Negative secondary signals seem necessary for induction of T-cell tolerance, while positive signals promote T-cell activation. While the simple two-signal model still provides a valid explanation for naive lymphocytes, a host's immune response is a dynamic process, and co-stimulatory signals can also be provided to antigen-exposed T-cells.

The mechanism of co-stimulation is of therapeutic interest because the manipulation of co-stimulatory signals has shown to provide a means to either enhance or terminate cell-based immune response. Recently, it has been discovered that T cell dysfunction or anergy occurs concurrently with an induced and sustained expression of the inhibitory receptor, programmed death 1 polypeptide (PD-1). As a result, therapeutic targeting PD-1 and other molecules which signal through interactions with PD-1, such as programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2) are an area of intense interest. The inhibition of PD-L1 signaling has been proposed as a means to enhance T cell immunity for the treatment of cancer (*e.g.*, tumor immunity) and infection, including both acute and chronic (*e.g.*, persistent) infection. However, as an optimal therapeutic directed to a target in this pathway has yet to be commercialized, a significant unmet medical need exists.

## Summary

The present disclosure provides for anti-PD-L1 antibodies, including nucleic acid encoding and compositions containing such antibodies, and for their use to enhance T-cell function to upregulate cell-mediated immune responses and for the treatment of T cell dysfunctional disorders, including infection (e.g., actue and chronic) and tumor immunity.

In one example, the disclosure provides for an isolated heavy chain variable region polypeptide comprising an HVR-H1, HVR-H2 and HVR-H3 sequence, wherein:

(a) the HVR-H1 sequence is is $GFTFSX_1SWIH$ (SEQ ID NO:1);

(b) the HVR-H2 sequence is $AWIX_2PYGGSX_3YYADSVKG$ (SEQ ID NO:2);

(c) the HVR-H3 sequence is RHWPGGFDY (SEQ ID NO:3);

further wherein: $X_1$ is D or G; $X_2$ is S or L; $X_3$ is T or S.

In one specific example, $X_1$ is D; $X_2$ is S and $X_3$ is T. In another example, the polypeptide further comprises variable region heavy chain framework sequences juxtaposed between the HVRs according to the formula: (HC-FR1)-(HVR-H1)-(HC-FR2)-(HVR-H2)-(HC-FR3)-(HVR-H3)-(HC-FR4). In yet another example, the framework sequences are derived from human consensus framework sequences. In a further example, the framework sequences are VH subgroup III consensus framework. In a still further example, at least one of the framework sequences is the following:

HC-FR1 is EVQLVESGGGLVQPGGSLRLSCAAS (SEQ ID NO:4)

HC-FR2 is WVRQAPGKGLEWV (SEQ ID NO:5)

HC-FR3 is RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR (SEQ ID NO:6)

HC-FR4 is WGQGTLVTVSA (SEQ ID NO:7).

In a still further example, the heavy chain polypeptide is further combined with a variable region light chain comprising an an HVR-L1, HVR-L2 and HVR-L3, wherein:

(a) the HVR-L1 sequence is $RASQX_4X_5X_6TX_7X_8A$ (SEQ ID NOs:8);

(b) the HVR-L2 sequence is $SASX_9LX_{10}S$, (SEQ ID NOs:9);

(c) the HVR-L3 sequence is $QQX_{11}X_{12}X_{13}X_{14}PX_{15}T$ (SEQ ID NOs:10);

further wherein: $X_4$ is D or V; $X_5$ is V or I; $X_6$ is S or N; $X_7$ is A or F; $X_8$ is V or L; $X_9$ is F or T; $X_{10}$ is Y or A; $X_{11}$ is Y, G, F, or S; $X_{12}$ is L, Y, F or W; $X_{13}$ is Y, N, A, T, G, F or I; $X_{14}$ is H, V, P, T or I; $X_{15}$ is A, W, R, P or T.

In a still further example, $X_4$ is D; $X_5$ is V; $X_6$ is S; $X_7$ is A; $X_8$ is V; $X_9$ is F; $X_{10}$ is Y; $X_{11}$ is Y; $X_{12}$ is L; $X_{13}$ is Y; $X_{14}$ is H; $X_{15}$ is A. In a still further example, the light chain further comprises variable region light chain framework sequences juxtaposed between the HVRs according to the formula: (LC-FR1)-(HVR-L1)-(LC-FR2)-(HVR-L2)-(LC-FR3)-(HVR-L3)-(LC-FR4). In a still further example, the framework sequences are derived from human consensus framework sequences. In a still further example, the framework sequences are VL kappa I consensus framework. In a still further example, at least one of the framework sequence is the following:

LC-FR1 is DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO:11)

LC-FR2 is WYQQKPGKAPKLLIY (SEQ ID NO:12)

LC-FR3 is GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC (SEQ ID NO:13)

LC-FR4 is FGQGTKVEIKR (SEQ ID NO:14).

In another example, the disclosure provides an isolated anti-PD-L1 antibody or antigen binding fragment comprising a heavy chain and a light chain variable region sequence, wherein:

(a) the heavy chain comprises and HVR-H1, HVR-H2 and HVR-H3, wherein further:

(i) the HVR-H1 sequence is $GFTFSX_1SWIH$; (SEQ ID NO:1)

(ii) the HVR-H2 sequence is $AWIX_2PYGGSX_3YYADSVKG$ (SEQ ID NO:2)

(iii) the HVR-H3 sequence is RHWPGGFDY, and (SEQ ID NO:3)

(b) the light chain comprises and HVR-L1, HVR-L2 and HVR-L3, wherein further:

(i) the HVR-L1 sequence is $RASQX_4X_5X_6TX_7X_8A$ (SEQ ID NOs:8)

(ii) the HVR-L2 sequence is $SASX_9LX_{10}S$; and (SEQ ID NOs:9)

(iii) the HVR-L3 sequence is $QQX_{11}X_{12}X_{13}X_{14}PX_{15}T$; (SEQ ID NOs:10)

Further wherein: $X_1$ is D or G; $X_2$ is S or L; $X_3$ is T or S; $X_4$ is D or V; $X_5$ is V or I; $X_6$ is S or N; $X_7$ is A or F; $X_8$ is V or L; $X_9$ is F or T; $X_{10}$ is Y or A; $X_{11}$ is Y, G, F, or S; $X_{12}$ is L, Y, F or W; $X_{13}$ is Y, N, A, T, G, F or I; $X_{14}$ is H, V, P, T or I; $X_{15}$ is A, W, R, P or T.

In a specific example, $X_1$ is D; $X_2$ is S and $X_3$ is T. In another example, $X_4$ is D; $X_5$ is V; $X_6$ is S; $X_7$ is A; $X_8$ is V; $X_9$ is F; $X_{10}$ is Y; $X_{11}$ is Y; $X_{12}$ is L; $X_{13}$ is Y; $X_{14}$ is H; $X_{15}$ is A. In yet another example, $X_1$ is D; $X_2$ is S and $X_3$ is T, $X_4$ is D; $X_5$ is V; $X_6$ is S; $X_7$ is A; $X_8$ is V; $X_9$ is F; $X_{10}$ is Y; $X_{11}$ is Y; $X_{12}$ is L; $X_{13}$ is Y; $X_{14}$ is H and $X_{15}$ is A.

In a further example, the heavy chain variable region comprises one or more framework sequences juxtaposed between the HVRs as: (HC-FR1)-(HVR-H1)-(HC-FR2)-(HVR-H2)-(HC-FR3)-(HVR-H3)-(HC-FR4), and the light chain variable regions comprises one or more framework sequences juxtaposed between the HVRs as: (LC-FR1)-(HVR-L1)-(LC-FR2)-(HVR-L2)-(LC-FR3)-(HVR-L3)-(LC-FR4). In a still further example, the framework sequences are derived from human consensus framework sequences. In a still further example, the heavy chain framework sequences are derived from a Kabat subgroup I, II, or III sequence. In a still further example, the heavyc chain framework sequence is a VH subgroup III consensus framework. In a still further example, one or more of the heavy chain framework sequences is the following:

| | | |
|---|---|---|
| HC-FR1 | EVQLVESGGGLVQPGGSLRLSCAAS | (SEQ ID NO:4) |
| HC-FR2 | WVRQAPGKGLEWV | (SEQ ID NO:5) |
| HC-FR3 | RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR | (SEQ ID NO:6) |
| HC-FR4 | WGQGTLVTVSA | (SEQ ID NO:7). |

In a still further example, the light chain framework sequences are derived from a Kabat kappa I, II, II or IV subgroup sequence. In a still further example, the light chain framework sequences are VL kappa I consensus framework. In a still further example, one or more of the light chain framework sequences is the following:

| | | |
|---|---|---|
| LC-FR1 | DIQMTQSPSSLSASVGDRVTITC | (SEQ ID NO:11) |
| LC-FR2 | WYQQKPGKAPKLLIY | (SEQ ID NO:12) |
| LC-FR3 | GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC | (SEQ ID NO:13) |
| LC-FR4 | FGQGTKVEIKR | (SEQ ID NO:14). |

In a still further specific example, the antibody further comprises a human or murine constant region. In a still further example, the human constant region is selected from the group consisting of IgG1, IgG2, IgG2, IgG3, IgG4. In a still further specific example, the human constant region is IgG1. In a still further example, the murine constant region is selected from the group consisting of IgG1, IgG2A, IgG2B, IgG3. In a still further example, the murine constant region if IgG2A. In a still further specific example, the antibody has reduced or minimal effector function. In a still further specific example the minimal effector function results from an "effector-less Fc mutation" or aglycosylation. In still a further example, the effector-less Fc mutation is an N297A or D265A/N297A substitution in the constant region.

In yet another example, the disclosure provides for an anti-PD-L1 antibody comprising a heavy chain and a light chain variable region sequence, wherein:

(a) the heavy chain further comprises and HVR-H1, HVR-H2 and an HVR-H3 sequence having at least 85% sequence identity to GFTFSDSWIH (SEQ ID NO:15), AWISPYGGSTYYADSVKG (SEQ ID NO:16) and RHWPGGFDY (SEQ ID NO:3), respectively, or

(b) the light chain further comprises an HVR-L1, HVR-L2 and an HVR-L3 sequence having at least 85% sequence identity to RASQDVSTAVA (SEQ ID NO:17), SASFLYS (SEQ ID NO:18) and QQYLYHPAT (SEQ ID NO:19), respectively.

In a specific example, the sequence identity is 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%. In another example, the heavy chain variable region comprises one or more framework sequences juxtaposed between the HVRs as: (HC-FR1)-(HVR-H1)-(HC-FR2)-(HVR-H2)-(HC-FR3)-(HVR-H3)-(HC-FR4), and the light chain variable regions comprises one or more framework sequences juxtaposed between the HVRs as: (LC-FR1)-(HVR-L1)-(LC-FR2)-(HVR-L2)-(LC-FR3)-(HVR-L3)-(LC-FR4). In yet another example, the framework sequences are derived from human consensus framework sequences. In a still further example, the heavy chain framework sequences are derived from a Kabat subgroup I, II, or III sequence. In a still further example, the heavy chain framework sequence is a VH subgroup III consensus framework. In a still further example, one or more of the heavy chain framework sequences is the following:

| | | |
|---|---|---|
| HC-FR1 | EVQLVESGGGLVQPGGSLRLSCAAS | (SEQ ID NO:4) |
| HC-FR2 | WVRQAPGKGLEWV | (SEQ ID NO:5) |
| HC-FR3 | RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR | (SEQ ID NO:6) |
| HC-FR4 | WGQGTLVTVSA | (SEQ ID NO:7). |

In a still further example, the light chain framework sequences are derived from a Kabat kappa I, II, II or IV subgroup sequence. In a still further example, the light chain framework sequences are VL kappa I consensus framework. In a still further example, one or more of the light chain framework sequences is the following:

| | | |
|---|---|---|
| LC-FR1 | DIQMTQSPSSLSASVGDRVTITC | (SEQ ID NO:11) |
| LC-FR2 | WYQQKPGKAPKLLIY | (SEQ ID NO:12) |
| LC-FR3 | GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC | (SEQ ID NO:13) |
| LC-FR4 | FGQGTKVEIKR | (SEQ ID NO:14). |

In a still further specific example, the antibody further comprises a human or murine constant region. In a still further example, the human constant region is selected from the group consisting of IgG1, IgG2, IgG2, IgG3, IgG4. In a still further specific example, the human constant region is IgG1. In a still further example, the murine constant region is selected from the group consisting of IgG1, IgG2A, IgG2B, IgG3. In a still further example, the murine constant region if IgG2A. In a still further specific example, the antibody has reduced or minimal effector function. In a still further specific example the minimal effector function results from an "effector-less Fc mutation" or aglycosylation. In still a further example, the effector-less Fc mutation is an N297A or D265A/N297A substitution in the constant region.

In one aspect, the present disclosure refers to use of an anti-PD-L1 antibody or antigen binding fragment thereof in the manufacture of a medicament for treating cancer or infection in a subject, wherein the anti-PD-L1 antibody or antigen binding fragment thereof comprises a heavy chain and a light chain variable region sequence, wherein:

(a) the heavy chain comprises an HVR-H1, HVR-H2 and HVR-H3, wherein:
  (i) the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 15;
  (ii) the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 16;
  (iii) the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 3;

(b) the light chain comprises an HVR-L1, HVR-L2 and HVR-L3, wherein:
  (iv) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 17;
  (v) the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 18;
  (vi) the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 19.

In a still further example, the disclosure provides for an isolated anti-PD-L1 antibody comprising a heavy chain and a light chain variable region sequence, wherein:

(a) the heavy chain sequence has at least 85% sequence identity to the heavy chain sequence: EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWIS PYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWG QGTLVTVSA (SEQ ID NO:20), or

(b) the light chain sequences has at least 85% sequence identity to the light chain sequence: DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIY SASF LYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGQGTKVEIKR (SEQ ID NO:21).

In a specific example, the sequence identity is 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%. In another example, the heavy chain variable region comprises one or more framework sequences juxtaposed between the HVRs as: (HC-FR1)-(HVR-H1)-(HC-FR2)-(HVR-H2)-(HC-FR3)-(HVR-H3)-(HC-FR4), and the light chain variable regions comprises one or more framework sequences juxtaposed between the HVRs as:

(LC-FR1)-(HVR-L1)-(LC-FR2)-(HVR-L2)-(LC-FR3)-(HVR-L3)-(LC-FR4). In yet another example, the framework sequences are derived from human consensus framework sequences. In a further example, the heavy chain framework sequences are derived from a Kabat subgroup I, II, or III sequence. In a still further example, the heavy chain framework sequence is a VH subgroup III consensus framework. In a still further example, one or more of the heavy chain framework sequences is the following:

| | | |
|---|---|---|
| HC-FR1 | EVQLVESGGGLVQPGGSLRLSCAAS | (SEQ ID NO:4) |
| HC-FR2 | WVRQAPGKGLEWV | (SEQ ID NO:5) |
| HC-FR3 | RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR | (SEQ ID NO:6) |
| HC-FR4 | WGQGTLVTVSA | (SEQ ID NO:7). |

In a still further example, the light chain framework sequences are derived from a Kabat kappa I, II, II or IV subgroup sequence. In a still further example, the light chain framework sequences are VL kappa I consensus framework. In a still further example, one or more of the light chain framework sequences is the following:

| | | |
|---|---|---|
| LC-FR1 | DIQMTQSPSSLSASVGDRVTITC | (SEQ ID NO:11) |
| LC-FR2 | WYQQKPGKAPKLLIY | (SEQ ID NO:12) |
| LC-FR3 | GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC | (SEQ ID NO:13) |
| LC-FR4 | FGQGTKVEIKR | (SEQ ID NO:14). |

In a still further specific example, the antibody further comprises a human or murine constant region. In a still further example, the human constant region is selected from the group consisting of IgG1, IgG2, IgG2, IgG3, IgG4. In a still further specific example, the human constant region is IgG1. In a still further example, the murine constant region is selected from the group consisting of IgG1, IgG2A, IgG2B, IgG3. In a still further example, the murine constant region if IgG2A. In a still further specific example, the antibody has reduced or minimal effector function. In a still further specific example, the minimal effector function results from production in prokaryotic cells. In a still further specific example the minimal effector function results from an "effector-less Fc mutation" or aglycosylation. In still a further example, the effector-less Fc mutation is an N297A or D265A/N297A substitution in the constant region.

In one aspect, the present disclosure refers to use of an anti-PD-L1 antibody or antigen binding fragment thereof in the manufacture of a medicament for treating cancer or infection in a subject, wherein the antibody or antigen binding fragment comprises a heavy chain and a light chain variable region sequence, wherein:

(a) the heavy chain variable region amino acid sequence has at least 90% sequence identity to the heavy chain variable region amino acid sequence of SEQ ID NO:20, and

(b) the light chain variable region amino acid sequence has at least 90% sequence identity to the light chain variable region amino acid sequence of SEQ ID NO:21.

In a still further example, the disclosure provides for compositions comprising any of the above described anti-PD-L1 antibodies in combination with at least one pharmaceutically-acceptable carrier.

In a still further example, the disclosure provides for isolated nucleic acid encoding a light chain or a heavy chain variable region sequence of an anti-PD-L1 antibody, wherein:

(a) the heavy chain further comprises and HVR-H1, HVR-H2 and an HVR-H3 sequence having at least 85% sequence identity to GFTFSDSWIH (SEQ ID NO:15), AWISPYGGSTYYADSVKG (SEQ ID NO:16) and RHWPGGFDY (SEQ ID NO:3), respectively, and

(b) the light chain further comprises an HVR-L1, HVR-L2 and an HVR-L3 sequence having at least 85% sequence identity to RASQDVSTAVA (SEQ ID NO:17), SASFLYS (SEQ ID NO:18) and QQYLYHPAT (SEQ ID NO:19), respectively.

In a specific example, the sequence identity is 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%. In example, the heavy chain variable region comprises one or more framework sequences juxtaposed between the HVRs as: (HC-FR1)-(HVR-H1)-(HC-FR2)-(HVR-H2)-(HC-FR3)-(HVR-H3)-(HC-FR4), and the light chain variable regions comprises one or more framework sequences juxtaposed between the HVRs as: (LC-FR1)-(HVR-L1)-(LC-FR2)-(HVR-L2)-(LC-FR3)-(HVR-L3)-(LC-FR4). In yet another example, the framework sequences are derived from human consensus framework sequences. In a further example, the heavy chain framework sequences are derived from a Kabat subgroup I, II, or III sequence. In a still further example, the heavy chain framework sequence is a VH subgroup III consensus framework. In a still further example, one or more of the heavy chain framework sequences is the following:

| | | |
|---|---|---|
| HC-FR1 | EVQLVESGGGLVQPGGSLRLSCAAS | (SEQ ID NO:4) |
| HC-FR2 | WVRQAPGKGLEWV | (SEQ ID NO:5) |
| HC-FR3 | RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR | (SEQ ID NO:6) |
| HC-FR4 | WGQGTLVTVSA | (SEQ ID NO:7). |

In a still further example, the light chain framework sequences are derived from a Kabat kappa I, II, II or IV subgroup sequence. In a still further example, the light chain framework sequences are VL kappa I consensus framework. In a still further example, one or more of the light chain framework sequences is the following:

| | | |
|---|---|---|
| LC-FR1 | DIQMTQSPSSLSASVGDRVTITC | (SEQ ID NO:11) |
| LC-FR2 | WYQQKPGKAPKLLIY | (SEQ ID NO:12) |
| LC-FR3 | GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC | (SEQ ID NO:13) |
| LC-FR4 | FGQGTKVEIKR | (SEQ ID NO:14). |

In a still further specific example, the antibody further comprises a human or murine constant region. In a still further example, the human constant region is selected from the group consisting of IgG1, IgG2, IgG2, IgG3, IgG4. In a still further specific example, the human constant region is IgG1. In a still further example, the murine constant region is selected from the group consisting of IgG1, IgG2A, IgG2B, IgG3. In a still further example, the murine constant region if IgG2A. In a still further specific example, the antibody has reduced or minimal effector function. In a still further specific example, the minimal effector function results from production in prokaryotic cells. In a still further specific example the minimal effector function results from an "effector-less Fc mutation" or aglycosylation. In still a further example, the effector-less Fc mutation is an N297A or D265A/N297A substitution in the constant region.

In a still further example, the nucleic acid further comprises a vector suitable for expression of the nucleic acid encoding any of the previously described anti-PD-L1 antibodies. In a still further specific example, the vector further comprises a host cell suitable for expression of the nucleic acid. In a still further specific example, the host cell is a eukaryotic cell or a prokaryotic cell. In a still further specific example, the eukaryotic cell is a mammalian cell, such as Chinese Hamster Ovary (CHO).

In a still further example, the disclosure provides for a process of making an anti-PD-L1 antibody or antigen binding fragment thereof, comprising culturing a host cell containing nucleic acid encoding any of the previously described anti-PD-L1 antibodies or antigen-binding fragment in a form suitable for expression, under conditions suitable to produce such antibody or fragment, and recovering the antibody or fragment.

In a still further example, the disclosure provides for a composition comprising an anti-PD-L1 antibody or antigen binding fragment thereos as provided herein and at least one pharmaceutically acceptable carrier.

In a still further example, the disclosure provides an article of manufacture comprising a container enclosing a therapeutically effective amount of a composition disclosed herein and a package insert indicating use for the treatment of a T-cell dysfunctional disorder.

In a still further example, the disclosure provides for an article of manufacture comprising any of the above described anti-PD-L1 compositions in combination with at least one BNCA molecules. In one example, the BNCA molecules is an antibody, antigen binding antibody fragment, BNCA oligopeptide, BNCA RNAi or BNCA small molecule. In another example, the B7 negative costimulatory molecule is selected from the group consisting of: CTLA-4, PD-1, PD-L1, PD-L2, B7.1, B7-H3 and B7-H4.

In a still further example, the article of manufacture comprises any of the above described anti-PD-L1 compositions in combination with a chemotherapeutic agent. In one example, the chemotherapeutic agent is gemcitabine.

In a still further example, the disclosure provides for an article of manufacture comprising any of the above described anti-PD-L1 antibodies in combination with one or more agonists of a positive costimulatory molecule. In one example, a positive costimulatory molecule is a B7 family costimulatory molecule. In another example the positive costimulatory molecule is selected from the group consisting of: CD28, CD80, CD86, ICOS/ICOSL. In yet another example, the positive costimulatory molecule is a TNFR family costimulatory molecule. In a further example, the TNFR costimulatory molecule is selected form the group consisting of: OX40/OX40L, 4-1BB/4-1BBL, CD27/CD27L, CD30/CD30L and HVEM/LIGHT, and soluble fragments, constructs and agonist antibodies thereof.

In a still further example, the disclosure provides for an article of manufacture comprising any of the above described anti-PD-L1 antibodies in combination with one or more antibiotics. In one example, the antibiotic is selected from the group consisting of an anti-viral agent, anti-bacterial agent, anti-fungal agent, anti-protozoan agent.

In another example the anti-viral agent is selected from the group consisting of reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, entry or fusion inhibitors, maturation inhibitors, viral rlease inhibitors, immune response enhancers, anti-viral synergistic enhancers, vaccines, hepatic agonists and herbal therapies. In yet another example, the combination comprises one or more categories of anti-viral agents.

In a still further example, the disclosure provides for an article of manufacture comprising any of the above described anti-PD-L1 antibodies in combination with one or more vaccines.

In a still further example, the disclosure provides for a method of enhancing T-cell function comprising administering an effective amount of any of the above described anti-PD-L1 antibodies or compositions. In one example, the anti-PD-L1 antibody or composition renders dysfunctional T-cells non-dysfunctional.

In a still further example, the disclosure provides for a method of treating a T-cell dysfunctional disorder comprising administering a therapeutically effective amount of any of the above described anti-PD-L1 antibodies or compositions. In one specific example, the T-cell dysfunctional disorder is infection or tumor immunity. In another example the infection is acute or chronic. In another example, the chronic infection is persistent, latent or slow. In yet another example, the chronic infection results from a pathogen selected from the group consisting of bacteria, virus, fungi and protozoan. In a further example, the pathogen level in the host is reduced.

In a still further example, the method further comprises treatment with a vaccine. In a still further example, the method further comprises treatment with an antibiotic. In a still further example, the pathogen is a bacteria, and the method further comprises the adminstration of an antibacterial agent. In a still further example, the bacteria is selected from the group consisting of: *Mycobacterium spp., Salmonella spp., Listeria spp,, Streptococcus spp., Haemophilus, spp., Neisseria spp., Klebsiella spp., Borrelia spp., Bacterioides fragillis, Treponema spp., and Helicobacter pylori*. In a still further example, the pathogen is a virus, and the method further comprises the administration of an anti-viral agent. In a still further example, the virus is selected from the group consisting of: hepatitis –B, -C, herpes simplex virus -I, -II, human immunodeficiency virus –I, -II, cytomegalovirus, Eppstein Barr virus, human papillomavirus, human T lymphotrophic viruses, -I, -II, varicalla zoster. In a still further example, the pathogen is a fungus, and the method further comprises the administration of an anti-fungal agent. In a still further example, the disorder is selected from the group consisting of: aspergilosis, blastomycosis, candidiasis albicans, coccidioiodmycosis immitis, histoplasmosis, paracoccidioiomycosis, microsporidiosis. In a still further example, the pathogen is a protozoan, and the method further comprises the administration of an anti-protozoan agent. In a still further example, the disorder is selected from the group consisting of: leishmaniasis, plasmodiosis (*i.e.*, malaria), cryptosporidiosis, toxoplasmosis, trypanosomiasis, and helminth infections, including those resulting from trematodes (*e.g.*, schistosomiasis), cestodes (*e.g.*, echinococcosis) and nemotodes (*e.g.*, trchinosis, ascariasis, filariosis and strongylodiosis).

In a still further example, the T-cell dysfunctional disorder is tumor immunity. In a still further example, the PD-L1 antibody or composition is combined with a treatment regimen further comprising a traditional therapy selected from the group consisting of: radiation therapy, chemotherapy, targeted therapy, immunotherapy, hormonal therapy, angiogenesis inhibition and palliative care. In a still further specific example, the chemotherapy treatment is selected from the group consisting of: gemcitabine, cyclophosphamide, doxorubicin, paclitaxel, cisplatin. In a still further specific example, the tumor immunity results from a cancer selected from the group consisting of: breast, lung, colon, ovarian, melanoma, bladder, kidney, liver, salivary, stomach, gliomas, thyroid, thymic, epithelial, head and neck cancers, gastric, and pancreatic cancer.

## Brief Description of the Drawings

Figure 1 is a graphical illustration depicting costimulation of T-cells by the B7 family of cell surface molecules.

**WHAT IS CLAIMED IS:**

1. Use of an anti-PD-L1 antibody or antigen binding fragment thereof in the manufacture of a medicament for treating cancer or infection in a subject, wherein the anti-PD-L1 antibody or antigen binding fragment thereof comprises a heavy chain and a light chain variable region sequence, wherein:

(a) the heavy chain comprises an HVR-H1, HVR-H2 and HVR-H3, wherein:

(i) the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 15;

(ii) the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 16;

(iii) the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 3;

(b) the light chain comprises an HVR-L1, HVR-L2 and HVR-L3, wherein:

(iv) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 17;

(v) the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 18;

(vi) the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 19.

2. The use of claim 1, wherein the variable region light chain framework sequences of said antibody or antigen binding fragment thereof are VL kappa I consensus framework and/or the variable region heavy chain framework sequences of said antibody or antigen binding fragment thereof are VH subgroup III consensus framework.

3. The use of claim 1 or 2, wherein the antibody or antigen binding fragment thereof further comprises variable region light chain framework sequences juxtaposed between the HVRs according to the formula: (LC-FR1)-(HVR-L1)-(LC-FR2)-(HVR-L2)-(LC-FR3)-(HVR-L3)-(LC-FR4), wherein one or more of the variable region light chain framework amino acid sequences comprises the following:

LC-FR1 comprises the amino acid sequence of SEQ ID NO: 11;

LC-FR2 comprises the amino acid sequence of SEQ ID NO: 12;

LC-FR3 comprises the amino acid sequence of SEQ ID NO: 13;

LC-FR4 comprises the amino acid sequence of SEQ ID NO: 14.

4. The use of any one of claims 1-3, wherein the antibody or antigen binding fragment thereof further comprises variable region heavy chain framework sequences juxtaposed between the HVRs according to the formula: (HC-FR1)-(HVR-H1)-(HC-FR2)-(HVR-H2)-

(HC-FR3)-(HVR-H3)-(HC-FR4), wherein one or more of the variable region heavy chain framework amino acid sequences comprises the following:

HC-FR1 comprises the amino acid sequence of SEQ ID NO: 4;

HC-FR2 comprises the amino acid sequence of SEQ ID NO: 5;

HC-FR3 comprises the amino acid sequence of SEQ ID NO: 6;

HC-FR4 comprises the amino acid sequence of SEQ ID NO: 7.

5. The use of any one of claims 1-4, wherein:

(a) the heavy chain variable region amino acid sequence of said antibody or antigen binding fragment thereof has at least 90% sequence identity to the heavy chain variable region amino acid sequence of SEQ ID NO: 20, and

(b) the light chain variable region amino acid sequence of said antibody or antigen binding fragment thereof has at least 90% sequence identity to the light chain variable region amino acid sequence of SEQ ID NO: 21.

6. The use of claim 5, wherein the light chain variable region amino acid sequence has at least 95% sequence identity to the light chain variable region amino acid sequence of SEQ ID NO: 21.

7. The use of claim 5, wherein the light chain variable region amino acid sequence has at least 99% sequence identity to the light chain variable region amino acid sequence of SEQ ID NO: 21.

8. The use of claim 5, wherein the light chain variable region amino acid sequence comprises the light chain variable region amino acid sequence of SEQ ID NO: 21.

9. The use of any one of claims 5-8, wherein the heavy chain variable region amino acid sequence has at least 95% sequence identity to the heavy chain variable region amino acid sequence of SEQ ID NO: 20.

10. The use of any one of claims 5-8, wherein the heavy chain variable region amino acid sequence has at least 99% sequence identity to the heavy chain variable region amino acid sequence of SEQ ID NO: 20.

11. The use of any one of claims 5-8, wherein the heavy chain variable region amino acid sequence comprises the heavy chain variable region amino acid sequence of SEQ ID NO: 20.

12. Use of an anti-PD-L1 antibody or antigen binding fragment thereof in the manufacture of a medicament for treating cancer or infection in a subject, wherein the antibody or antigen binding fragment comprises a heavy chain and a light chain variable region sequence, wherein:

(a) the heavy chain variable region amino acid sequence has at least 90% sequence identity to the heavy chain variable region amino acid sequence of SEQ ID NO:20, and

(b) the light chain variable region amino acid sequence has at least 90% sequence identity to the light chain variable region amino acid sequence of SEQ ID NO:21.

13. The use of claim 12, wherein the light chain variable region amino acid sequence has at least 95% sequence identity to the light chain variable region amino acid sequence of SEQ ID NO:21.

14. The use of claim 12, wherein the light chain variable region amino acid sequence has at least 99% sequence identity to the light chain variable region amino acid sequence of SEQ ID NO:21.

15. The use of claim 12, wherein the light chain variable region amino acid sequence comprises the light chain variable region amino acid sequence of SEQ ID NO: 21.

16. The use of any one of claims 12-15, wherein the heavy chain variable region amino acid sequence has at least 95% sequence identity to the heavy chain variable region amino acid sequence of SEQ ID NO: 20.

17. The use of any one of claims 12-15, wherein the heavy chain variable region amino acid sequence has at least 99% sequence identity to the heavy chain variable region amino acid sequence of SEQ ID NO: 20.

18. The use of any one of claims 12-15, wherein the heavy chain variable region amino acid sequence comprises the heavy chain variable region amino acid sequence of SEQ ID NO: 20.

19. The use of any one of claims 1-18, wherein the antibody or antigen binding fragment thereof further comprising a human constant region.

20. The use of claim 19, wherein the constant region is selected from the group consisting of IgG1, IgG2, IgG3 and IgG4.

21. The use of Claim 20, wherein the constant region is IgG1.

22. The use of any one of claims 1-21, wherein the antibody or antigen binding fragment thereof has reduced or minimal effector function.

23. The use of claim 22, wherein the minimal effector function results from an effector-less Fc mutation.

24. The use of claim 23, wherein the effector-less Fc mutation is N297A.

25. The use of claim 23, wherein the effector-less Fc mutation is D265A/N297A.

26. The use of claim 22, wherein the minimal effector function results from aglycosylation.

27. The use of any one of claims 1-26, wherein the use is for treating cancer in a subject.

28. The use of claim 27, wherein the cancer is selected from the group consisting of breast, lung, colon, ovarian, melanoma, bladder, kidney, liver, salivary, stomach, gliomas, thyroid, thymic, epithelial, head and neck, gastric and pancreatic.

29. The use of claim 7 or 28, wherein the medicament is for use in combination with a chemotherapeutic agent.

30. The use of claim 29, wherein the chemotherapeutic agent is an anti-VEGF antibody.

31. The use of claim 30, wherein the anti-VEGF antibody is bevacizumab.

32. The use of claim 29, wherein the chemotherapeutic agent is FOLFOX.

33. The use of claim 32, wherein FOLFOX is a combination of oxaliplatin, 5-fluorouracil and leucovorin.

34. The use of claim 29, wherein the chemotherapeutic agent is oxaliplatin.

35. The use of claim 29, wherein the chemotherapeutic agent is a RAF inhibitor.

36. The use of any one of claims 1-26, wherein the use is for treating infection in a subject.

37. The use of claim 36, wherein the medicament is for use in combination with an antibiotic.

38. The use of claim 36, wherein the medicament is for use in combination with an anti-viral agent.

39. The use of claim 38, wherein the anti-viral agent is a reverse transcriptase inhibitor.

40. The use of claim 39, wherein the reverse transcriptase inhibitor is a polymerase inhibitor.

41. The use of claim 38, wherein the anti-viral agent is a protease inhibitor.

42. The use of claim 36, wherein the medicament is for use in combination with at least one vaccine.

43. The use of any one of claims 36-42, wherein the infection is chronic.

44. The use of claim 43, wherein the chronic infection is persistent.

45. The use of claim 43, wherein the chronic infection is latent.

46. The use of claim 43, wherein the chronic infection is slow.

47. The use of any one of claims 36-46, wherein the infection results from a pathogen selected from the group consisting of bacteria, viruses, fungi and protozoa.

48. The use of claim 47, wherein the pathogen is a bacterium, and the medicament is for use in combination with an anti-bacterial agent.

49. The use of claim 47, wherein the pathogen is a virus, and the medicament is for use in combination with an anti-viral agent.

50. The use of claim 47, wherein the pathogen is a fungus, and the medicament is for use in combination with an anti-fungal agent.

51. The use of claim 47, wherein the pathogen is a protozoan, and the medicament is for use in combination with an anti-protozoan agent.