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 (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

(a) (i) said sense strand comprises 5'-ACCUGCAUUAAUUUAAUAAAA-3' (SEQ ID NO: 116) and said antisense strand comprises 5'-UUUUAUUAAAUUAAUGCAGGUAC-3' (SEQ ID NO: 117); or (ii) said sense strand comprises 5'-UACCUGCAUUAAUUUAAUAAA-3' (SEQ ID NO: 110) and said antisense strand comprises 5'-UUUAUUAAAUUAAUGCAGGUACA-3' (SEQ ID NO: 111);

(b) substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides; and

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

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 viral infection or cancer.

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.

We claim:

1. A double stranded 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:

(a) (i) said sense strand comprises 5'-ACCUGCAUUAAUUUAAUAAAA-3' (SEQ ID NO: 116) and said antisense strand comprises 5'-UUUUAUUAAAUUAAUGCAGGUAC-3' (SEQ ID NO: 117); or (ii) said sense strand comprises 5'-UACCUGCAUUAAUUUAAUAAA-3' (SEQ ID NO: 110) and said antisense strand comprises 5'-UUUAUUAAAUUAAUGCAGGUACA-3' (SEQ ID NO: 111);

(b) substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides; and

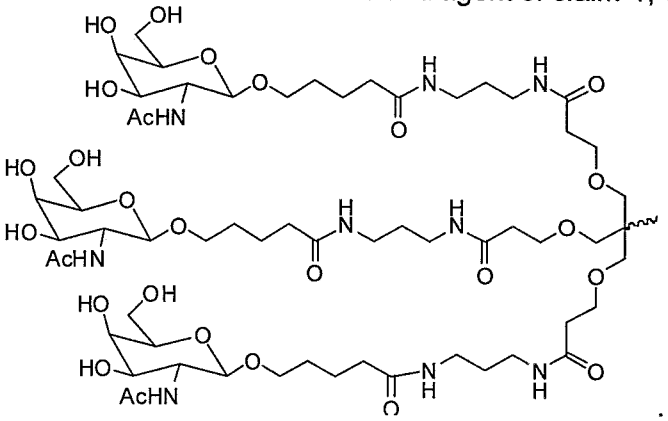
(c) said sense strand is conjugated to a ligand attached at the 3'-terminus, and the ligand is one or more N-acetylgalactosamine (GalNAc) derivatives attached through a bivalent or trivalent branched linker.

2. The double stranded RNAi agent of claim 1, 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, 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.

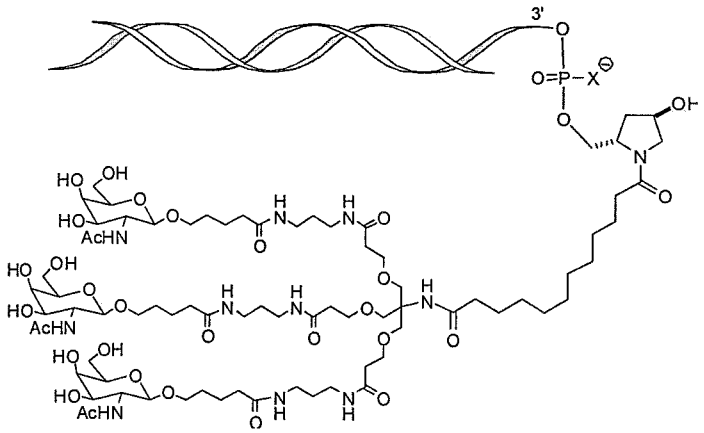
3. The double stranded RNAi agent of claim 1, wherein each strand is no more than 30 nucleotides in length.

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

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



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



and wherein X is O or S.

7. The double stranded 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.

8. The double stranded RNAi agent of claim 1, wherein:
(a) said sense strand comprises 5'-ascscugcAfuUfAfAfuuuaauaaaaL96-3' (SEQ ID NO: 218) and said antisense strand comprises 5'-usUfsuuaUfuAfAfauuaAfuGfcaggusasc-3' (SEQ ID NO: 219);
(b) said sense strand comprises 5'-ascscugcAfuUfAfAfuuuaauaaaaL96-3' (SEQ ID NO: 220) and said antisense strand comprises 5'-UfsUfsuuaUfuAfAfauuaAfuGfcaggusasc-3' (SEQ ID NO: 221);
(c) said sense strand comprises 5'-usasccugCfaUfUfAfauuuaauaaaL96-3' (SEQ ID NO: 212) and said antisense strand comprises 5'-usUfsuauUfaAfAfuuaaUfgCfagguascsa-3' (SEQ ID NO: 213); or
(d) said sense strand comprises 5'-usasccugCfaUfUfAfauuuaauaaaL96-3' (SEQ ID NO: 214) and said antisense strand comprises 5'-UfsUfsuauUfaAfAfuuaaUfgCfagguascsa-3' (SEQ ID NO: 215);
wherein a, g, c, and u are 2'-O-methyl (2'-OMe) A, 2'-OMe G, 2'-OMe C, and 2'OMe U, respectively; Af, Cf, Gf , and Uf are 2'-fluoro A, 2'-fluoro C, 2'-fluoro G, and 2'-fluoro U, respectively; s is a phosphorothioate linkage; and L96 is N[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol.

9. A pharmaceutical composition for inhibiting expression of a PD-L1 gene comprising the RNAi agent of any one of claims 1-8.

10. The pharmaceutical composition of claim 9, further comprising a lipid formulation.

11. Use of an RNAi agent of any one of claims 1-8 or the pharmaceutical composition of any one of claims 9-10 in the manufacture of a medicament for treating a viral infection.

12. The use of claim 11, wherein the PD-L1-associated disease is a hepatitis virus infection.

13. Use of an RNAi agent of any one of claims 1-8 or the pharmaceutical composition of any one of claims 9-10 in the manufacture of a medicament for treating cancer.