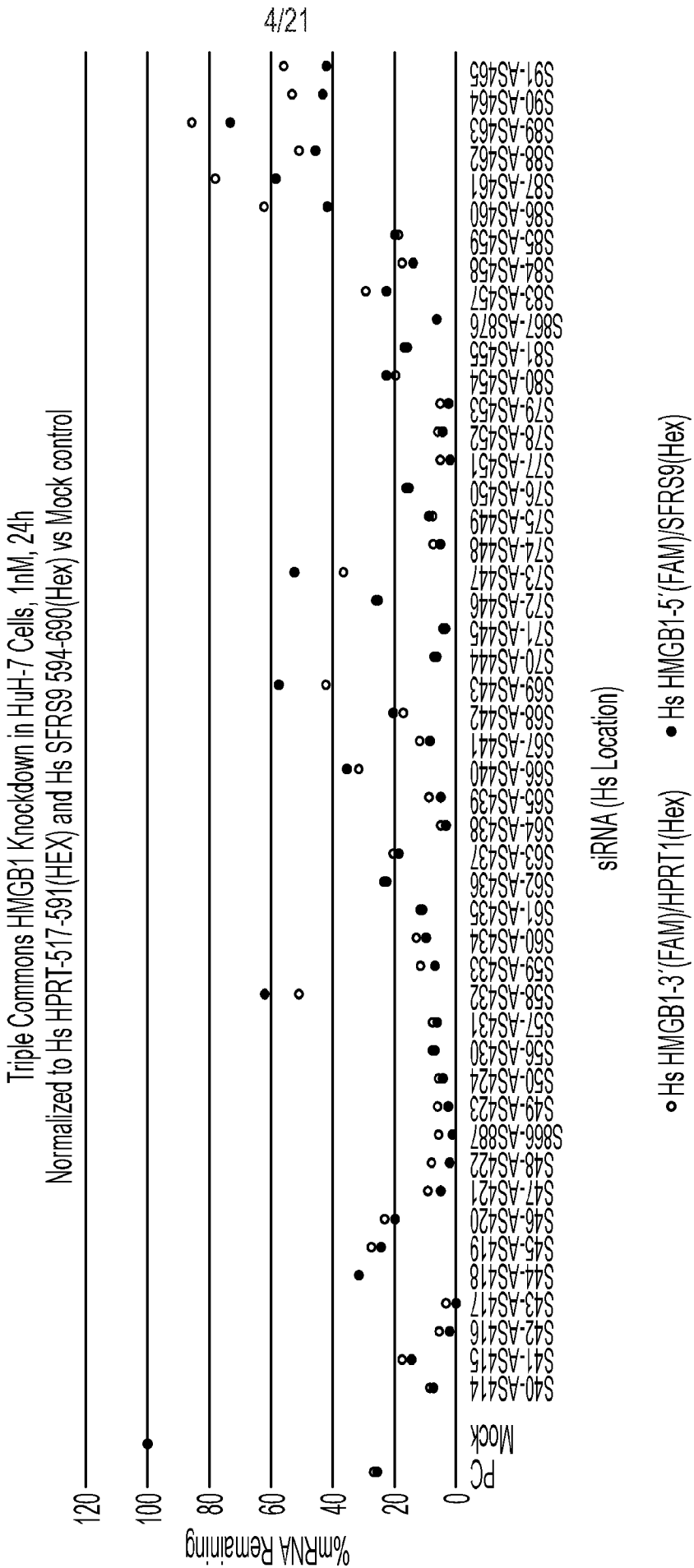


FIG. 4A

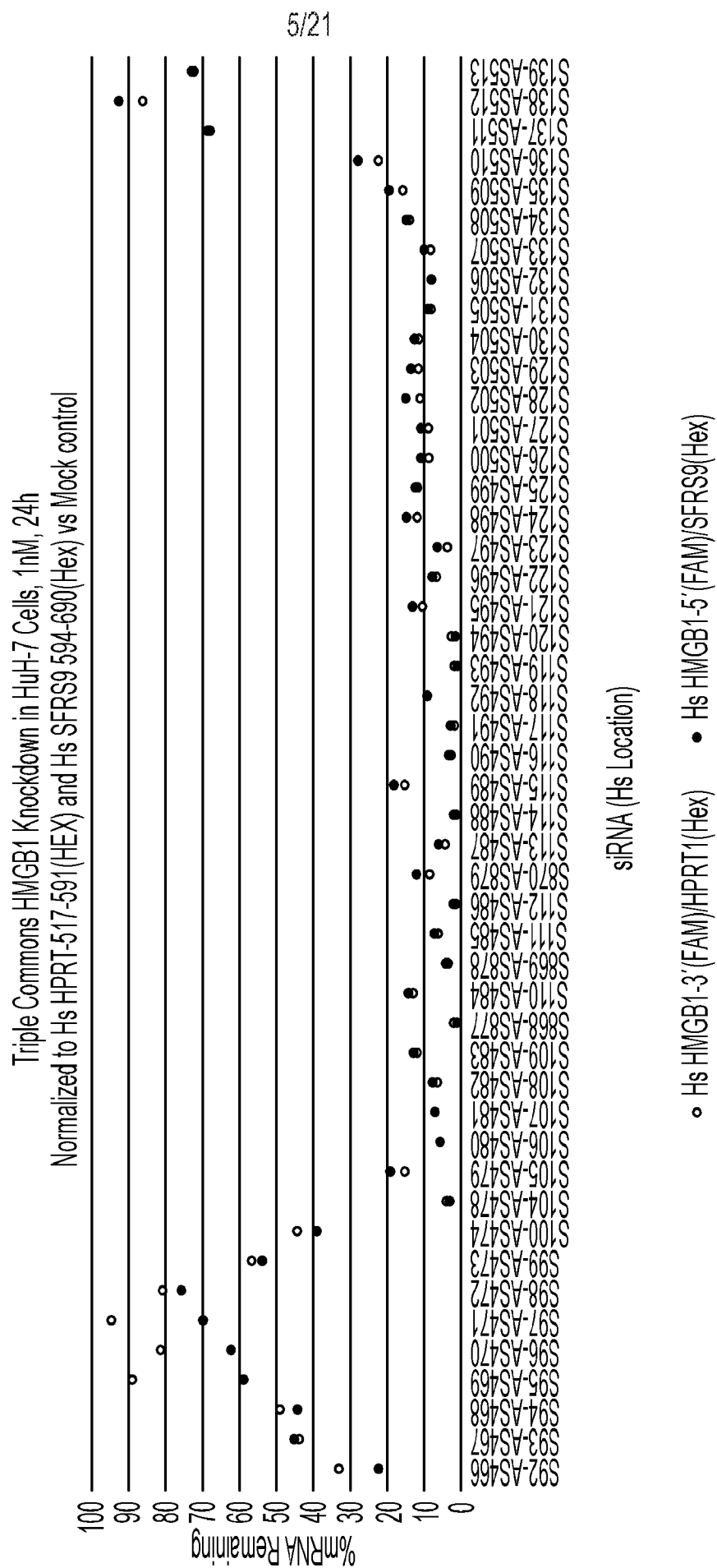


FIG. 4B

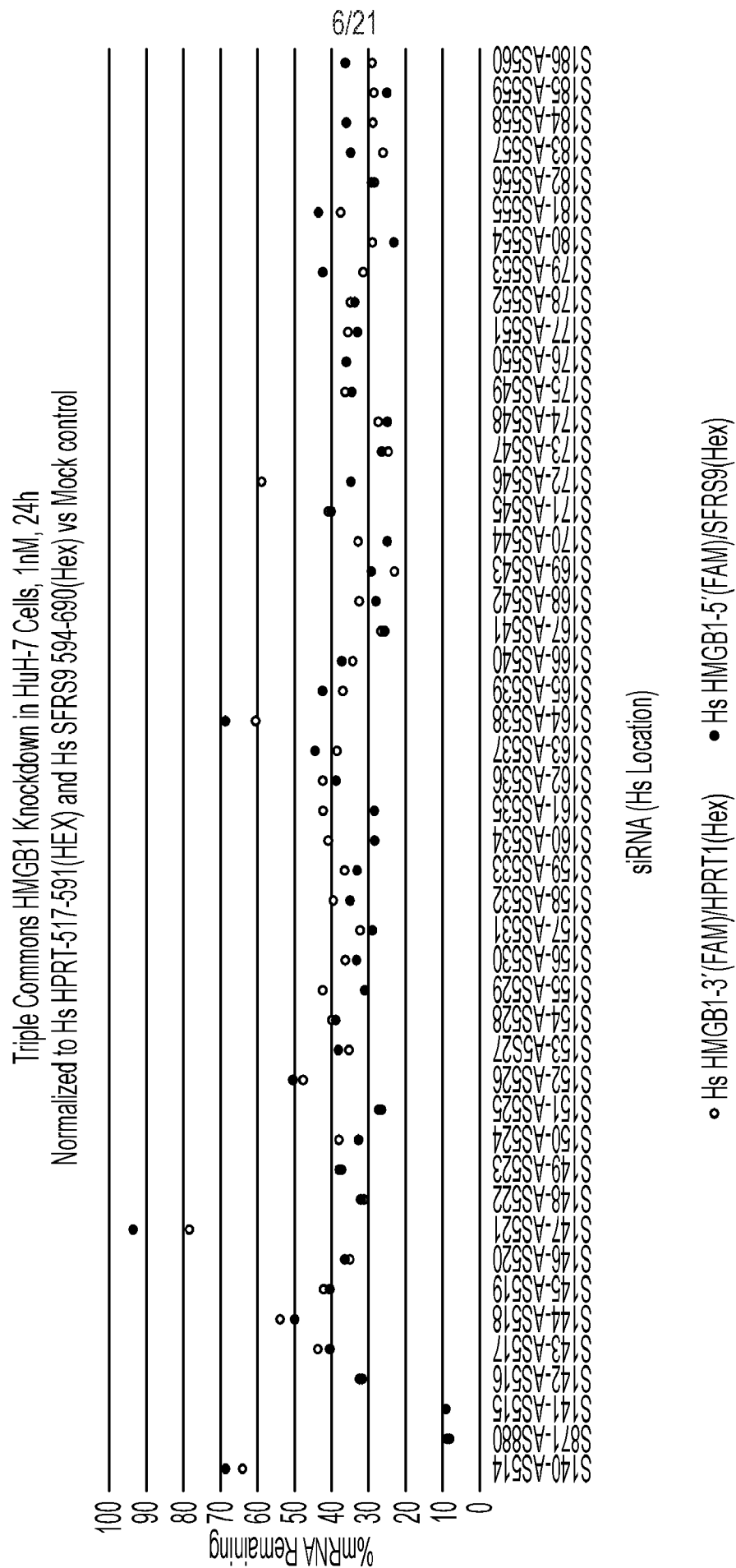


FIG. 4C

Triple Commons HMGB1 Knockdown in HuH-7 Cells, 1nM, 24h
Normalized to Hs HPRT-517-591(HEX) and Hs SFRS9 594-690(HEX) vs Mock control

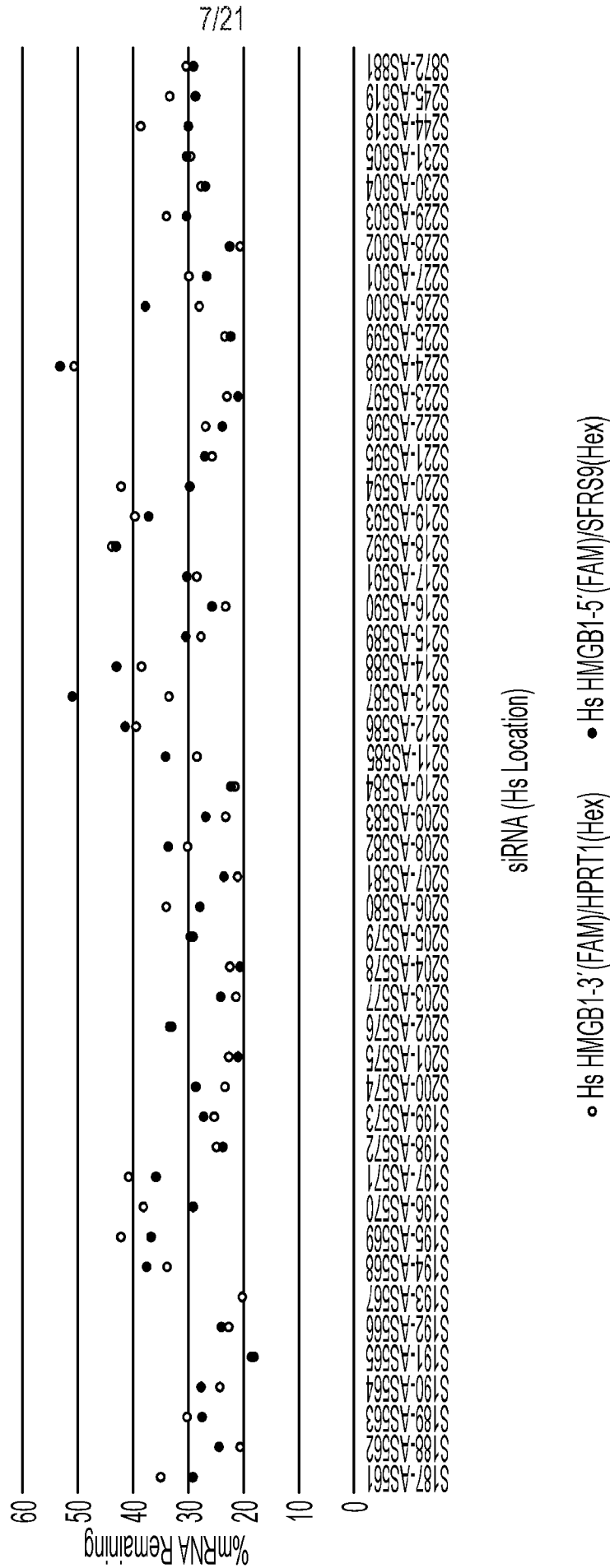


FIG. 4D

Triple Commons HMGB1 Knockdown in HuH-7 Cells, 1nM, 24h
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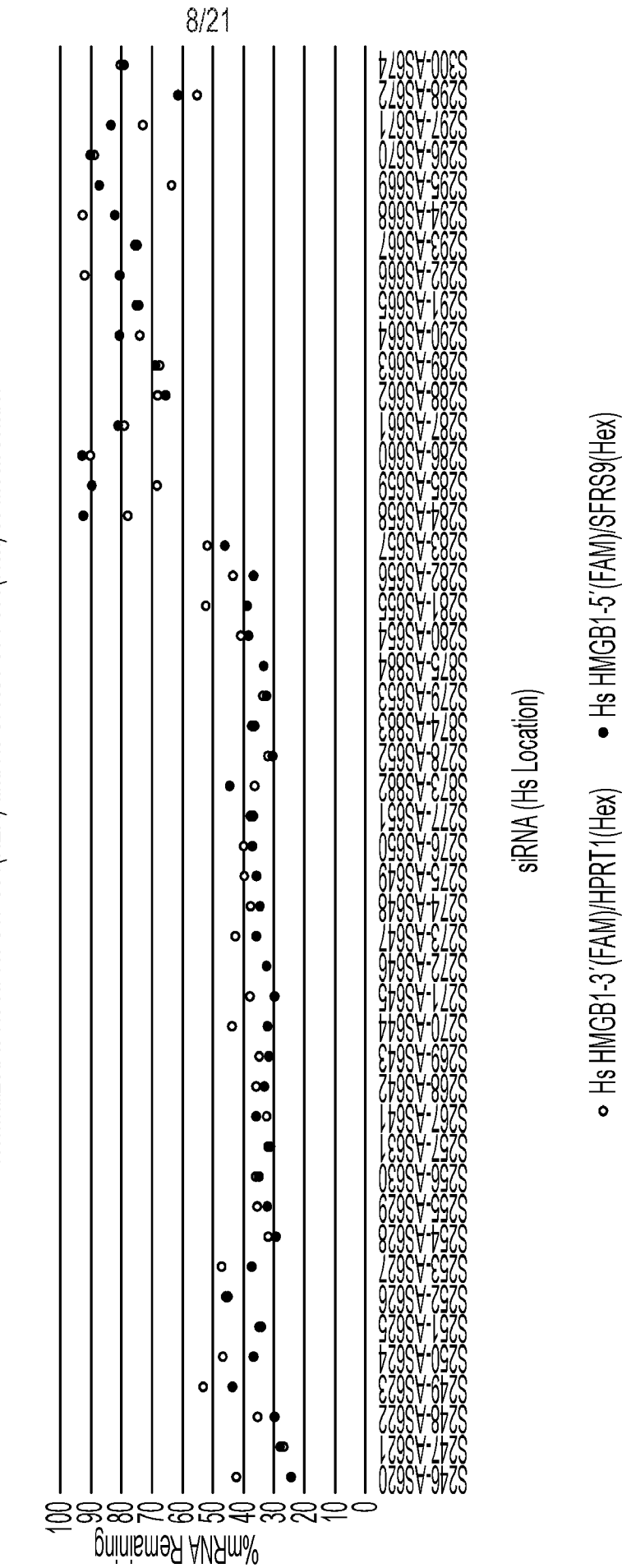


FIG. 4E

Triple Commons HMGB1 Knockdown in HuH-7 Cells, 1nM, 24h
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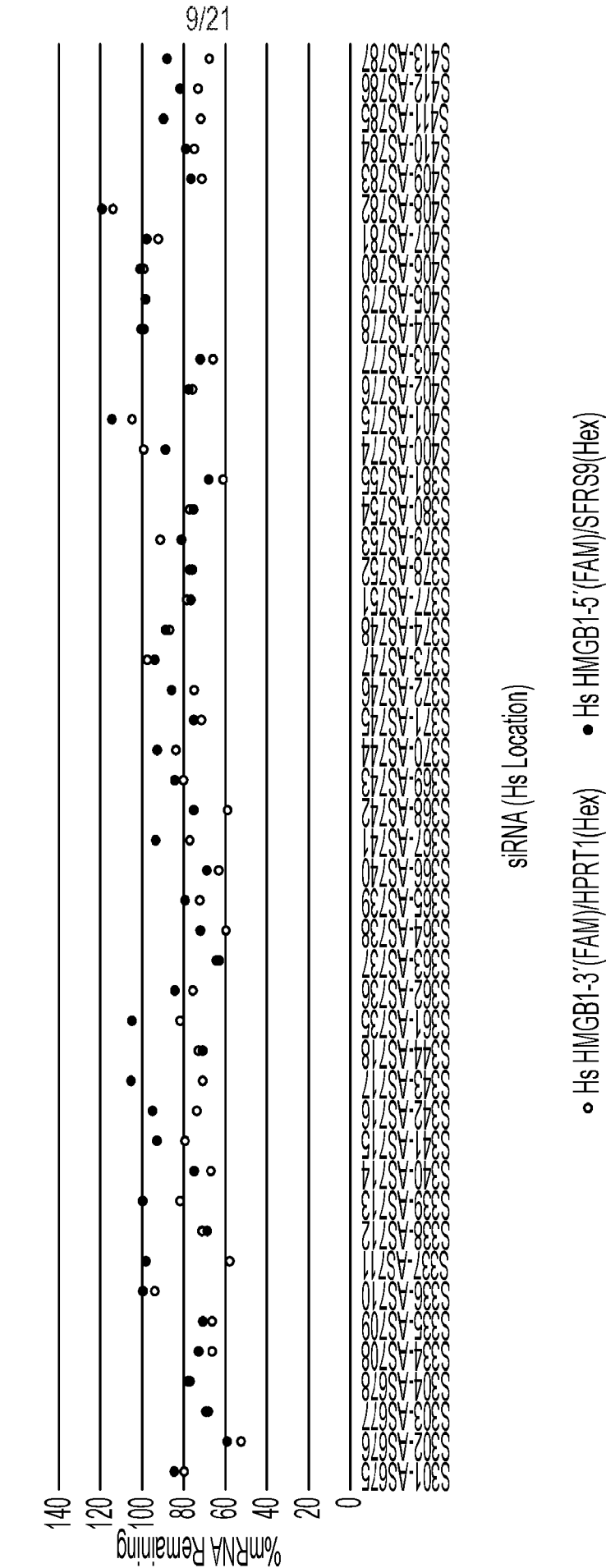
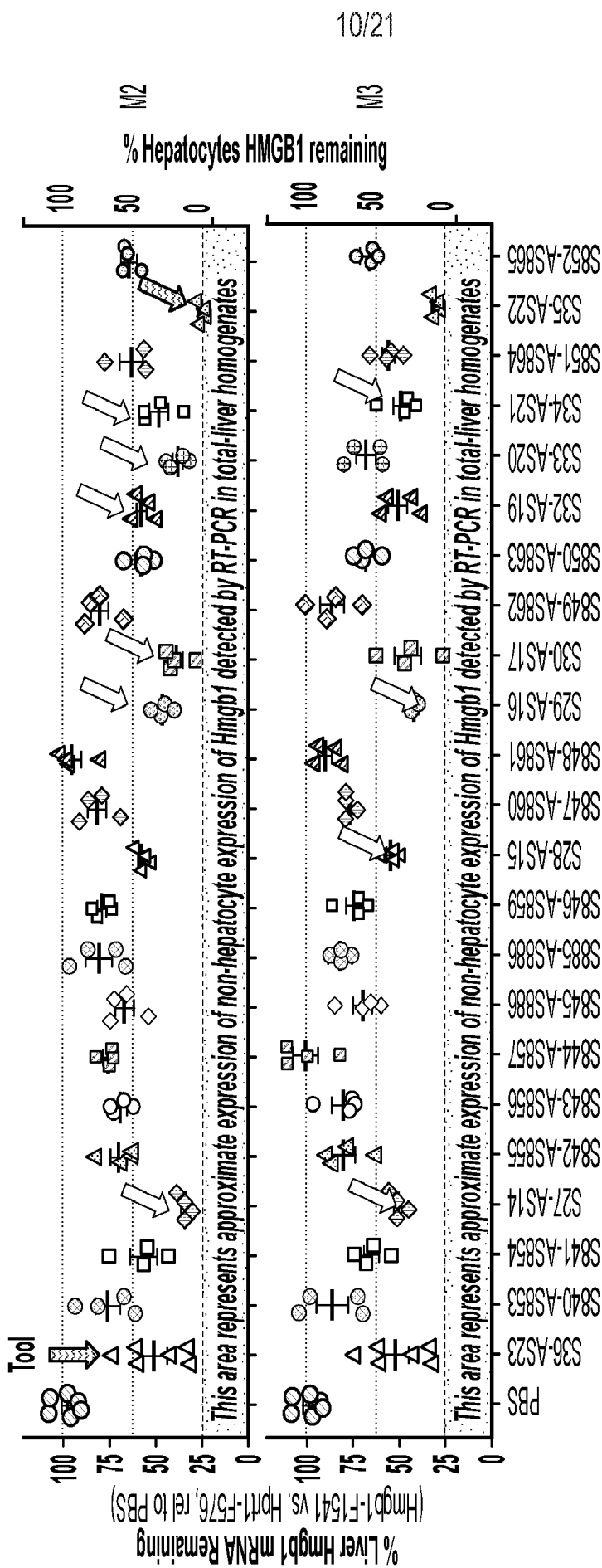


FIG. 4F



GalNAc-conjugated HMGB1 oligonucleotides

FIG. 5

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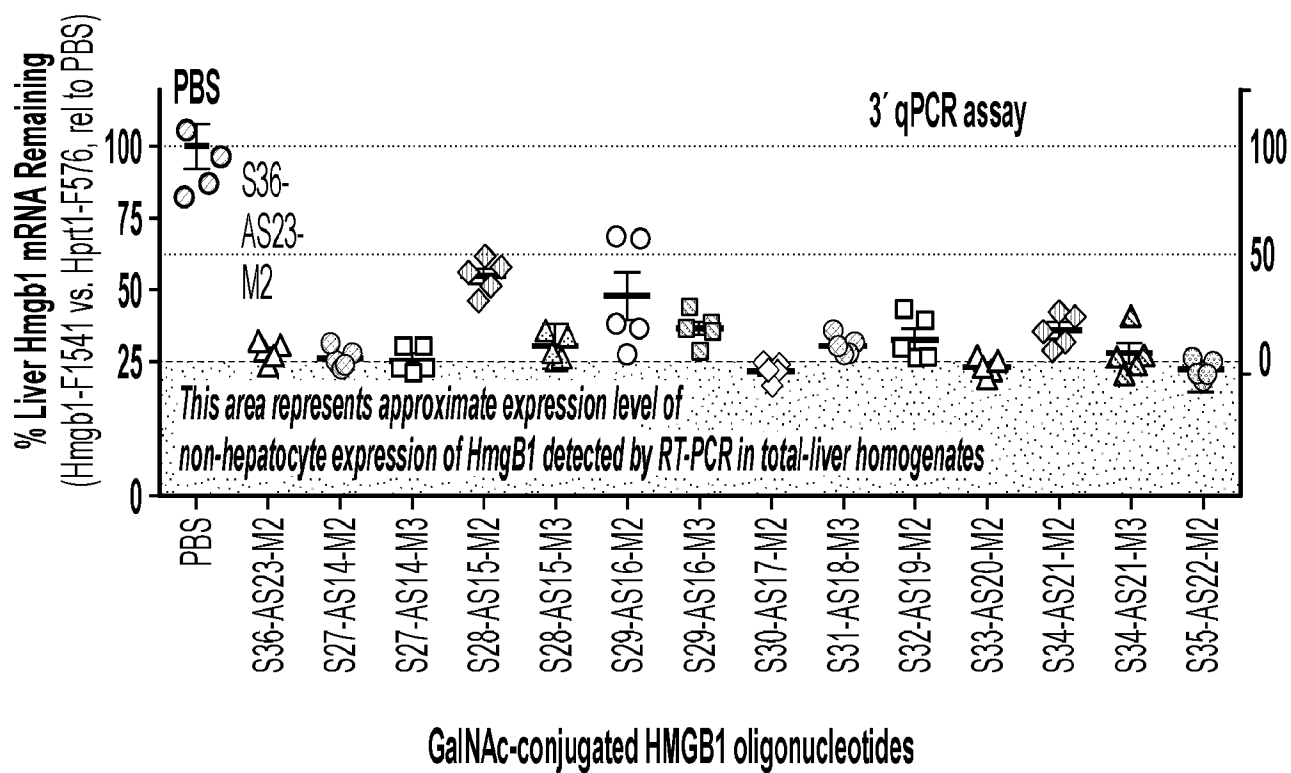


FIG. 6

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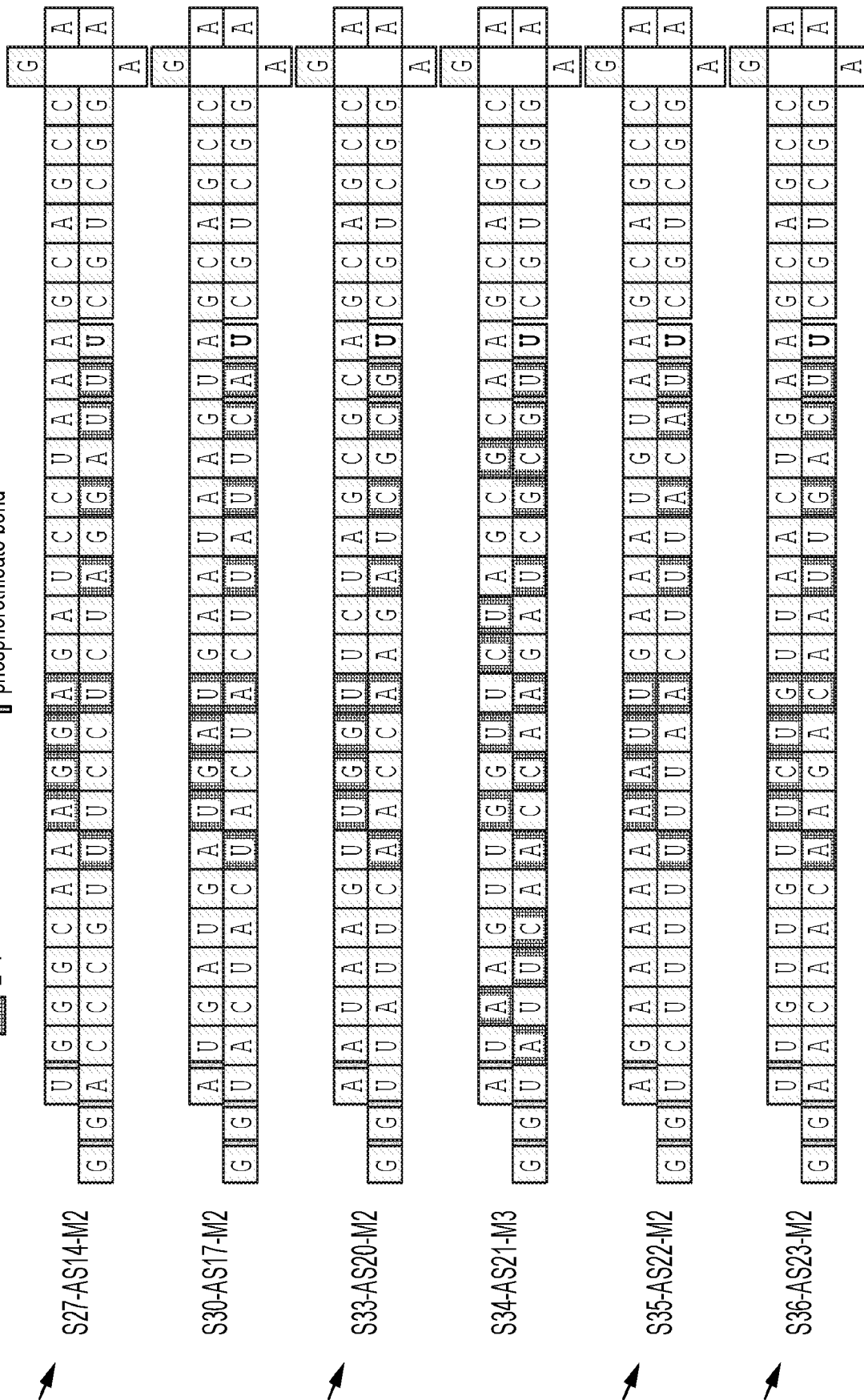
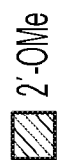


FIG. 7

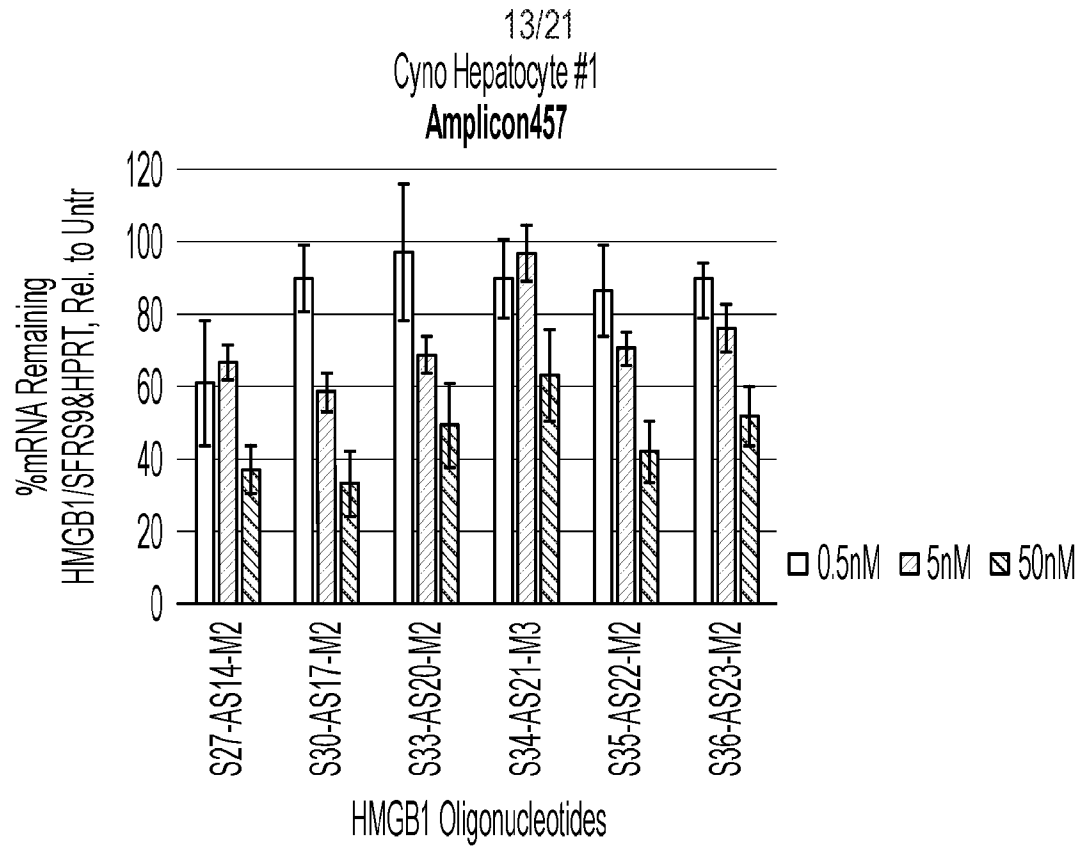


FIG. 8A

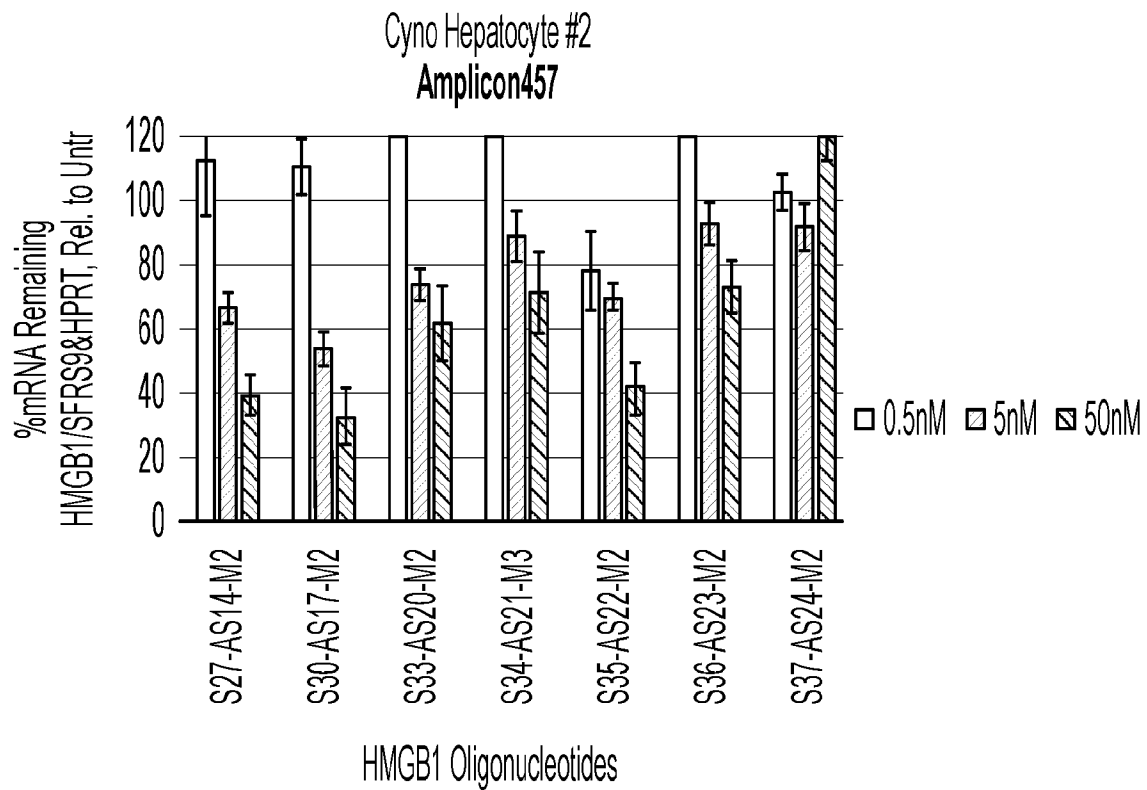


FIG. 8B

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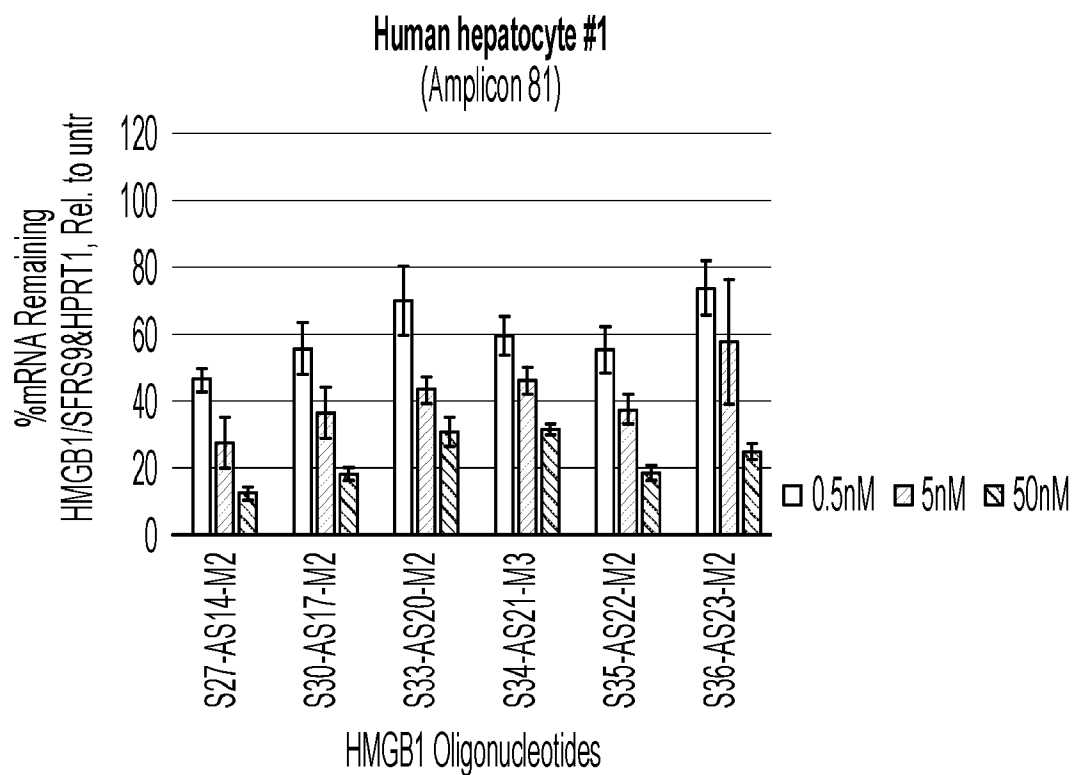


FIG. 8C

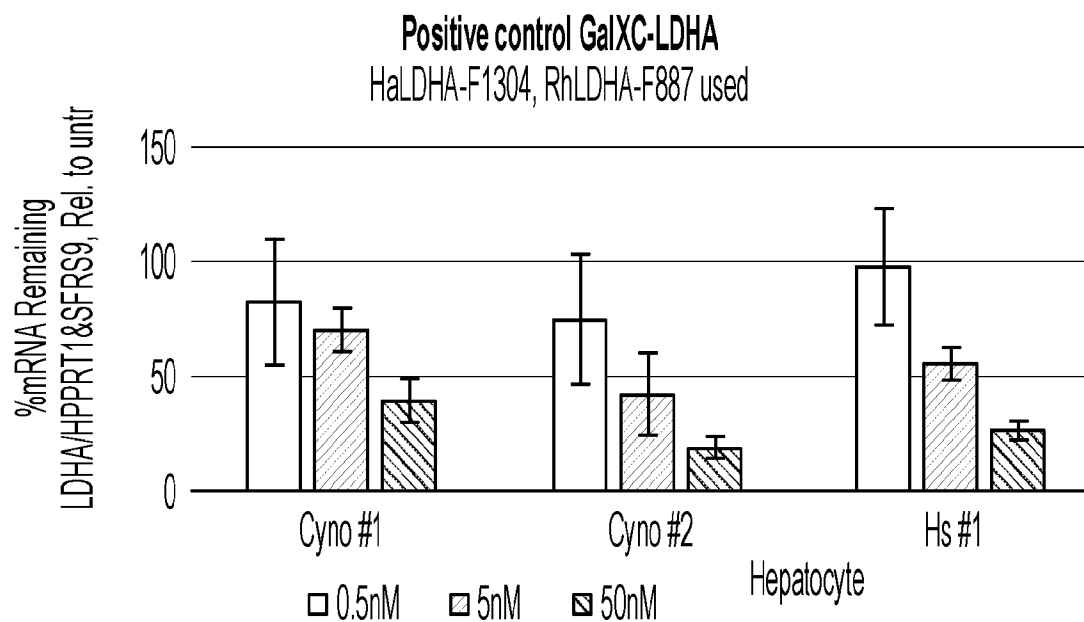


FIG. 8D

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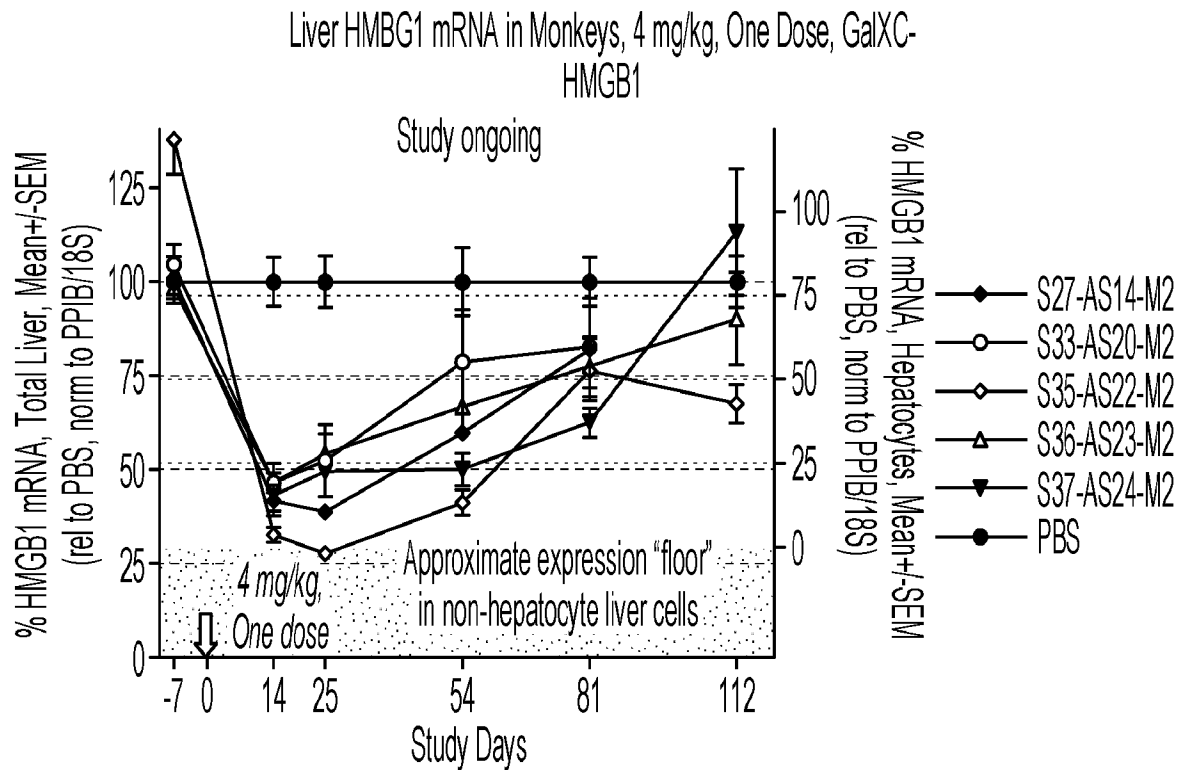


FIG. 9A

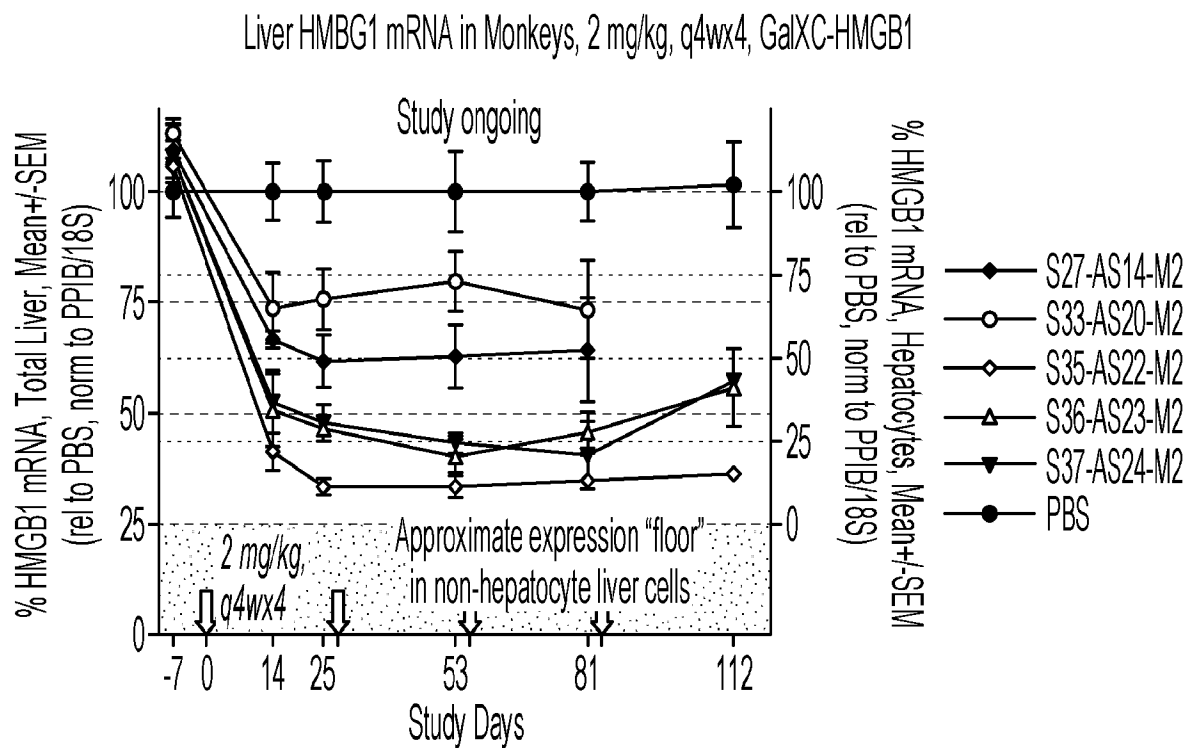


FIG. 9B

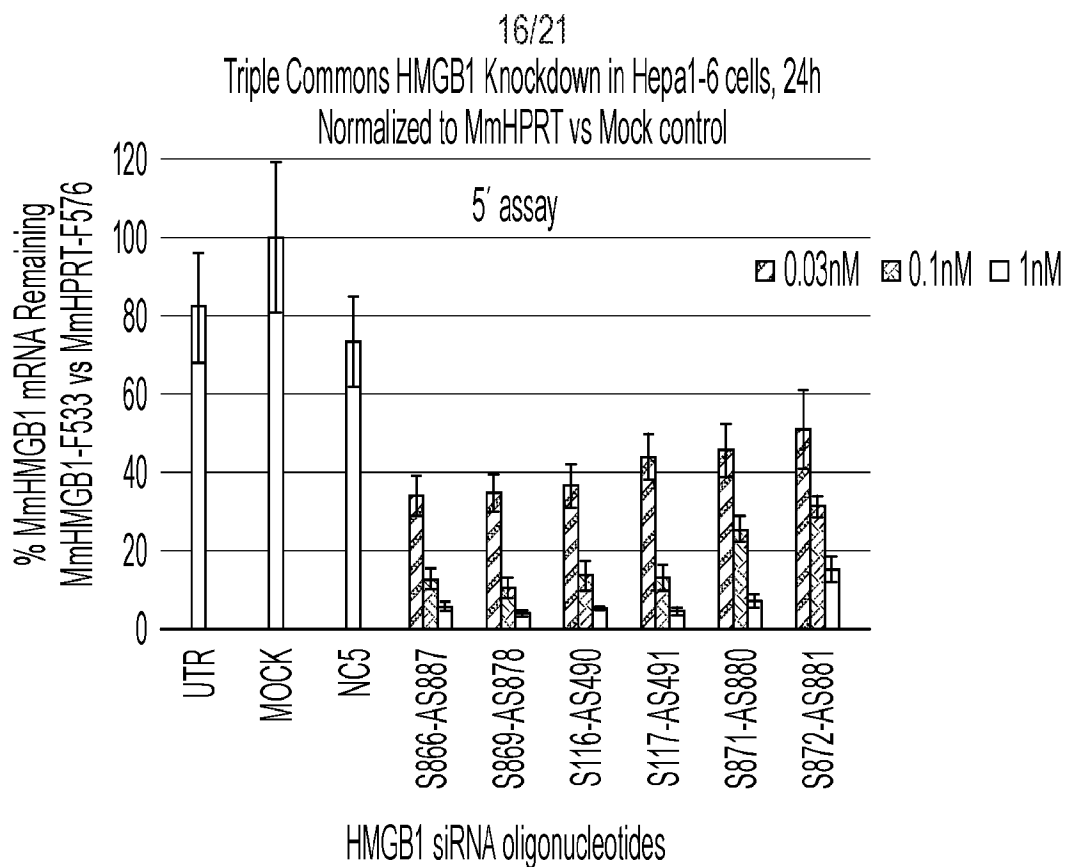


FIG. 10A

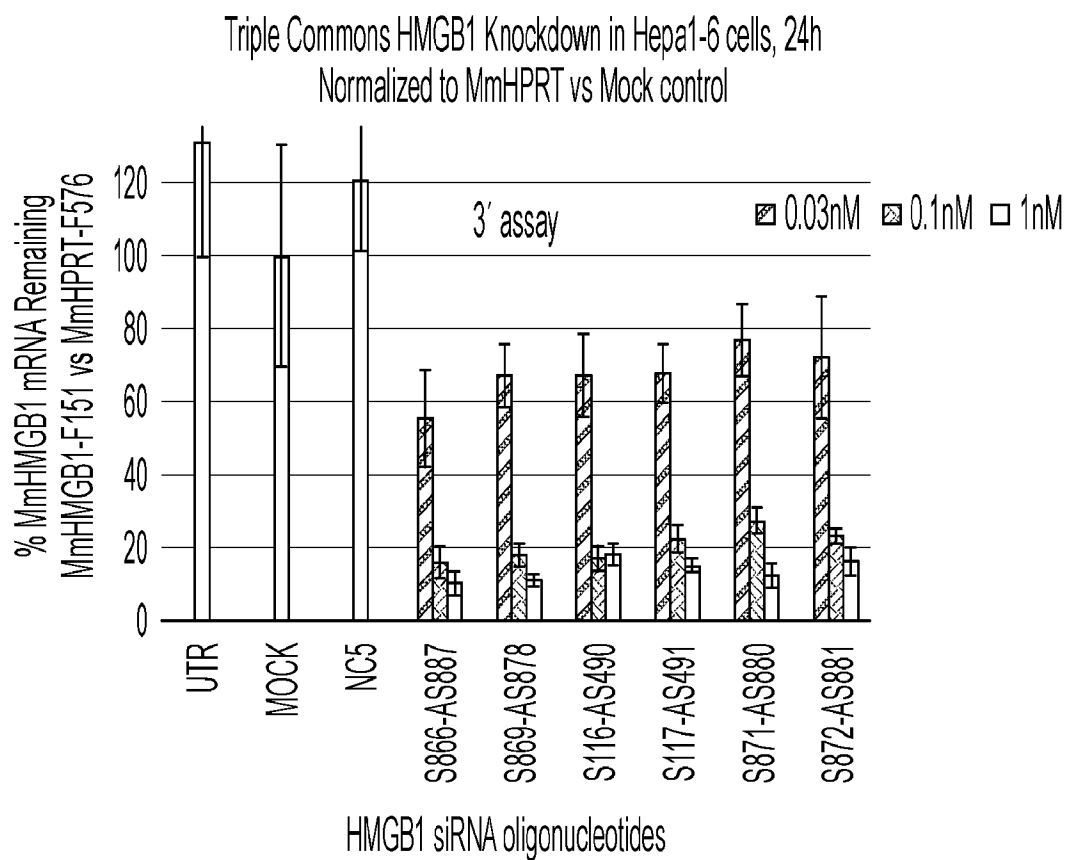


FIG. 10B

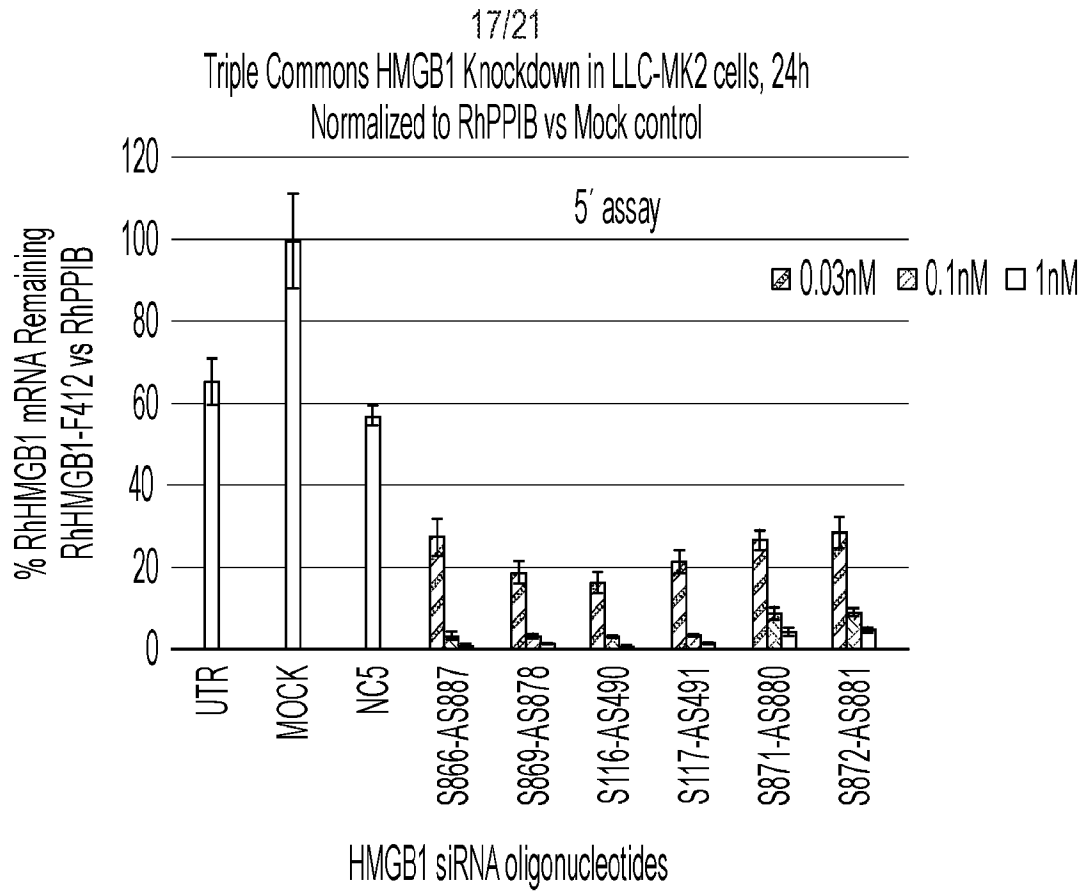


FIG. 10C

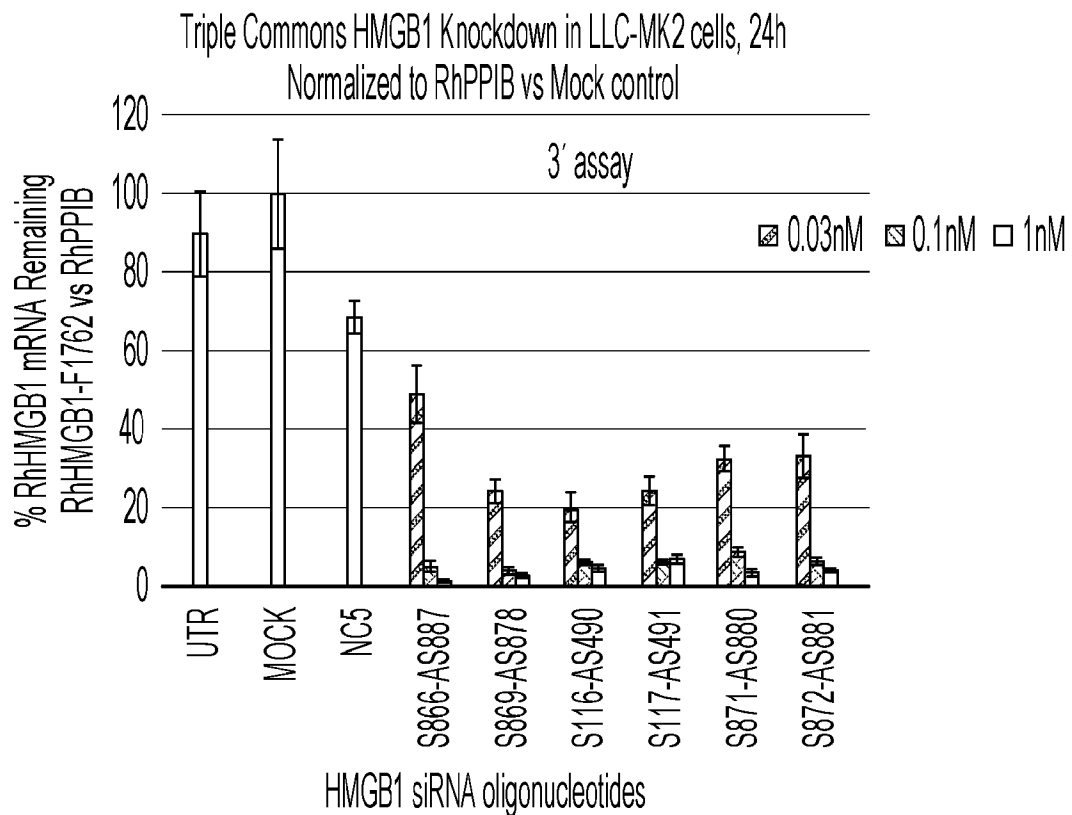


FIG. 10D

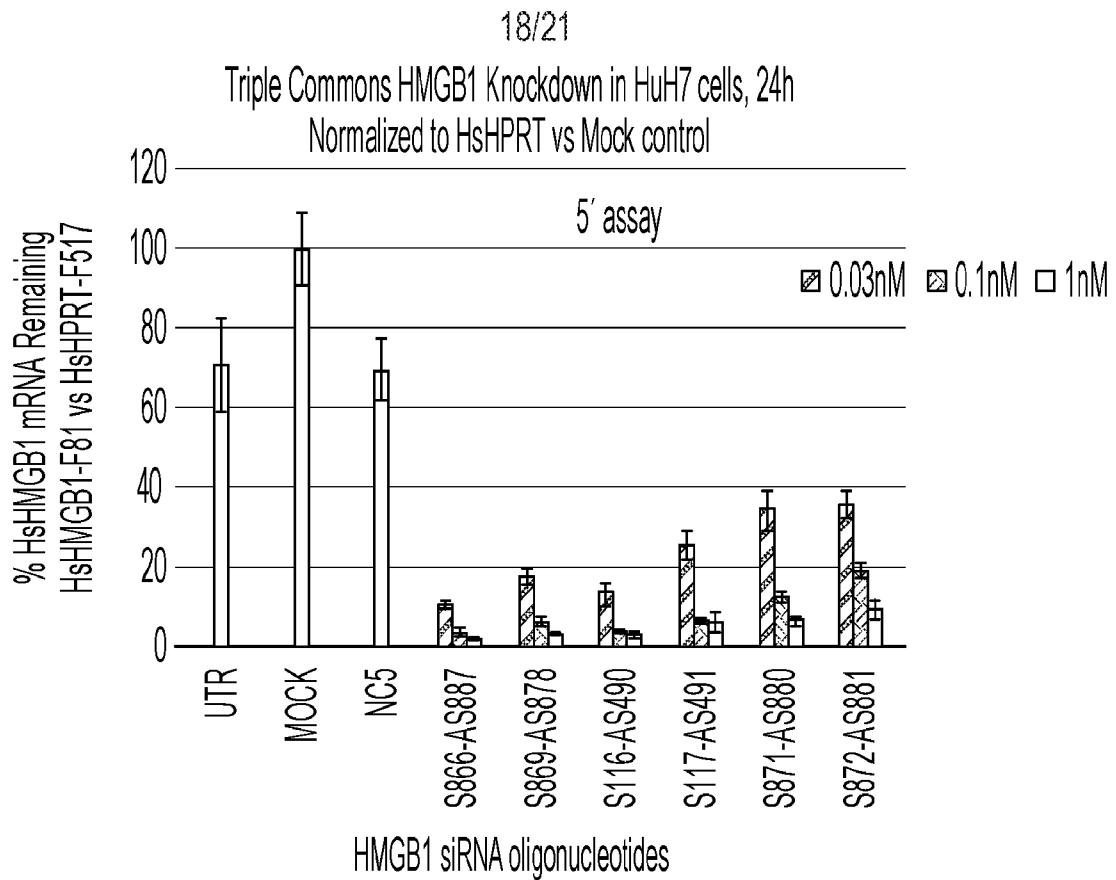


FIG. 10E

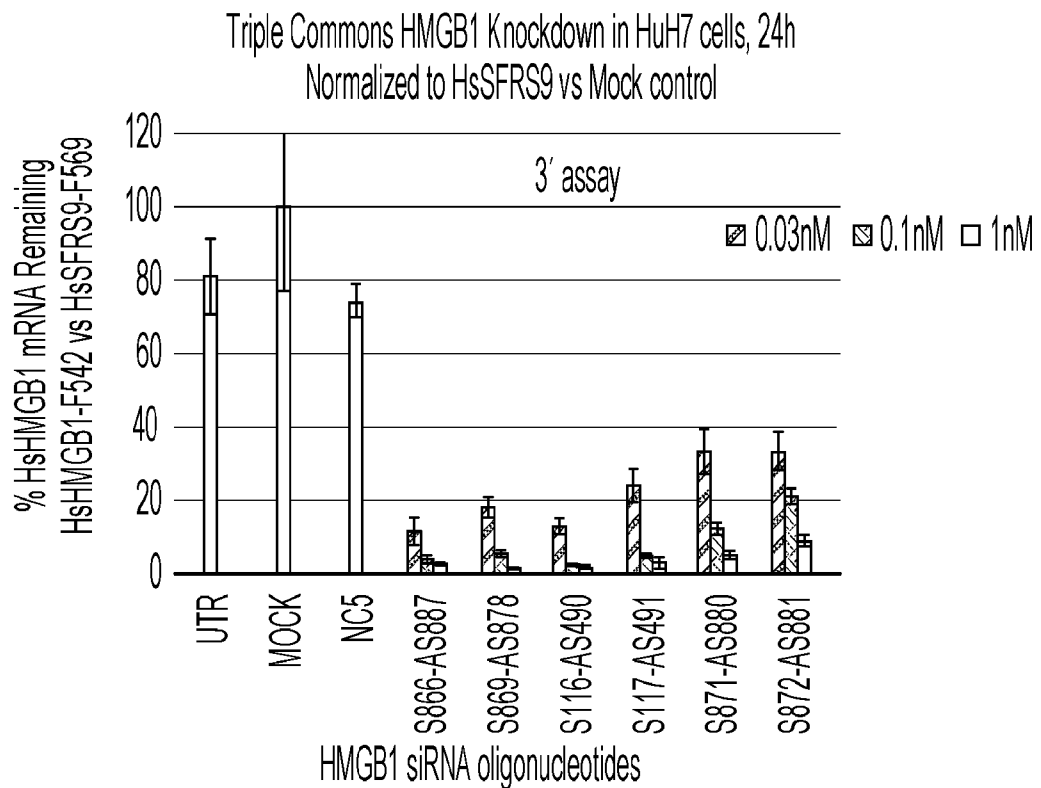


FIG. 10F

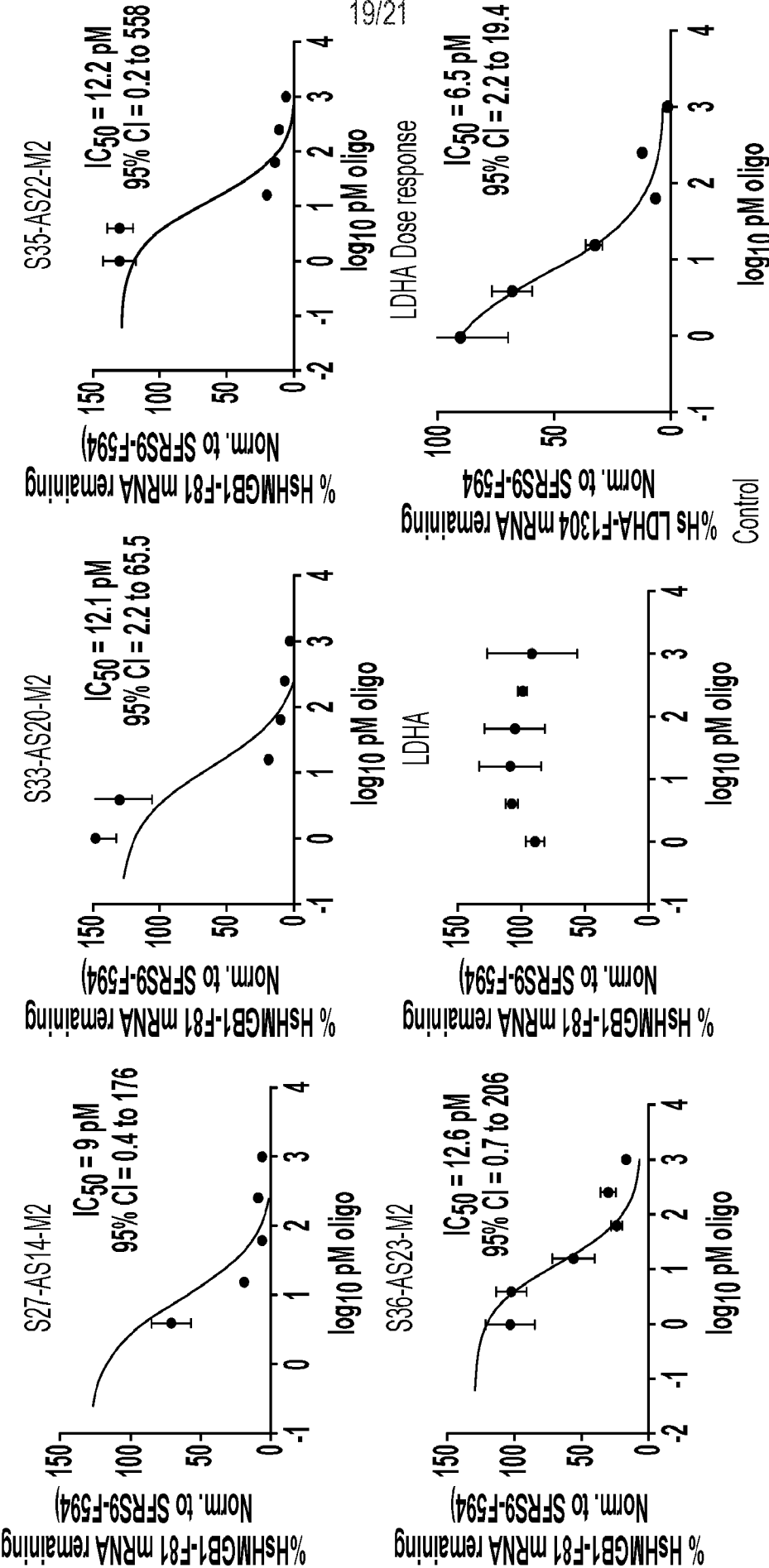


FIG. 11A

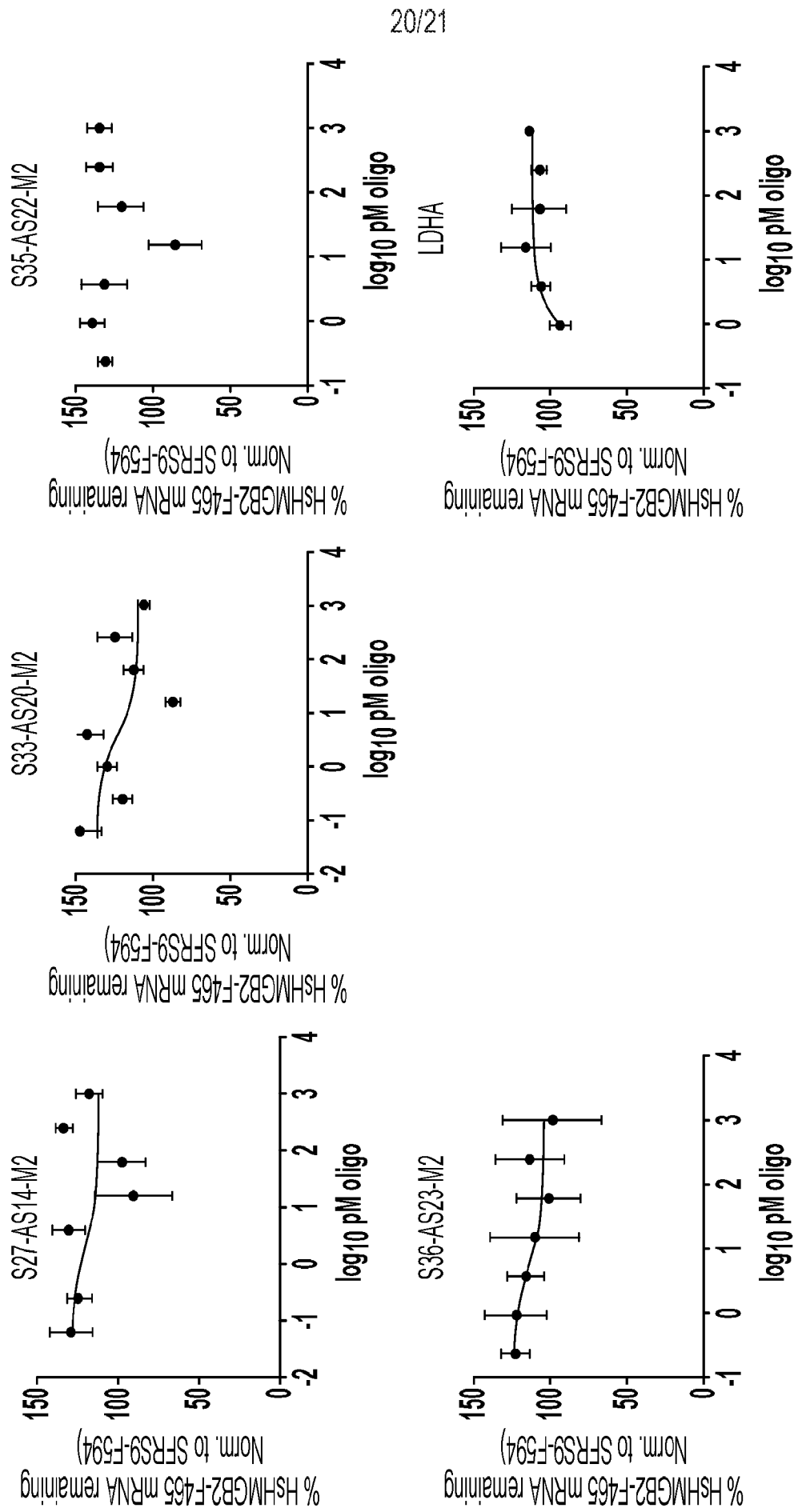


FIG. 11B

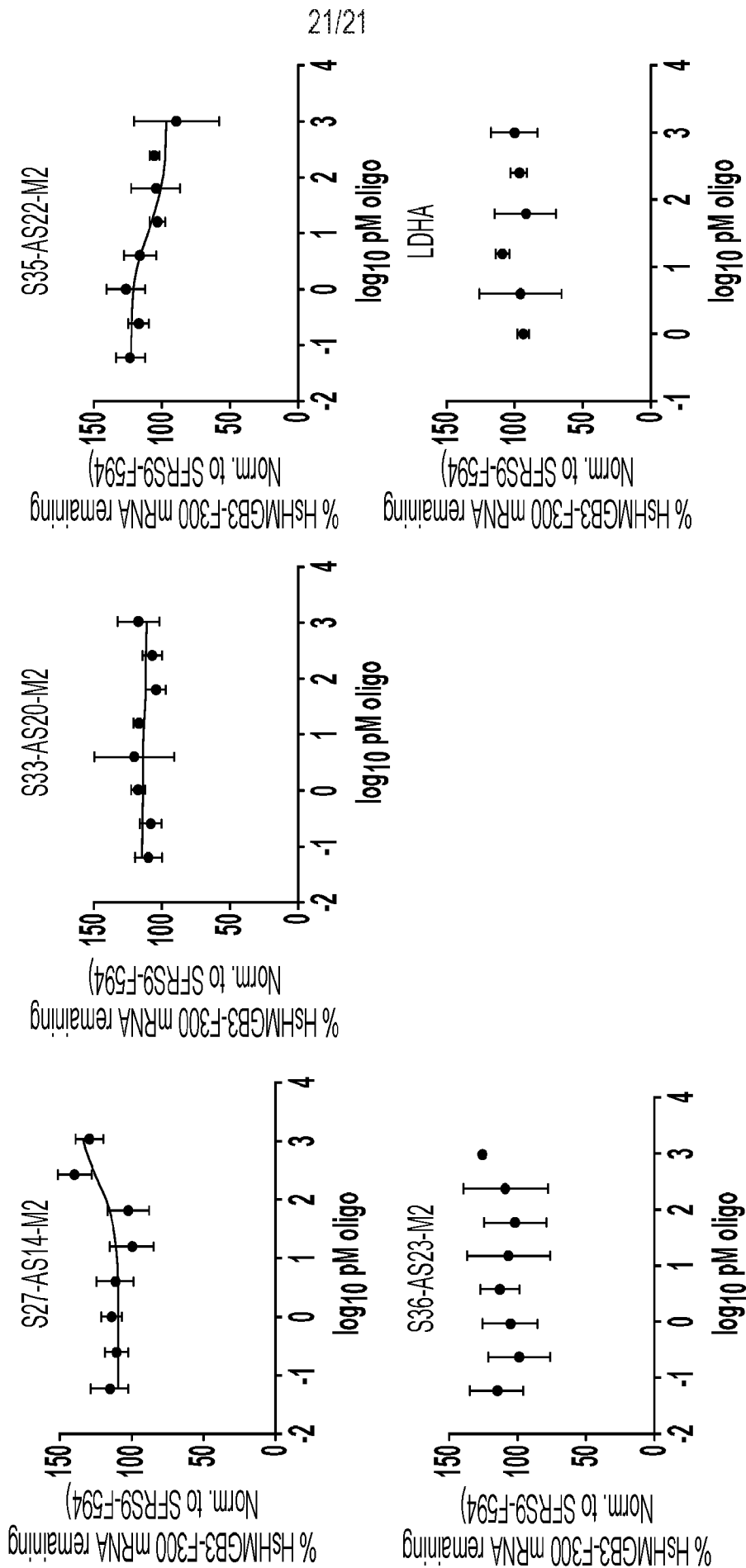


FIG. 11C

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