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 embodiment, 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 embodiment, X_1 is D; X_2 is S and X_3 is T. In another embodiment, 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 embodiment, the framework sequences are derived from human consensus framework sequences. In a further embodiment, the framework sequences are VH subgroup III consensus framework. In a still further embodiment, 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 embodiment, 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 embodiment, 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 embodiment, 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 embodiment, the framework sequences are derived from human consensus framework sequences. In a still further embodiment, the framework sequences are VL kappa I consensus framework. In a still further embodiment, 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 embodiment, 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 embodiment, X_1 is D; X_2 is S and X_3 is T. In another embodiment, 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 embodiment, 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 embodiment, 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 embodiment, the framework sequences are derived from human consensus framework sequences. In a still further embodiment, the heavy chain framework sequences are derived from a Kabat subgroup I, II, or III sequence. In a still further embodiment, the heavyc chain framework sequence is a VH subgroup III consensus framework. In a still further embodiment, 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 embodiment, the light chain framework sequences are derived from a Kabat kappa I, II, II or IV subgroup sequence. In a still further embodiment, the light chain framework sequences are VL kappa I consensus framework. In a still further embodiment, 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 embodiment, the antibody further comprises a human or murine constant region. In a still further embodiment, the human constant region is selected from the group consisting of IgG1, IgG2, IgG2, IgG3, IgG4. In a still further specific embodiment, the human constant region is IgG1. In a still further embodiment, the murine constant region is selected from the group consisting of IgG1, IgG2A, IgG2B, IgG3. In a still further embodiment, the murine constant region if IgG2A. In a still further specific embodiment, the antibody has reduced or minimal effector function. In a still further specific embodiment the minimal effector function results from an "effector-less Fc mutation" or aglycosylation. In still a further embodiment, the effector-less Fc mutation is an N297A or D265A/N297A substitution in the constant region.

In yet another embodiment, 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 embodiment, the sequence identity is 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%. In another embodiment, 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 embodiment, the framework sequences are derived from human consensus framework sequences. In a still further embodiment, the heavy chain framework sequences are derived from a Kabat subgroup I, II, or III sequence. In a still further embodiment, the heavy chain framework sequence is a VH subgroup III consensus framework. In a still further embodiment, 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 embodiment, the light chain framework sequences are derived from a Kabat kappa I, II, II or IV subgroup sequence. In a still further embodiment, the light chain framework sequences are VL kappa I consensus framework. In a still further embodiment, 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 embodiment, the antibody further comprises a human or murine constant region. In a still further embodiment, the human constant region is selected from the group consisting of IgG1, IgG2, IgG2, IgG3, IgG4. In a still further specific embodiment, the human constant region is IgG1. In a still further embodiment, the murine constant region is selected from the group consisting of IgG1, IgG2A, IgG2B, IgG3. In a still further embodiment, the murine constant region if IgG2A. In a still further specific embodiment, the antibody has reduced or minimal effector function. In a still further specific embodiment the minimal effector function results from an "effector-less Fc mutation" or aglycosylation. In still a further embodiment, the effector-less Fc mutation is an N297A or D265A/N297A substitution in the constant region.

In a still further embodiment, 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 one aspect, there is provided an isolated nucleic acid encoding an anti-PD-L1 antibody or antigen binding fragment thereof, wherein the antibody or antigen binding fragment thereof comprises a heavy chain and light chain variable region sequence, wherein:

(a) the heavy chain comprises the sequence: EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWIS PYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPG GFDYWGQGTLVTVSA (SEQ ID NO:20), and

(b) the light chain comprises the sequence: DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVA WYQQKPGKAPKLLIYSASFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQYLYH PATFGQGTKVEIKR (SEQ ID NO:21).

In a specific embodiment, the sequence identity is 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%. In another embodiment, 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 embodiment, the framework sequences are derived from human consensus framework sequences. In a further embodiment, the heavy chain framework sequences are derived from a Kabat subgroup I, II, or III sequence. In a still further embodiment, the heavy chain framework sequence is a VH subgroup III consensus framework. In a still further embodiment, 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 embodiment, the light chain framework sequences are derived from a Kabat kappa I, II, II or IV subgroup sequence. In a still further embodiment, the light chain framework sequences are VL kappa I consensus framework. In a still further embodiment, 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 embodiment, the antibody further comprises a human or murine constant region. In a still further embodiment, the human constant region is selected from the group consisting of IgG1, IgG2, IgG2, IgG3, IgG4. In a still further specific embodiment, the human constant region is IgG1. In a still further embodiment, the murine constant region is selected from the group consisting of IgG1, IgG2A, IgG2B, IgG3. In a still further embodiment, the murine constant region if IgG2A. In a still further specific embodiment, the antibody has reduced or minimal effector function. In a still further specific embodiment, the minimal effector function results from production in prokaryotic cells. In a still further specific embodiment the minimal effector function results from an "effector-less Fc mutation" or aglycosylation. In still a further embodiment, the effector-less Fc mutation is an N297A or D265A/N297A substitution in the constant region.

In a still further embodiment, 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 another aspect, there is provided an isolated nucleic acid encoding an anti-PD-L1 antibody or antigen binding fragment thereof, wherein the 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 further:
(i) the HVR-H1 sequence is GFTFSDSWIH (SEQ ID NO: 15);
(ii) the HVR-H2 sequence is AWISPYGGSTYYADSVKG (SEQ ID NO: 16);
(iii) the HVR-H3 sequence is RHWPGGFDY (SEQ ID NO:3); and
(b) the light chain comprises an HVR-L1, HVR-L2 and HVR-L3, wherein further:
(iv) the HVR-L1 sequence is RASQDVSTAVA (SEQ ID NO: 17);
(v) the HVR-L2 sequence is SASFLYS (SEQ ID NO: 18);
(vi) the HVR-L3 sequence is QQYLYHPAT (SEQ ID NO: 19).

In a still further embodiment, 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 embodiment, the sequence identity is 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%. In embodiment, 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 embodiment, the framework sequences are derived from human consensus framework sequences. In a further embodiment, the heavy chain framework sequences are derived from a Kabat subgroup I, II, or III sequence. In a still further embodiment, the heavy chain framework sequence is a VH subgroup III consensus framework. In a still further embodiment, 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 embodiment, the light chain framework sequences are derived from a Kabat kappa I, II, II or IV subgroup sequence. In a still further embodiment, the light chain framework sequences are VL kappa I consensus framework. In a still further embodiment, 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 embodiment, the antibody further comprises a human or murine constant region. In a still further embodiment, the human constant region is selected from the group consisting of IgG1, IgG2, IgG2, IgG3, IgG4. In a still further specific embodiment, the human constant region is IgG1. In a still further embodiment, the murine constant region is selected from the group consisting of IgG1, IgG2A, IgG2B, IgG3. In a still further embodiment, the murine constant region if IgG2A. In a still further specific embodiment, the antibody has reduced or minimal effector function. In a still further specific embodiment, the minimal effector function results from production in prokaryotic cells. In a still further specific embodiment the minimal effector function results from an "effector-less Fc mutation" or aglycosylation. In still a further embodiment, the effector-less Fc mutation is an N297A or D265A/N297A substitution in the constant region.

In another aspect, there is a provided a vector comprising the nucleic acid described herein. In a still further embodiment, 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 another aspect, there is provided a host cell comprising the vector described herein. In a still further specific embodiment, the vector further comprises a host cell suitable for expression of the nucleic acid. In a still further specific embodiment, the host cell is a eukaryotic cell or a prokaryotic cell. In a still further specific embodiment, the eukaryotic cell is a mammalian cell, such as Chinese Hamster Ovary (CHO).

In another aspect, there is provided a procees for making an anti-PD-L1 antibody or antigen binding fragment thereof comprising culturing the host cell described herein under conditions suitable for the expression of the vector encoding the anti-PD-L1 antibody or antigen binding fragment thereof, and recovering the antibody or fragment. In a still further embodiment, 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 embodiment, 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 embodiment, 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 embodiment, 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 embodiment, the BNCA molecules is an antibody, antigen binding antibody fragment, BNCA oligopeptide, BNCA RNAi or BNCA small molecule. In another embodiment, 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 embodiment, the article of manufacture comprises any of the above described anti-PD-L1 compositions in combination with a chemotherapeutic agent. In one embodiment, the chemotherapeutic agent is gemcitabine.

In a still further embodiment, 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 embodiment, a positive costimulatory molecule is a B7 family costimulatory molecule. In another embodiment the positive costimulatory molecule is selected from the group consisting of: CD28, CD80, CD86, ICOS/ICOSL. In yet another embodiment, the positive costimulatory molecule is a TNFR family costimulatory molecule. In a further embodiment, 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 embodiment, 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 embodiment, the antibiotic is selected from the group consisting of an anti-viral agent, anti-bacterial agent, anti-fungal agent, anti-protozoan agent.

In another embodiment 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 embodiment, the combination comprises one or more categories of anti-viral agents.

In a still further embodiment, 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 embodiment, 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 embodiment, the anti-PD-L1 antibody or composition renders dysfunctional T-cells non-dysfunctional.

In a still further embodiment, 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 embodiment, the T-cell dysfunctional disorder is infection or tumor immunity. In another embodiment the infection is acute or chronic. In another embodiment, the chronic infection is persistent, latent or slow. In yet another embodiment, the chronic infection results from a pathogen selected from the group consisting of bacteria, virus, fungi and protozoan. In a further embodiment, the pathogen level in the host is reduced.

In a still further embodiment, the method further comprises treatment with a vaccine. In a still further embodiment, the method further comprises treatment with an antibiotic. In a still further embodiment, the pathogen is a bacteria, and the method further comprises the adminstration of an antibacterial agent. In a still further embodiment, 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 embodiment, the pathogen is a virus, and the method further comprises the administration of an anti-viral agent. In a still further embodiment, 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 embodiment, the pathogen is a fungus, and the method further comprises the administration of an anti-fungal agent. In a still further embodiment, the disorder is selected from the group consisting of: aspergilosis, blastomycosis, candidiasis albicans, coccidioiodmycosis immitis, histoplasmosis, paracoccidioiomycosis, microsporidiosis. In a still further embodiment, the pathogen is a protozoan, and the method further comprises the administration of an anti-protozoan agent. In a still further embodiment, 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 embodiment, the T-cell dysfunctional disorder is tumor immunity. In a still further embodiment, 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 embodiment, the chemotherapy treatment is selected from the group consisting of: gemcitabine, cyclophosphamide, doxorubicin, paclitaxel, cisplatin. In a still further specific embodiment, 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. An isolated nucleic acid encoding an anti-PD-L1 antibody or antigen binding fragment thereof, wherein the 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 further:

(i) the HVR-H1 sequence is GFTFSDSWIH (SEQ ID NO: 15);

(ii) the HVR-H2 sequence is AWISPYGGSTYYADSVKG (SEQ ID NO: 16);

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

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

(iv) the HVR-L1 sequence is RASQDVSTAVA (SEQ ID NO: 17);

(v) the HVR-L2 sequence is SASFLYS (SEQ ID NO: 18);

(vi) the HVR-L3 sequence is QQYLYHPAT (SEQ ID NO: 19).

2. The nucleic acid of Claim 1, wherein the heavy chain variable region comprises framework sequences juxtaposed between the HVRs according to the formula: (HC-FR1)-(HVR-H1)-(HC-FR2)-(HVR-H2)-(HC-FR3)-(HVR-H3)-(HC-FR4).

3. The nucleic acid of claim 2, wherein the framework sequences are derived from human consensus framework sequences.

4. The nucleic acid of Claim 3, wherein the framework sequences are VH subgroup III consensus framework.

5. The nucleic acid of Claim 3, wherein one or more 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).