ovarian, bladder, breast, gastric, and pancreatic cancer (Hamanishi J *et al.* 2007. *Proc. Natl. Acad. Sci. USA* 104:3360–65; Inman BA *et al.* 2007. *Cancer* 109:1499–505; Konishi J *et al.* 2004. *Clin. Cancer Res.* 10:5094–100; Nakanishi J *et al.* 2007. *Cancer Immunol. Immunother.* 56:1173–82; Nomi T *et al.* 2007. *Clin. Cancer Res.* 13:2151–57; Thompson RH *et al.* 2004. *Proc. Natl. Acad. Sci. USA* 101:17174–79; Wu C, Zhu Y, Jiang J, Zhao J, Zhang XG, Xu N. 2006. *Acta Histochem.* 108:19–24). In addition, these studies suggest that higher levels of PD-L1 expression on tumors may facilitate advancement of tumor stage and invasion into deeper tissue structures.

The PD-1 pathway can also play a role in hematologic malignancies. PD-L1 is expressed on multiple myeloma cells but not on normal plasma cells (Liu J *et al.* 2007. *Blood* 110:296–304). PD-L1 is expressed on some primary T cell lymphomas, particularly anaplastic large cell T lymphomas (Brown JA *et al.*, 2003. *J. Immunol.* 170:1257–66). PD-1 is highly expressed on the T cells of angioimmunoblastic lymphomas, and PD-L1 is expressed on the associated follicular dendritic cell network (Dorfman DM *et al.* 2006. *Am. J. Surg. Pathol.* 30:802–10). In nodular lymphocyte-predominant Hodgkin lymphoma, the T cells associated with lymphocytic or histiocytic (L&H) cells express PD-1. Microarray analysis using a readout of genes induced by PD-1 ligation suggests that tumor-associated T cells are responding to PD-1 signals *in situ* in Hodgkin lymphoma (Chemnitz JM *et al.* 2007. *Blood* 110:3226–33). PD-1 and PD-L1 are expressed on CD4 T cells in HTLV-1-mediated adult T cell leukemia and lymphoma (Shimauchi T *et al.* 2007. *Int. J. Cancer* 121: 2585–90). These tumor cells are hyporesponsive to TCR signals.

Studies in animal models demonstrate that PD-L1 on tumors inhibits T cell activation and lysis of tumor cells and in some cases leads to increased tumor-specific T cell death (Dong H *et al.* 2002. *Nat. Med.*8:793–800; Hirano F *et al.* 2005. *Cancer Res.*65:1089–96). Tumor-associated APCs can also utilize the PD-1:PD-L pathway to control antitumor T cell responses. PD-L1 expression on a population of tumor-associated myeloid DCs is upregulated by tumor environmental factors (Curiel TJ *et al.* 2003. *Nat. Med.* 9:562–67). Plasmacytoid dendritic cells (DCs) in the tumor-draining lymph node of B16 melanoma express IDO, which strongly activates the suppressive activity of regulatory T cells. The suppressive activity of IDO-treated regulatory T cells required cell contact with IDO-expressing DCs (Sharma MD *et al.* 2007. *J. Clin. Invest.* 117:2570–82).

Accordingly, there is a need in the art for effective treatments for PD-L1-associated diseases, such as an infectious disease, such as a chronic intracellular infectious disease, *e.g.*, a viral disease, *e.g.*, hepatitis infection, or a bacterial infection, *e.g.,* tuberculosis infection; and cancer, *e.g.*, a hepatic cancer, *e.g.*, hepatocellular carcinoma.

## Summary

In one aspect, the present invention refers to a double stranded ribonucleic acid (RNAi) agent for inhibiting expression of programmed cell death 1 ligand 1 (PD-L1), wherein said RNAi agent comprises a sense strand and an antisense strand, wherein said sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of nucleotides 3221-

3243 of the nucleotide sequence of SEQ ID NO:1 and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the complementary portion of the nucleotide sequence of SEQ ID NO:2, and wherein the RNAi agent comprises at least one modified nucleotide.

In another aspect, the present invention refers to a pharmaceutical composition for inhibiting expression of a PD-L1 gene comprising the RNAi agent of the present invention.

In yet another aspect, the present invention refers to the use of an RNAi agent of the present invention or the pharmaceutical composition of the present invention in the manufacture of a medicament for treating a subject having a disease or disorder that would benefit from reduction in PD-L1.

The present disclosure provides iRNA compositions which affect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a PD-L1 gene. The PD-L1 gene may be within a cell, *e.g.,* a cell within a subject, such as a human.

Accordingly, in one example, the disclosure provides a double stranded ribonucleic acid (RNAi) agent for inhibiting expression of programmed cell death 1 ligand 1 (PD-L1), wherein the RNAi comprises a sense strand and an antisense strand, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2.

In certain examples, the sense strands and antisense strands comprise sequences selected from any of the sequences in Table 3. In other examples, the sense strands and antisense strands comprise sequences selected from any of the sequences in Table 5.

In an example, the disclosure provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of programmed cell death 1 ligand 1 (PD-L1), wherein the RNAi comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in Table 3. In certain examples, the sense strands and antisense strands comprise sequences selected from any of the sequences in Table. 5

In certain examples, the RNAi comprises at least one modified nucleotide. In some examples, substantially all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification. In some examples, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

In one example, the present disclosure provides double stranded ribonucleic acid (RNAi) agents for inhibiting expression of programmed cell death 1 ligand 1 (PD-L1), wherein the RNAi agents comprise a sense strand and an antisense strand, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of nucleotides 3221-3243, 351-372, 618-641, 618-639, 619-640, 620-641, 1093-1115, 1093-1114, 1094-1115, 1167-1188, 1293-1314, 1518-1539, 2103-2124, 2220-2261, 2220-2241, 2240-2261, 2648-2680, 2648-2669, 2658-2679, 2659-2680, 3143-3164, 3198-3219, 3221-3242, or 3222-3243 of the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the complementary portion of the nucleotide sequence of SEQ ID NO:2, and wherein the RNAi agent comprises at least one modified nucleotide.

In another example, the present disclosure provides double stranded ribonucleic acid (RNAi) agents for inhibiting expression of programmed cell death 1 ligand 1 (PD-L1), wherein the RNAi agents comprise a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences in any one of the duplexes AD-67635, AD-67637, AD-67658, AD-67632, AD-67629, AD-67631, AD-67633, AD-67643, AD-67653, AD-67640, AD-67650, AD-67676, AD-67661, AD-67667, AD-67655, AD-67672, AD-67659, AD-67673, AD-67664, AD-67662, AD-67660, AD-67656, AD-67628, AD-67647, AD-67626, or AD-67645.

In one example, the sense and antisense strands comprise nucleotide sequences selected from the group consisting of any one of the nucleotide sequences in any one of the duplexes AD-67635, AD-67637, AD-67658, AD-67632, AD-67629, AD-67631, AD-67633, AD-67643, AD-67653, AD-67640, AD-67650, AD-67676, AD-67661, AD-67667, AD-67655, AD-67672, AD-67659, AD-67673, AD-67664, AD-67662, AD-67660, AD-67656, AD-67628, AD-67647, AD-67626, or AD-67645.

In one example, the disclosure provides a double stranded RNAi agent for inhibiting expression of programmed cell death 1 ligand 1 (PD-L1), wherein the double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2, wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, and wherein the sense strand is conjugated to a ligand attached at the 3'-terminus.

In one example, the present disclosure provides double stranded RNAi agents for inhibiting expression of PD-L1, which comprise a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from nucleotides 3221-3243, 351-372, 618-641, 618-639, 619-640, 620-641, 1093-1115, 1093-1114, 1094-1115, 1167-1188, 1293-1314, 1518-1539, 2103-2124, 2220-2261, 2220-2241, 2240-2261, 2648-2680, 2648-2669, 2658-2679, 2659-2680, 3143-3164, 3198-3219,3221-3242, or 3222-3243 of the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the complementary corresponding position of the nucleotide sequence of SEQ ID NO:2 such that the antisense strand is complementary to the at least 15 contiguous nucleotides differing by no more than 3 nucleotides in the sense strand.

In certain examples, the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from nucleotides 3221-3243, 351-372, 1093-1115, 1093-1114, 1094-1115, 1167-1188, 1293-1314, 1518-1539, 2103-2124, 2220-2261, 2220-2241, 2240-2261, 2648-2680, 2648-2669, 2658-2679, 2659-2680, 3143-3164, 3198-3219, 3221-3242, or 3222-3243 of the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the complementary corresponding position of the nucleotide sequence of SEQ ID NO:2 such that the antisense strand is complementary to the at least 15 contiguous nucleotides differing by no more than 3 nucleotides in the sense strand.

In certain examples, the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from nucleotides 3221-3243, 1093-1115, 1093-1114, 1094-1115, 3221-3242, or 3222-3243 of the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the complementary corresponding position of the nucleotide sequence of SEQ ID NO:2 such that the antisense strand is

complementary to the at least 15 contiguous nucleotides differing by no more than 3 nucleotides in the sense strand.

In another example, the present disclosure provides double stranded ribonucleic acid (RNAi) agents for inhibiting expression of programmed cell death 1 ligand 1 (PD-L1), wherein the double stranded RNAi agents comprise a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of nucleotides 3221-3243, 351-372, 618-641, 618-639, 619-640, 620-641, 1093-1115, 1093-1114, 1094-1115, 1167-1188, 1293-1314, 1518-1539, 2103-2124, 2220-2261, 2220-2241, 2240-2261, 2648-2680, 2648-2669, 2658-2679, 2659-2680, 3143-3164, 3198-3219, 3221-3242, or 3222-3243 of the nucleotide sequence of SEQ ID NO:1 and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the complementary portion of the nucleotide sequence of SEQ ID NO:2, wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand comprise nucleotide modifications, and wherein the sense strand is conjugated to a ligand attached at the 3'-terminus.

In certain examples, substantially all of the nucleotides of the sense strand or substantially all of the nucleotides of the antisense strand are modified nucleotides, or substantially all of the nucleotides of both strands are modified; and wherein the sense strand is conjugated to a ligand attached at the 3'-terminus.

In one example, the present disclosure provides double stranded RNAi agents for inhibiting expression of PD-L1, which comprise a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides from nucleotides 3221-3243, 351-372, 618-641, 618-639, 619-640, 620-641, 1093-1115, 1093-1114, 1094-1115, 1167-1188, 1293-1314, 1518-1539, 2103-2124, 2220-2261, 2220-2241, 2240-2261, 2648-2680, 2648-2669, 2658-2679, 2659-2680, 3143-3164, 3198-3219, 3221-3242, or 3222-3243 of the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides from the complementary corresponding position of the nucleotide sequence of SEQ ID NO:2 such that the antisense strand is complementary to the at least 15 contiguous nucleotides in the sense strand.

In certain embodimetns, the agents comprise a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides from nucleotides 3221-3243, 351-372, 1093-1115, 1093-1114, 1094-1115, 1167-1188, 1293-1314, 1518-1539, 2103-2124, 2220-2261, 2220-2241, 2240-2261, 2648-2680, 2648-2669, 2658-2679, 2659-2680, 3143-3164, 3198-3219, 3221-3242, or 3222-3243 of the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides from the complementary corresponding position of the nucleotide sequence of SEQ ID NO:2 such that the antisense strand is complementary to the at least 15 contiguous nucleotides in the sense strand.

In certan examples, the agents comprise a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides from

nucleotides 3222-3243 1093-1115, 1093-1114, 1094-1115, 3221-3243, or 3221-3242, of the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides from the complementary corresponding position of the nucleotide sequence of SEQ ID NO:2 such that the antisense strand is complementary to the at least 15 contiguous nucleotides in the sense strand. In certain examples, substantially all of the nucleotides of the sense strand are modified nucleotides. In certain examples, substantially all of the nucleotides of the antisense strand are modified nucleotides. In certain examples, substantially all of the nucleotides of both strands are modified. In preferred examples, the sense strand is conjugated to a ligand attached at the 3'-terminus.

In certain examples, the sense strand and the antisense strand comprise a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in any one of Tables 3 and 5. For example, in certain example, the sense strand and the antisense strand comprise a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences of the duplexes AD-67635, AD-67637, AD-67658, AD-67632, AD-67629, AD-67631, AD-67633, AD-67643, AD-67653, AD-67640, AD-67650, AD-67676, AD-67661, AD-67667, AD-67655, AD-67672, AD-67659, AD-67673, AD-67664, AD-67662, AD-67660, AD-67656, AD-67628, AD-67647, AD-67626, or AD-67645. In certain examples, the sense strand and the antisense strand comprise a region of complementarity which comprises at least 15 contiguous nucleotides of any one of the antisense sequences of the foregoing duplexes.

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

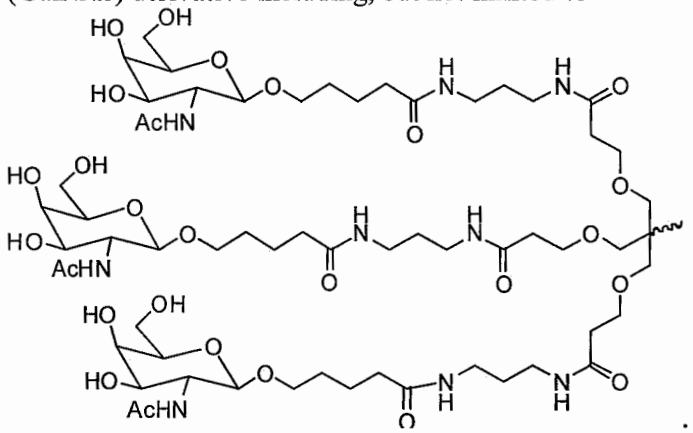
In certain examples, substantially all of the nucleotides of the sense strand are modified. In certain examples, substantially all of the nucleotides of the antisense strand are modified. In certain examples, substantially all of the nucleotides of both the sense strand and the antisense strand are modified.

In certain examples, the duplex comprises a modified antisense strand provided in Table 5. In certain examples, the duplex comprises a modified sense strand provided in Table 5. In certain examples, the duplex comprises a modified duplex provided in Table 5.

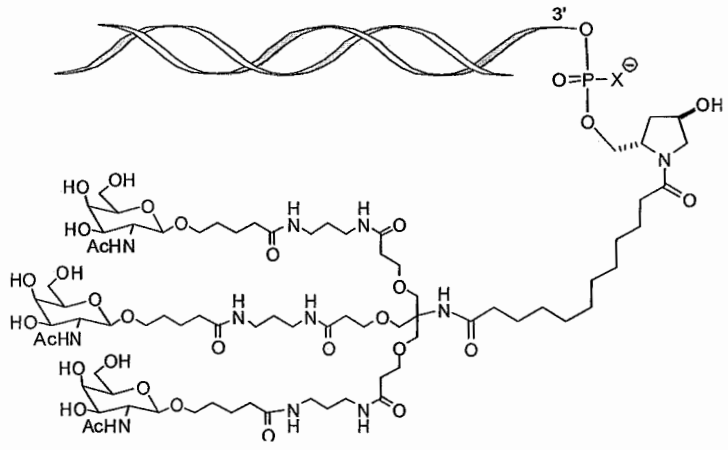
In certain examples, the region of complementarity between the antisense strand and the target is at least 17 nucleotides in length. For example, the region of complementarity between the antisense strand and the target is 19 to 21 nucleotides in length, for example, the region of complementarity is 21 nucleotides in length. In preferred examples, each strand is no more than 30 nucleotides in length.

In some examples, at least one strand comprises a 3' overhang of at least 1 nucleotide, *e.g.*, at least one strand comprises a 3' overhang of at least 2 nucleotides.

In many examples, the RNAi agent further comprises a ligand. The ligand can be conjugated to the 3' end of the sense strand of the RNAi agent. The ligand can be an N-acetylgalactosamine (GalNAc) derivative including, but not limited to



An exemplary RNAi agent conjugated to the ligand as shown in the following schematic:



and, wherein X is O or S. In one example, the X is O.

In certain examples, the ligand can be a cholesterol moiety.

In certain examples, the region of complementarity comprises one of the antisense sequences of any one of Table 3 and Table 5. In another example, the region of complementarity consists of one of the antisense sequences of any one of Table 3 and Table 5.

In another example, the disclosure provides a double stranded RNAi agent capable of inhibiting the expression of PD-L1, wherein the double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding PD-L1, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: 5' $n_p$ -$N_a$ -(X X X) $_i$-$N_b$ -Y Y Y -$N_b$ -(Z Z Z)$_j$ -$N_a$ - $n_q$ 3'

antisense: 3' $n_p$'-$N_a$'-(X'X'X')$_k$-$N_b$'-Y'Y'Y'-$N_b$'-(Z'Z'Z')$_l$-$N_a$'- $n_q$' 5' (III)

wherein: i, j, k, and l are each independently 0 or 1; p, p', q, and q' are each independently 0-6; each $N_a$ and $N_a$' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides; each $N_b$ and $N_b$' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof; each $n_p$, $n_p$', $n_q$, and $n_q$', each of which may or may not be present, independently represents an overhang nucleotide; XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides; modifications on $N_b$ differ from the modification on Y and modifications on $N_b$' differ from the modification on Y'; and wherein the sense strand is conjugated to at least one ligand.

In certain examples, i is 0; j is 0; i is 1; j is 1; both i and j are 0; or both i and j are 1. In another example, k is 0; l is 0; k is 1; l is 1; both k and l are 0; or both k and l are 1. In another example, XXX is complementary to X'X'X', YYY is complementary to Y'Y'Y', and ZZZ is complementary to Z'Z'Z'. In another example, the YYY motif occurs at or near the cleavage site of the sense strand. In another example, the Y'Y'Y' motif occurs at the 11, 12 and 13 positions of the antisense strand from the 5'-end. In one example, the Y' is 2'-O-methyl.

For example, formula (III) can be represented by formula (IIIa):

sense: 5' $n_p$ -$N_a$ -Y Y Y -$N_a$ - $n_q$ 3'

antisense: 3' $n_p$'-$N_a$'- Y'Y'Y'- $N_a$'- $n_q$' 5' (IIIa).

In another example, formula (III) is represented by formula (IIIb):

sense: 5' $n_p$ -$N_a$ -Y Y Y -$N_b$ -Z Z Z -$N_a$ - $n_q$ 3'

antisense: 3' $n_p$'-$N_a$'- Y'Y'Y'-$N_b$'-Z'Z'Z'- $N_a$'- $n_q$' 5' (IIIb)

wherein each $N_b$ and $N_b$' independently represents an oligonucleotide sequence comprising 1-5 modified nucleotides.

Alternatively, formula (III) can be represented by formula (IIIc):

sense: 5' $n_p$ -$N_a$ –X X X -$N_b$ -Y Y Y -$N_a$ - $n_q$ 3'

antisense: 3' $n_p$'-$N_a$'- X'X'X'-$N_b$'- Y'Y'Y'- $N_a$'- $n_q$' 5' (IIIc)

wherein each $N_b$ and $N_b$' independently represents an oligonucleotide sequence comprising 1-5 modified nucleotides.

Further, formula (III) can be represented by formula (IIId):

sense: 5' $n_p$ -$N_a$ –X X X- $N_b$ -Y Y Y -$N_b$ -Z Z Z -$N_a$ - $n_q$ 3'

antisense: $3'\ n_{p'}\text{-}N_{a'}\text{-}\ X'X'X'\text{-}\ N_{b'}\text{-}Y'Y'Y'\text{-}N_{b'}\text{-}Z'Z'Z'\text{-}\ N_{a'}\text{-}\ n_{q'}\ 5'$ (IIId)

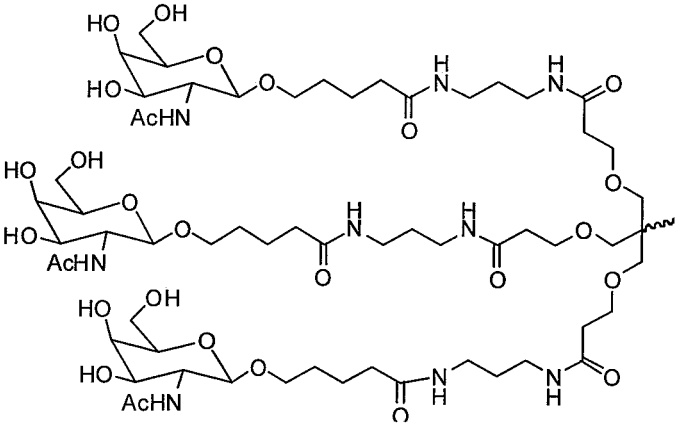
wherein each $N_b$ and $N_b'$ independently represents an oligonucleotide sequence comprising 1-5 modified nucleotides and each $N_a$ and $N_a'$ independently represents an oligonucleotide sequence comprising 2-10 modified nucleotides.

In certain example, the double stranded region is 15-30 nucleotide pairs in length. For example, the double stranded region can be 17-23 nucleotide pairs in length. The double stranded region can be 17-25 nucleotide pairs in length. The double stranded region can be 23-27 nucleotide pairs in length. The double stranded region can be 19-21 nucleotide pairs in length. The double stranded region can be 21-23 nucleotide pairs in length.

In certain examples, each strand has 15-30 nucleotides. In other examples, each strand has 19-30 nucleotides.

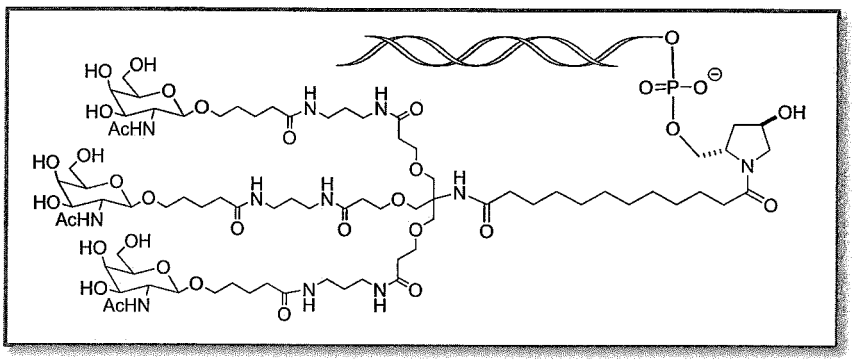
Modifications on the nucleotides may be selected from the group including, but not limited to, LNA, HNA, CeNA, 2'-methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-C- allyl, 2'-fluoro, 2'-deoxy, 2'-hydroxyl, and combinations thereof. In another example, the modifications on the nucleotides are 2'-O-methyl or 2'-fluoro modifications.

In certain examples, the ligand is one or more GalNAc derivatives attached through a monovalent linker or a bivalent or trivalent branched linker. In one example, the ligand is



The ligand can be attached to the 3' end of the sense strand.

An exemplary structure of a RNAi agent conjugated to the ligand is shown in the following schematic



In certain examples, the ligand can be a cholesterol moiety.

In certain examples, the RNAi agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage. For example the phosphorothioate or methylphosphonate internucleotide linkage can be at the 3'-terminus of one strand, *i.e.*, the sense strand or the antisense strand; or at the ends of both strands, the sense strand and the antisense strand.

In certain examples, the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand, *i.e.*, the sense strand or the antisense strand; or at the ends of both strands, the sense strand and the antisense strand.

In certain examples, the phosphorothioate or methylphosphonate internucleotide linkage is at the both the 5'- and 3'-terminus of one strand, *i.e.*, the sense strand or the antisense strand; or at the ends of both strands, the sense strand and the antisense strand.

In certain examples, the base pair at the 1 position of the 5′-end of the antisense strand of the duplex is an AU base pair.

In certain examples, the Y nucleotides contain a 2′-fluoro modification. In another example, the Y′ nucleotides contain a 2′-O-methyl modification. In another example, p′>0. In some examples, p′=2. In some examples, q'=0, p=0, q=0, and p' overhang nucleotides are complementary to the target mRNA. In some examples, q'=0, p=0, q=0, and p' overhang nucleotides are non-complementary to the target mRNA.

In certain examples, the sense strand has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides.

In certain examples, at least one $n_p'$ is linked to a neighboring nucleotide via a phosphorothioate linkage. In other examples, all $n_p'$ are linked to neighboring nucleotides via phosphorothioate linkages.

In certain examples, the RNAi agent is selected from the group of RNAi agents listed in any one of Tables 3 and 5. In certain examples, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

In one example, the disclosure provides a double stranded RNAi agent capable of inhibiting the expression of PD-L1 in a cell, wherein the double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding PD-L1, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: $5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$ (III)

wherein i, j, k, and l are each independently 0 or 1; p, p', q, and q′ are each independently 0-6; each $N_a$ and $N_a'$ independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides; each $N_b$ and $N_b'$ independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof; each $n_p$, $n_p'$, $n_q$, and $n_q'$, each of which may or may not be present independently represents an

overhang nucleotide; XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications; modifications on $N_b$ differ from the modification on Y and modifications on $N_b$′ differ from the modification on Y′; and wherein the sense strand is conjugated to at least one ligand.

In one example, the disclosure provides a double stranded RNAi agent capable of inhibiting the expression of PD-L1 in a cell, wherein the double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding PD-L1, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: 5′ $n_p$ -$N_a$ -(X X X) $_i$-$N_b$ -Y Y Y -$N_b$ -(Z Z Z)$_j$ -$N_a$ - $n_q$ 3′

antisense: 3′ $n_p$′-$N_a$′-(X′X′X′)$_k$-$N_b$′-Y′Y′Y′-$N_b$′-(Z′Z′Z′)$_l$-$N_a$′- $n_q$′ 5′ (III)

wherein: i, j, k, and l are each independently 0 or 1; each $n_p$, $n_q$, and $n_q$′, each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q′ are each independently 0-6; $n_p$′ >0 and at least one $n_p$′ is linked to a neighboring nucleotide via a phosphorothioate linkage; each $N_a$ and $N_a$′ independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides; each $N_b$ and $N_b$′ independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof; XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications; modifications on $N_b$ differ from the modification on Y and modifications on $N_b$′ differ from the modification on Y′; and wherein the sense strand is conjugated to at least one ligand.

In one example, the disclosure provides a double stranded RNAi agent capable of inhibiting the expression of PD-L1 in a cell, wherein the double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding PD-L1, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: 5′ $n_p$ -$N_a$ -(X X X) $_i$-$N_b$ -Y Y Y -$N_b$ -(Z Z Z)$_j$ -$N_a$ - $n_q$ 3′

antisense: 3′ $n_p$′-$N_a$′-(X′X′X′)$_k$-$N_b$′-Y′Y′Y′-$N_b$′-(Z′Z′Z′)$_l$-$N_a$′- $n_q$′ 5′ (III)

wherein i, j, k, and l are each independently 0 or 1; each $n_p$, $n_q$, and $n_q$′, each of which may or may not be present, independently represents an overhang nucleotide; p, q, and q′ are each independently 0-6; $n_p$′ >0 and at least one $n_p$′ is linked to a neighboring nucleotide via a phosphorothioate linkage; each $N_a$ and $N_a$′ independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides; each $N_b$ and $N_b$′ independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or

unmodified or combinations thereof; XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications; modifications on $N_b$ differ from the modification on Y and modifications on $N_b'$ differ from the modification on Y′; and wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a monovalent linker or a bivalent or trivalent branched linker.

In one example, the disclosure provides a double stranded RNAi agent capable of inhibiting the expression of PD-L1 in a cell, wherein the double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding PD-L1, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: $5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$ (III)

wherein i, j, k, and l are each independently 0 or 1; each $n_p$, $n_q$, and $n_q'$, each of which may or may not be present, independently represents an overhang nucleotide; p, q, and q′ are each independently 0-6; $n_p' > 0$ and at least one $n_p'$ is linked to a neighboring nucleotide via a phosphorothioate linkage; each $N_a$ and $N_a'$ independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides; each $N_b$ and $N_b'$ independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof; XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications; modifications on $N_b$ differ from the modification on Y and modifications on $N_b'$ differ from the modification on Y′; wherein the sense strand comprises at least one phosphorothioate linkage; and wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a monovalent linker or a bivalent or trivalent branched linker.

In one example, the disclosure provides a double stranded RNAi agent capable of inhibiting the expression of PD-L1 in a cell, wherein the double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding PD-L1, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: $5'\ n_p\text{-}N_a\text{-}Y\ Y\ Y\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_p'\text{-}N_a'\text{-}Y'Y'Y'\text{-}N_a'\text{-}n_q'\ 5'$ (IIIa)

wherein each $n_p$, $n_q$, and $n_q'$, each of which may or may not be present, independently represents an overhang nucleotide; p, q, and q′ are each independently 0-6; $n_p' > 0$ and at least one $n_p'$ is linked to a neighboring nucleotide via a phosphorothioate linkage; each $N_a$ and $N_a'$ independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or

unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides; YYY and Y'Y'Y' each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2'-O-methyl or 2'-fluoro modifications; wherein the sense strand comprises at least one phosphorothioate linkage; and wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a monovalent linker or a bivalent or trivalent branched linker.

In one example, the disclosure provides a double stranded RNAi agent for inhibiting expression of PD-L1, wherein the double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2, wherein substantially all of the nucleotides of the sense strand comprise a modification selected from a 2'-O-methyl modification and a 2'-fluoro modification, wherein the sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus, wherein substantially all of the nucleotides of the antisense strand comprise a modification selected from a 2'-O-methyl modification and a 2'-fluoro modification, wherein the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, and wherein the sense strand is conjugated to one or more GalNAc derivatives attached through a monovalent linker or a branched bivalent or trivalent linker at the 3'-terminus.

In another example, the present disclosure provides double stranded ribonucleic acid (RNAi) agents for inhibiting expression of PD-L1, wherein the double stranded RNAi agents comprise a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from nucleotides 3221-3243, 351-372, 618-641, 618-639, 619-640, 620-641, 1093-1115, 1093-1114, 1094-1115, 1167-1188, 1293-1314, 1518-1539, 2103-2124, 2220-2261, 2220-2241, 2240-2261, 2648-2680, 2648-2669, 2658-2679, 2659-2680, 3143-3164, 3198-3219, 3221-3242, or 3222-3243 of the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the complementary portion of the nucleotide sequence of SEQ ID NO:2, wherein substantially all of the nucleotides of the sense strand comprise a nucleotide modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification, wherein the sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus, wherein substantially all of the nucleotides of the antisense strand comprise a nucleotide modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification, wherein the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, and wherein the sense strand is conjugated to one or more GalNAc derivatives attached through a branched bivalent or trivalent linker at the 3'-terminus.

In certain examples, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides. In certain examples, each strand has 19-30 nucleotides.

In certain examples, substantially all of the nucleotides of the sense strand are modified. In certain examples, substantially all of the nucleotides of the antisense strand are modified. In certain examples, substantially all of the nucleotides of both the sense strand and the antisense strand are modified.

In one example, the disclosure provides a cell containing the RNAi agent as described herein.

In one example, the disclosure provides a vector encoding at least one strand of a RNAi agent, wherein the RNAi agent comprises a region of complementarity to at least a part of an mRNA encoding PD-L1, wherein the RNAi is 30 base pairs or less in length, and wherein the RNAi agent targets the mRNA for cleavage. In certain examples, the region of complementarity is at least 15 nucleotides in length. In certain examples, the region of complementarity is 19 to 23 nucleotides in length.

In one example, the disclosure provides a cell comprising a vector as described herein.

In one example, the disclosure provides a pharmaceutical composition for inhibiting expression of a PD-L1 gene comprising the RNAi agent of the disclosure. In one example, the RNAii agent is administered in an unbuffered solution. In certain examples, the unbuffered solution is saline or water. In other examples, the RNAii agent is administered in a buffered solution. In such examples, the buffer solution can comprise acetate, citrate, prolamine, carbonate, or phosphate, or any combination thereof. For example, the buffer solution can be phosphate buffered saline (PBS).

In one example, the disclosure provides a pharmaceutical composition comprising the double stranded RNAi agent of the disclosure and a lipid formulation. In certain examples, the lipid formulation comprises a LNP. In certain examples, the lipid formulation comprises an MC3.

In one example, the disclosure provides a method of inhibiting PD-L1 expression in a cell, the method comprising (a) contacting the cell with the double stranded RNAi agent of the disclosure or a pharmaceutical composition of the disclosure; and (b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of a PD-L1 gene, thereby inhibiting expression of the PD-L1 gene in the cell. In certain examples, the cell is within a subject, for example, a human subject, for example a female human or a male human. In preferred examples, PD-L1 expression is inhibited by at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95%, or to below the threshold of detection of the assay method used.

In one example, the disclosure provides a method of treating a subject having a disease or disorder that would benefit from reduction in PD-L1 expression, the method comprising administering to the subject a therapeutically effective amount of the RNAi agent of the disclosure or a pharmaceutical composition of the disclosure, thereby treating the subject.

In one example, the disclosure provides a method of preventing at least one symptom in a subject having a disease or disorder that would benefit from reduction in PD-L1 expression, the method comprising administering to the subject a prophylactically effective amount of the RNAi

agent of the disclosure or a pharmaceutical composition of the disclosure, thereby preventing at least one symptom in the subject having a disorder that would benefit from reduction in PD-L1 expression.

In certain examples, the administration of the RNAi to the subject causes a decrease in the PD-L1 signaling pathway. In certain examples, the administration of the RNAi causes a decrease in the level of PD-L1in the subject, *e.g.*, serum levels of PD-L1 in the subject.

In certain examples, the PD-L1-associated disease is an infectious disease, such as a chronic, intracellular infectious disease, *e.g.*, a viral disease, *e.g.*, hepatitis infection, or a bacterial infection, *e.g.*, tuberculosis infection.

In certain examples, the PD-L1-associated disease is cancer, *e.g.*, a hepatic cancer, *e.g.*, hepatocellular carcinoma.

In certain examples, the disclosure further comprises administering an anti-viral agent to a subject with a PD-L1-associated disease. In certain examples, the anti-viral agent is a nucleotide or nucleoside analog. In certain examples, the anti-viral agent is for treatment of a hepatitis virus infection, *e.g.*, an HBV infection, an HDV infection. In certain examples, the anti-viral agent is not an immune stimulatory agent.

In certain examples, the disclosure further comprises administering a chemotherapeutic agent to a subject with a PD-L1-associated disease.

In certain examples wherein the PD-L1-associated disease is cancer, the subject is further treated for cancer. In certain examples, the treatment for cancer includes surgery. In certain examples, the treatment for cancer includes radiation. In certain examples, the treatment for cancer includes administration of a chemotherapeutic agent.

In various examples, the RNAi agent is administered at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 50 mg/kg. In some examples, the RNAi agent is administered at a dose of about 10 mg/kg to about 30 mg/kg. In certain examples, the RNAi agent is administered at a dose selected from about 0.5 mg/kg 1 mg/kg, 1.5 mg/kg, 3 mg/kg, 5 mg/kg, 10 mg/kg, and 30 mg/kg. In certain examples, the RNAi agent is administered about once per week, once per month, once every other two months, or once a quarter (*i.e.*, once every three months) at a dose of about 0.1 mg/kg to about 5.0 mg/kg.

In certain examples, the RNAi agent is administered to the subject once a week. In certain examples, the RNAii agent is administered to the subject once a month. In certain examples, the RNAii agent is administered once per quarter (*i.e.*, every three months).

In some example, the RNAi agent is administered to the subject subcutaneously.

In various examples, the methods of the disclosure further comprise measuring PD-L1levels in the subject. In certain examples, a decrease in the levels of expression or activity of the PD-L1 signaling pathway indicates that the PD-L1-associated disease is being treated.

In various examples, a surrogate marker of PD-L1 expression is measured. For example, in the treatment of infectious disease, the presence of the pathogen is detected, *e.g.*, a protein or nucleic acid from the pathogen, *e.g.*, HBsAg, HBeAg, HB cccDNA. In certain examples, an indicator of an

immune response against the pathogen is detected, *e.g.*, anti-HBs antibody. In certain examples, a change, preferably a clinically relevant change in the surrogate marker indicating effective treatment of the infection is detected. In the treatment of cancer, a demonstration of stabilization or reduction of tumor burden using RECIST criteria can be used as a surrogate marker for a reduction of PD-L1 expression or activity.

## Brief Description of the Drawings

Figure 1 is a schematic showing a PD-L1 signaling between an antigen presenting cell and a T-cell.

## Detailed Description of the Invention

The present invention provides iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of an programmed cell death 1 ligand 1 (PD-L1) gene. The gene may be within a cell, *e.g.*, a cell within a subject, such as a human. The use of these iRNAs enables the targeted degradation of mRNAs of the correponding gene (PD-L1 gene) in mammals.

The iRNAs of the invention have been designed to target the human PD-L1 gene, including portions of the gene that are conserved in the PD-L1 othologs of other mammalian species. Without intending to be limited by theory, it is believed that a combination or sub-combination of the foregoing properties and the specific target sites or the specific modifications in these iRNA agents confer to the iRNAs of the invention improved efficacy, stability, potency, durability, and safety.

Accordingly, the present invention also provides methods for treating a subject having a disorder that would benefit from inhibiting or reducing the expression of a PD-L1 gene, *e.g.*, an PD-L1-associated disease, such as infection, *e.g.*, a viral infection, *e.g.*, a hepatitis virus infection, or cancer, such as a liver cancer, *e.g.*, hepatic cellular carcinoma, using iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of an PD-L1 gene.

We claim:

1. A double stranded ribonucleic acid (RNAi) agent for inhibiting expression of programmed cell death 1 ligand 1 (PD-L1), wherein said RNAi agent comprises a sense strand and an antisense strand, wherein said sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of nucleotides 3221-3243 of the nucleotide sequence of SEQ ID NO:1 and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the complementary portion of the nucleotide sequence of SEQ ID NO:2, and wherein the RNAi agent comprises at least one modified nucleotide.

2. The dsRNA agent of claim 1, wherein the sense and antisense strands comprise nucleotide sequences selected from the group consisting of any one of the nucleotide sequences in any one of the duplexes AD-67635, AD-67637, AD-67628, AD-67647, AD-67626, or AD-67645.

3. The dsRNA agent of any one of claims 1-2, wherein substantially all of the nucleotides of said sense strand or substantially all of the nucleotides of said antisense strand comprise a nucleotide modification.

4. The dsRNA agent of claim 1,

wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand comprise nucleotide modifications, and

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

5. The RNAi agent of any one of claims 1-4, wherein at least one of said nucleotide modifications is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxyl-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, and a nucleotide comprising a 5'-phosphate mimic.

6. The RNAi agent of any one of claims 1 and 4, wherein each strand is no more than 30 nucleotides in length.

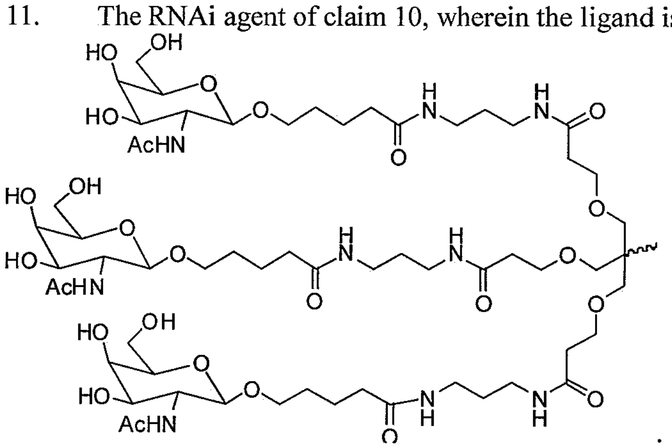
7. The RNAi agent of any one of claims 1 and 4, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

8. The RNAi agent of any one of claims 1-3, further comprising a ligand.

9. The RNAi agent of claim 8, wherein the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

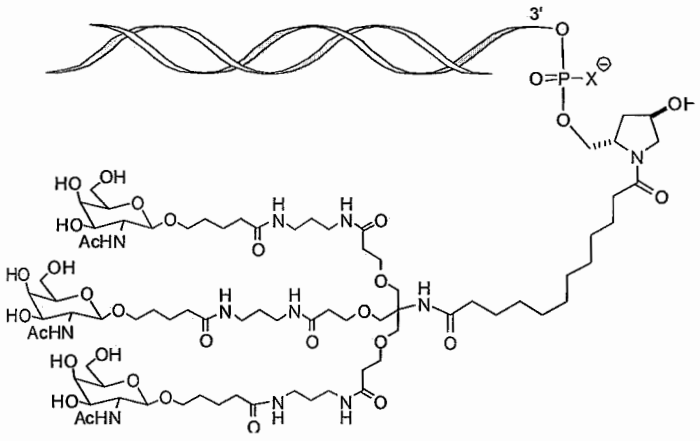
10. The RNAi agent of claim 4 or 8, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

11. The RNAi agent of claim 10, wherein the ligand is




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



and, wherein X is O or S.

13. The double stranded ribonucleic acid (RNAi) agent of claim 1,

wherein substantially all of the nucleotides of said sense strand comprise a nucleotide modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification,

wherein said sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus,

wherein substantially all of the nucleotides of said antisense strand comprise a nucleotide modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification,

wherein said antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, and

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

14. A pharmaceutical composition for inhibiting expression of a PD-L1 gene comprising the RNAi agent of any one of claims 1-13.

15. The pharmaceutical composition of claim 14, further comprising a lipid formulation.

16. Use of an RNAi agent of any one of claims 1-13 or the pharmaceutical composition of any one of claims 14-15 in the manufacture of a medicament for treating a subject having a disease or disorder that would benefit from reduction in PD-L1.

17. The RNAi agent or pharmaceutical composition for use of claim 16, wherein the PD-L1-associated disease is a viral infection.